Clinical Practice Guideline: Uses of Serum Tumor Markers in Male Adults with Germ Cell Tumors
Introduction

• Serum Tumor Markers (STMs) are well-established in guiding management decisions for patients with germ cell tumors (GCT)
• Long history of using serum concentrations of human chorionic gonadotropin (hCG), alpha-fetoprotein (AFP), and lactate dehydrogenase (LDH)
• ASCO developed a new guideline for using GCT markers
Methodology

• The panel completed a review and analysis of the medical literature available from January 1990 through February 2009
  – Medline
  – EMBASE

• In addition, members of the Expert Panel suggested additional literature
Clinical Questions

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

2. In the following circumstances, are STM assays indicated to diagnose male 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?
Clinical Questions

Recommendations address questions 3 and 4 separately for non-seminoma GCTs (NSGCT) and seminoma

3. In adult male patients undergoing treatment (or observation), are STM assays indicated for the following:
   a. To stage patients before primary therapy and predict prognosis?
   b. To predict response to or benefit from treatment?
   c. To monitor treatment response or progression during or immediately after therapy?
Clinical Questions

4. In adult male patients, are STM assays indicated after potentially definitive therapy for surveillance and routine monitoring to detect asymptomatic recurrence?
Recommendations: Screening

Recommendation 1.

• *Not recommended: use of STMs or any other blood tests to screen for GCTs*

Recommendations: Diagnosis

Recommendation 2A.

• *Draw blood to measure serum AFP and hCG before diagnostic orchiectomy for patients suspected of having a testicular GCT*  
• *Purpose – to help establish diagnosis and interpret post-orchiectomy levels*

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Recommendations: Diagnosis

Recommendation 2A, cont’d

• Not recommended: use of STM assay results to guide decisions on need for an orchiectomy
• STM concentrations in the normal range do not rule out testicular neoplasm or the need for diagnostic orchiectomy
• Significantly elevated serum AFP establishes the diagnosis of mixed GCT in a patient whose histopathology shows pure seminoma.
• Interpret borderline-elevated values cautiously
Recommendations: Diagnosis, cont’d

- Recommendation 2B. Not recommended: using serum AFP and hCG assay results to guide treatment of patients with CUP and indeterminate histology
- No evidence to support this use
- Consider treatment with a chemotherapy regimen for disseminated GCT in patients presenting with undifferentiated carcinoma in the midline even if serum hCG and AFP concentrations are within normal ranges
Recommendations: Diagnosis, cont’d

• Recommendation 2C. *In rare male patients presenting with testicular, retroperitoneal or anterior mediastinal primary tumor and whose disease burden necessitates urgently starting treatment, very substantially elevated serum AFP and/or hCG is sufficient for diagnosis of GCT*

• *For such rare, medically unstable patients, treatment need not be delayed for tissue diagnosis*
Caveat on Evidence Available for Questions 3 and 4

• Conclusive direct evidence was lacking to compare survival or other health outcomes after treatment decisions made with versus without STM assay results. Consequently, nearly all recommendations on monitoring treatment (I-3 and II-3) or surveillance after treatment (I-4 and II-4) for NSGCT (I-3 and I-4) or seminoma (II-3 and II-4) are based on evidence from secondary outcomes. (look for * on individual slides)
Recommendations: NSGCT
For staging and prognosis before chemotherapy and/or additional surgery

Recommendation I-3A-1*.

- **Recommended to measure serum AFP, hCG, and LDH for all patients with testicular NSGCT shortly after orchiectomy and before any subsequent treatment**

- **Magnitude of post-orchiectomy STM elevations influence risk stratification and treatment decisions; use appropriate interpretation**

(continued on next slide)
Recommendations: NSGCT

For staging and prognosis before chemotherapy and/or additional surgery

Recommendation I-3A-1*, cont’d

- Pay particular attention to possible reasons for false-positive elevations
- Serial measurements may be needed to determine whether levels are rising or falling and, if falling, whether rates approximate the marker’s biological half-life

- Marker half-life:
  - hCG=24 to 36 hours
  - AFP= 7 days
Recommendations: NSGCT

For staging and prognosis before chemotherapy and/or additional surgery

Recommendation I-3A-2*.

- **Measure AFP, hCG, and LDH before chemotherapy begins for those with mediastinal or retroperitoneal NSGCTs**
- **Purpose:** stratify risk and guide treatment

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Recommendations: NSGCT

To predict response to or benefit from treatment

Recommendation I-3B-1.

- Measure AFP and hCG shortly before retroperitoneal lymph node dissection (RPLND) in patients with clinical stage I or II NSGCT.
- Those with rising or persistently elevated serum tumor marker concentrations generally require the same systemic therapy as those with stage III disease, due to a very high risk of relapse if treated with RPLND.
Recommendations: NSGCT
To predict response to or benefit from treatment

Recommendation I-3B-2*.

- Measure hCG, AFP, and LDH elevations immediately before chemotherapy for stage I-III testicular NSGCT
- Magnitude of markers elevations guides chemotherapy regimen choices and treatment duration
Recommendations: NSGCT

To monitor response or progression during or soon after therapy

Recommendation I-3C*.

- Measure serum AFP and hCG at the start of each chemotherapy cycle, and again when chemotherapy concludes
- No indication to delay starting chemotherapy until after results of STM assays. Rising levels of AFP and/or hCG levels during chemotherapy usually imply progressive disease and the need to change regimen

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Recommendations: NSGCT
To monitor response or progression during or soon after therapy
Recommendation I-3C*, cont’d

• 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 post-chemotherapy levels do not indicate immediate need for additional chemotherapy; resection of residual masses need not be delayed until they normalize.

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Recommendations: NSGCT
After presumably definitive therapy

Recommendation I-4*.

• **Measure AFP and hCG at each visit during surveillance after definitive therapy for NSGCT, regardless of stage**

• **Not evidence to directly compare outcomes for different monitoring intervals or durations, therefore recommended to use intervals within the range used by available uncontrolled series: every 1-2 months in year 1, every 2-4 months in year 2, every 3-6 months in years 3 and 4, every 6 months in year 5, and annually thereafter**

• **Surveillance should continue for at least 10 years after therapy is completed**
Recommendations: Seminoma-Monitoring: For staging and diagnosis during RPLND, RT, or chemotherapy

Recommendation II-3A.

• Measure post-orchiectomy serum concentrations of hCG and/or LDH for patients with testicular pure seminoma and pre-orchiectomy elevations
  – Persistently elevated or rising concentrations may indicate metastatic disease and warrant a thorough work-up

• Not recommended: using post-orchiectomy serum concentrations of either hCG or LDH to stage or predict prognosis of patients with seminoma and involved nodes and/or metastatic disease
Recommendations: Seminoma-Monitoring
To predict response to or benefit from treatment

- Recommendation II-3B*.
- *Not recommended: using hCG or LDH concentrations to guide treatment decisions for seminoma*
- *Evidence is lacking that selecting therapy based on tumor marker levels yields better outcomes*
Recommendations: Seminoma-Monitoring

To predict response to or benefit from treatment

- Recommendation II-3C. *Not recommended: using tumor markers to monitor response or progression of seminomas during treatment*
- *However, measure serum hCG and AFP when seminoma treatment concludes*
- *Rising concentrations usually indicate progressive disease and the need for salvage therapy (usually chemotherapy)*

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Recommendations: Seminoma: Surveillance after presumably definitive therapy

- Recommendation II-4*.
- **Not recommended:** using STMs in post-treatment surveillance for stage I seminoma
- **Recommended:** using STMs in post-treatment surveillance for stage II and III seminoma
- **Rising levels may be the earliest sign of relapse after therapy for advanced seminoma and it is recommended to measure STMs at each visit for these patients**

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Recommendations: Seminoma: Surveillance after presumably definitive therapy, cont’d

- Recommendation II-4, cont’d*
- No evidence to directly compare outcomes for different monitoring intervals or durations, therefore recommended to use intervals within the range used by available uncontrolled series

- Ranges: Every two to four months in year 1, every three to four months in year 2, every four to six months in years 3 and 4, and annually thereafter

- Surveillance should continue for at least 10 years post-therapy

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## Risk stratification

<table>
<thead>
<tr>
<th>Marker¹ (units)</th>
<th>NSGCT</th>
<th>SEMINOMAS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>AFP (μg/L)</strong></td>
<td>Good Risk</td>
<td>Intermediate Risk</td>
</tr>
<tr>
<td>&lt;1,000</td>
<td>≥1,000 but ≤10,000³</td>
<td>&gt;10,000⁴</td>
</tr>
<tr>
<td><strong>hCG (U/L)</strong></td>
<td>&lt;5,000</td>
<td>≥5,000 but ≤50,000³</td>
</tr>
<tr>
<td><strong>LDH (X UL-NR²)</strong></td>
<td>&lt;1.5</td>
<td>≥1.5 but ≤10³</td>
</tr>
<tr>
<td>Primary tumor site</td>
<td>testis or retroperitoneum (RP)</td>
<td>testis or RP</td>
</tr>
<tr>
<td>Sites of Metastases</td>
<td>no non-pulmonary visceral</td>
<td>no non-pulmonary visceral</td>
</tr>
<tr>
<td>approximate proportion of patients in this risk group</td>
<td>56%</td>
<td>28%</td>
</tr>
<tr>
<td>predicted OS at 5 yrs</td>
<td>92%</td>
<td>80%</td>
</tr>
<tr>
<td>predicted PFS at 5 yrs</td>
<td>89%</td>
<td>75%</td>
</tr>
</tbody>
</table>

¹ Concentrations of each marker must be in the ranges shown in patients assigned to each risk category. See original IGCCCG report for other criteria associated with each risk group (reference in full guideline).
² fold increase over upper limit of the normal range. ³ Any one of these findings is sufficient by itself to classify a patient as intermediate risk. ⁴ Any one of these findings is sufficient by itself to classify a patient as poor risk. ⁵ This is the only factor distinguishing good-risk from intermediate-risk seminoma.

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<table>
<thead>
<tr>
<th>Assay Techniques (as recommended by NACB)</th>
<th>AFP</th>
<th>hCG</th>
<th>LDH</th>
</tr>
</thead>
<tbody>
<tr>
<td>2-site immunometric assays with MoAbs ± polyclonal antisera</td>
<td>double-antibody immunometric assays that measure total hCGβ (intact αβ dimer plus free β monomer)</td>
<td>enzymatic activity assays measuring conversion of lactate to pyruvate or vice versa</td>
<td></td>
</tr>
<tr>
<td>Upper Limits, Normal Range</td>
<td>10-15 μg/L (≤9 if &lt;40 yrs of age; ≥13 if &gt;40)</td>
<td>5-10 U/L (0.7 U/L in men &lt;50 years of age; 2.1 U/L if &gt;50 years)</td>
<td>highly variable and laboratory-specific; depends on assay conditions; elevated if &gt;1.5 times lab-specific UL-NR</td>
</tr>
<tr>
<td>Units (and conversion factors, if applicable)</td>
<td>International units (kU/L) or mass units (μg/L); 1 U = 1.21 ng</td>
<td>International units (U/L); 5 U/L of hCG corresponds to 15 pmol/L</td>
<td>U/L and fold-increase over UL-NR</td>
</tr>
<tr>
<td>Detection Limit (as recommended by NACB)</td>
<td>&lt;1 μg/L (0.8 kU/L) of serum or plasma</td>
<td>&lt;1 U/L of serum or plasma (and ≤2% cross-reactivity with LH)</td>
<td>highly dependent on assay method and conditions</td>
</tr>
<tr>
<td>Approximate Biological Half-life</td>
<td>5 to 7 days</td>
<td>1.5 to 3 days</td>
<td>not reported</td>
</tr>
<tr>
<td>Seminomatous GCT (approximate proportion of patients with elevations)</td>
<td>Never elevated in pure seminoma</td>
<td>Yes (15-20% in advanced disease)</td>
<td>Yes (in 40% to 60% of patients)</td>
</tr>
<tr>
<td>Non-Seminomatous GCT (approximate proportion of patients with elevations)</td>
<td>Yes (10-20% in stage I; 20-40% in low-volume stage II; 40-60% in advanced disease)</td>
<td>Yes (10-20% in stage I, 20-30% in low-volume stage II; 40% in advanced disease)</td>
<td>Yes (in 40% to 60% of patients)</td>
</tr>
<tr>
<td>Other Malignancies sometimes associated with elevations</td>
<td>Hepatocellular carcinoma, gastric cancer, lung*, colon*, and pancreatic cancer*</td>
<td>Neuroendocrine, bladder, kidney, lung, head, neck, GI, cervix, uterus and vulva, lymphoma* and leukemia*</td>
<td>Lymphoma, small cell lung, Ewing’s sarcoma, osteogenic sarcoma</td>
</tr>
<tr>
<td>Non-malignant conditions sometimes associated with elevations</td>
<td>Alcohol abuse, hepatitis, cirrhosis, biliary tract obstruction, hereditary persistence*</td>
<td>Marijuana, hypogonadism</td>
<td>Many (processes that involve cell or tissue damage, e.g., MI, liver or muscle disease), hemolysis of blood sample</td>
</tr>
</tbody>
</table>

Abbreviations: GI: gastrointestinal; LH: leuteinizing hormone; MI: myocardial infarction; MoAb: monoclonal antibodies; NACB: National Academy of Clinical Biochemistry; STM: serum tumor markers; UL-NR: upper limit of the normal range

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## Causes of False Positive Test Results for Serum Tumor Markers

<table>
<thead>
<tr>
<th>Marker</th>
<th>Cause of False Positive</th>
<th>Pathophysiology and management</th>
</tr>
</thead>
<tbody>
<tr>
<td>AFP</td>
<td>Benign liver disease</td>
<td>Hepatitis, hepatic toxicity from chemotherapy, and certain other benign liver disorders may elevate serum AFP.</td>
</tr>
<tr>
<td>Constitutively elevated AFP</td>
<td></td>
<td>Some individuals have serum AFP levels that are chronically mildly elevated in the range of 15 to 30 ng/ml. Elevated AFP levels due to cancer will generally show a consistent pattern of increasing in value.</td>
</tr>
<tr>
<td>Tumor lysis</td>
<td></td>
<td>Serum tumor markers levels may rise during the first week of chemotherapy due to tumor lysis. If tumor markers rise between day 1 of cycle 1 and day 1 of cycle 2, tumor marker levels should be repeated midway through cycle 2 to determine if they begin to decline.</td>
</tr>
<tr>
<td>Hepatocellular carcinoma and other cancers</td>
<td></td>
<td>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.</td>
</tr>
</tbody>
</table>
## Causes of False Positive Test Results for Serum Tumor Markers, cont’d.

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<th>Marker</th>
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<th>Pathophysiology and management</th>
</tr>
</thead>
<tbody>
<tr>
<td>hCG</td>
<td>Pituitary hCG/ hypogonadism</td>
<td>Unilateral orchiectomy and chemotherapy can cause low testosterone levels, which in turn can lead to increased production of LH and hCG by the pituitary. 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.</td>
</tr>
<tr>
<td>Tumor lysis</td>
<td></td>
<td>Serum tumor markers levels may rise during the first week of chemotherapy due to tumor lysis. If tumor markers rise between day 1 of cycle 1 and day 1 of cycle 2, tumor marker levels should be repeated midway through cycle 2 to ensure that they begin to decline.</td>
</tr>
<tr>
<td>Other cancers</td>
<td></td>
<td>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.</td>
</tr>
<tr>
<td>Heterophilic antibodies</td>
<td></td>
<td>Heterophilic antibodies have been reported in women to result in false-positive hCG results.</td>
</tr>
<tr>
<td>LDH</td>
<td>Almost anything that results in cellular lysis or injury.</td>
<td>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.</td>
</tr>
</tbody>
</table>
Limitations

- No RCTs
- Few prospective studies
- No studies compared outcomes of patient management decisions based on marker assay results to those made without knowing marker levels or level changes over time or with treatment
- In many reports, little or no evidence was reported on primary outcomes specified in study protocol
- Variability across studies with respect to outcomes they reported (and how they reported the same or similar outcomes), precluded pooled data analyses
# Guideline Methodology:
## Expert Panel Members

<table>
<thead>
<tr>
<th>Panel Member</th>
<th>Institution</th>
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<tbody>
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<td>Taussig Cancer Institute; Cleveland Clinic</td>
</tr>
<tr>
<td>Daniel F. Hayes, MD, Co-chair</td>
<td>University of Michigan Comprehensive Cancer Center</td>
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<tr>
<td>Timothy Fancher, patient representative</td>
<td>Lockport, NY</td>
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<tr>
<td>Lawrence H. Einhorn, MD</td>
<td>Indiana Cancer Pavilion, Indiana University</td>
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<td>David C. Smith, MD</td>
<td>University of Michigan Comprehensive Cancer Center</td>
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<td>Andrew J. Stephenson, MD</td>
<td>Cleveland Clinic Foundation</td>
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<td>David J. Vaughn, MD</td>
<td>Abramson Cancer Center, University of Pennsylvania</td>
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<td>Ethan M. Basch, MD, ASCO Health Services Committee Liaison</td>
<td>Memorial Sloan Kettering Cancer Center</td>
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Clinical Tools & Resources

• The full text of the guideline, an abridged version of the guideline, an Executive Summary, this slide set, and additional clinical tools and resources can be found at: http://www.asco.org/guidelines/germcelltm.

• A patient guide, “What to Know” about this guideline, is available at: http://www.cancer.net/whattoknow
It is important to realize that many management questions have not been comprehensively addressed in randomized trials and guidelines cannot always account for individual variation among patients. A guideline is not intended to supplant physician judgment with respect to particular patients or special clinical situations and cannot be considered inclusive of all proper methods of care or exclusive of other treatments reasonably directed at obtaining the same results. Accordingly, ASCO considers adherence to this guideline to be voluntary, with the ultimate determination regarding its application to be made by the physician in light of each patient's individual circumstances. In addition, the guideline describes administration of therapies in clinical practice; it cannot be assumed to apply to interventions performed in the context of clinical trials, given that clinical studies are designed to test innovative and novel therapies in a disease and setting for which better therapy is needed. Because guideline development involves a review and synthesis of the latest literature, a practice guideline also serves to identify important questions for further research and those settings in which investigational therapy should be considered.