

Gestational Trophoblastic Diseases: 3. Human Chorionic Gonadotropin Free β -subunit a Reliable Marker of Placental Site Trophoblastic Tumors

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Abbreviated title: hCG free β -subunit in PSTT

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Objectives:

Placental site trophoblastic tumor (PSTT) commonly presents with low and variable concentration of hCG immunoreactivity in serum which can be difficult to differentiate from early stage choriocarcinoma/gestational trophoblastic neoplasm (GTN) or quiescent gestational trophoblastic disease (quiescent GTD). Non-trophoblastic malignancies such as germ cell tumors or other tumors secreting low hCG must also be considered in the differential diagnosis. Since treatments for these conditions are different, a means of differentiating PSTT from other diagnoses is important. We investigate the usefulness of hCG free β -subunit to make this discrimination.

Methods:

Data collected on cases referred to the USA hCG Reference Service for consultation served as a basis for this retrospective analysis. There were 13 cases with histology proven PSTT and 12 with non-trophoblastic malignancy. hCG free β -subunit was measured by immunoassay and reported as a proportion of total hCG (hCG free β -subunit(%)). hCG free β -subunit(%) results were determined for all histologically proven cases of PSTT and for the non-trophoblastic malignancies. Comparisons of hCG free β -subunit(%) were made and compared with those of the 82 choriocarcinoma/GTN cases and 69 quiescent GTD cases. The accuracy of hCG free β -subunit(%) to discriminate these malignancies was analyzed by investigating the areas under receiver-operating characteristics curve \pm standard error).

Results:

hCG free β -subunit(%) was the predominant hCG form in cases of PSTT (mean \pm standard deviation, $60 \pm 19\%$) and non-trophoblastic malignancies ($91 \pm 11\%$), thus discriminating these diagnoses from choriocarcinoma/GTN ($9.3 \pm 9.2\%$) and from quiescent GTD ($5.4 \pm 7.8\%$). The cut off of $>35\%$ free β -subunit is proposed. At this cut-off 100% detection at 0% false positive is achieved. The accuracy of hCG free β -subunit(%) for this discrimination is $100 \pm 0\%$. At a proposed cut-off of $>80\%$, the free β -subunit test will also distinguish PSTT from non-trophoblastic malignancy, with 77% detection at 23% false positive or an accuracy of $92 \pm 3.2\%$.

Conclusion:

Measurement of the proportion hCG free β -subunit(%) was found to be useful in the diagnosis of PSTT using proposed cut off values of $>35\%$ and $>80\%$. While this finding needs to be confirmed by larger studies, it would be reasonable to measure hCG free β -subunit(%) whenever the diagnosis of PSTT is considered.

INTRODUCTION

Placental site trophoblastic tumors (PSTT) usually presents with amenorrhea or irregular vaginal bleeding often remotely following a normal pregnancy, spontaneous abortion or occasional hydatidiform mole [1-3]. The interval between the occurrence of PSTT and the antecedent gestational event is unusually long compared with choriocarcinoma and other gestational trophoblastic neoplasms (GTN). The mean is 3.4 years, with a range of <2 to >5 years [1,4]. PSTT is generally associated with significantly lower hCG levels than choriocarcinoma (<200 mIU/ml), that fail to rise sharply over time [1]. Clinically, PSTT can readily be confused with quiescent gestational trophoblastic disease (GTD) or inactive choriocarcinoma [5]. Additionally, the accuracy of the initial pathologic diagnosis may be limited by the small amounts of tissue obtained by endometrial curettage. The definitive diagnosis may be difficult to achieve short of performing a hysterectomy. Although human placental lactogen (hPL) may be useful for diagnosing PSTT, the use is frequently limited to immunohistochemistry rather than to serum tumor marker measurements. Because of the difficulty of discriminating malignant PSTT clinically, from quiescent GTD and choriocarcinoma/GTN, a reliable marker for differentiating these conditions is needed. hCG free β -subunit measurements may fulfill this role.

Choriocarcinoma characteristically comprises hyperglycosylated hCG-producing mononuclear villous-origin cytotrophoblast cells with a variable content of regular hCG-producing multinucleated syncytiotrophoblast cells [1, 7-9]. PSTT, in contrast, is a malignancy of non-villous trophoblasts, a functionally separate, morphologically different tissue with dense eosinophilic cytoplasm [1]. Commonly, PSTT comprises mononucleated tissue with much necrosis [1]. While choriocarcinoma cells predominantly infiltrate through an intravascular mechanism, PSTT characteristically lacks this tendency for early and widespread vascular invasion. This makes PSTT different from the hyperglycosylated hCG-producing invasive cytotrophoblast described in the initial article in this series [9].

The hCG subunits produced in PSTT appear to be produced in insufficient concentrations to produce dimers, as governed by the law of mass action, thus leading to hCG free β -subunit production. This is indicated by the high proportions of β -core fragment detected in PSTT patient urine samples [10]. It is well established that hCG free β -subunit is also produced by some non-trophoblastic malignancies [11-14]. As such, any study

considering the clinical use of this test to detect PSTT would also need to consider non-trophoblastic malignancies in the differential diagnosis. With the aim of finding a specific tumor marker to differentiate PSTT from quiescent GTD and choriocarcinoma, we examined the proportions of hCG free β -subunit, hyperglycosylated hCG and total hCG in PSTT and in patients with non-trophoblastic malignancies referred to the USA hCG Reference Service.

METHODS

Patients

The USA hCG Reference Service Reference Service evaluates parallel serum and urine samples from women with unusual, idiopathic or questionable hCG results. All cases were those referred to the Reference Service at Yale University (n = 15) and the University of New Mexico (n = 292), USA, between January 1998 and June 2005, and were retrospectively reviewed. This article concentrates on 13 patients demonstrated by histology to have PSTT -

In 7 cases, the patients had an incidental pregnancy test. This was positive but no intra- or extra-uterine pregnancy was found. Although the patients had no physical or imaging evidence of disease, they were suspected of having GTN. They were referred to the Reference Service to find out whether the hCG was false positive or real and to determine the source of hCG. In all seven cases a predominance of hCG free β -subunit immunoreactivity was shown, and PSTT or non-trophoblastic malignancy was predicted. PSTT was subsequently confirmed by histology 2 to 8 weeks after the referral.

In 6 cases with a recent history of PSTT, persistent low levels of hCG immunoreactivity were found. These 4 cases were referred to examine the nature and find the source of the hCG. Real hCG free β -subunit immunoreactivity was detected, indicating the persistence of PSTT.

This report also describes 12 patients demonstrated by pathology to have a non-trophoblastic malignancy -

Five patients each had an incidental positive pregnancy test and intra- and extra-uterine pregnancy was excluded. They had no physical or imaging evidence of disease, and were suspected of having GTN. They were referred to the Reference Service to investigate the nature (false positive or real hCG) and deduce the source of hCG. Real hCG was shown together with a high proportion of hCG free β -subunit immunoreactivity, PSTT or non-trophoblastic malignancy was predicted. From feedback information from referring physicians, non-trophoblastic malignancy was demonstrated by histology, one week to 2 months after the referral. These 5 cases were one embryonal ovarian malignancy, 3 ovarian dysgerminomas and one parathyroid malignancy.

In 7 cases non-trophoblastic malignancies had been diagnosed previously. Patients were referred to the Reference Service to determine if hCG results was real or false positive.

In all cases real hCG immunoreactivity was demonstrated, mainly due to hCG free β -subunit immunoreactivity.

All PSTT and non-trophoblastic malignancy cases referred to the USA hCG Reference Service are included, with the exception of 10 additional cases for whom no follow-up information or firm diagnosis became available. In these cases Health Insurance Portability and Accountability (HIPAA) rules precluded us from obtaining outcome information.

For comparison in this study we have included the 82 cases with choriocarcinoma or GTN, and the 69 with quiescent gestational trophoblastic disease described in the second article in this series [5]. Evaluation of the databases of the Reference Service data, and examination of patient records were all approved by the University of New Mexico Human Research Review Committee (protocols 99-349 and 02-548).

The USA hCG Reference Service evaluates parallel serum and urine samples from women with unusual, idiopathic or questionable hCG results. In all cases, records are carefully evaluated, and hCG and hCG-related molecule tests are performed [5, 15-18]. These have always included our basic tests for total hCG (all forms of hCG-related molecule), a repeated total hCG test at multiple serum dilutions (to confirm results), a total hCG test after treatment with heterophilic antibody blocking agent (HBR, to consider false positive results). An hCG free β -subunit only test was performed, at multiple dilutions to confirm results [15-18]. Concentrations of hCG free β -subunit were converted into molar units (pmol/L) and the molar percentage of immunoreactivity due to hCG free β -subunit (pmol/L / pmol/L) was calculated. This percentage is called hCG free β -subunit(%). In addition, a hyperglycosylated hCG (hCG-H) test was performed. This was also repeated at multiple dilutions, where possible, to confirm results. The percentage of hCG-H in relation to total hCG (hCG-H(%)) was calculated as described in the preceding article [5]. Additional tests were performed as needed. These were an intact hCG only test, a nicked hCG only test, a nicked free β -subunit only test, and a β -subunit core fragment only test [17, 18]. This article is restricted to our basic tests, total hCG, hCG free β -subunit and hCG-H.

Laboratory Tests

All laboratory testing was performed in the Reference Service laboratories. This is certified by the Department of Health and Human Services for performing clinical tests for

patient records (CLIA certification 32D0972561). The consistency of the tests is monitored by the College of American Pathologists (CAP certification 7176750-01).

In all cases parallel serum and urine samples were received. The samples were shipped frozen and thawed and tested immediately upon arrival. All basic testing involved automated assays, using pre-formulated reagent packs. Serum total hCG was measured using the robotic chemiluminescence DPC Immulite hCG tests (DPC Inc., Los Angeles CA). This assay detects hCG, hCG-H and free β -subunit on an equal molar basis. When the concentration of pure hCG, hCG-H and free β -subunit were determined in molar units (nmol/L) by absorbance at 278 nm, near-identical results were observed (in mIU/ml) in the DPC Immulite hCG test (H-hCG result 99% and free β -subunit result 100% of hCG standard concentration) [2, 4, 7].

Serum samples were tested for H-hCG using the Nichols Institute Diagnostics robotic chemiluminescence hCG-H assay (Nichols Institute Diagnostics, San Clemente CA). This assay has <0.1% cross-reactivity with hCG [7]. This assay is calibrated in ng/ml using a choriocarcinoma hCG-H standard. As published, hCG-H mass values can be converted to hCG equivalents (in mIU/ml) by multiplying by 11 [2, 4, 7]. hCG-H(%) was calculated as the proportion of total hCG immunoreactivity due to hCG-H, or $\text{hCG-H} / \text{total hCG}$.

Serum hCG free β -subunit was measured using the robotic chemiluminescence DPC Immulite hCG tests (DPC Inc., Los Angeles CA). This assay is calibrated in ng/ml.

It should be noted, that while the total hCG, hCG-H, and hCG free β -subunit assay are all commercially available and are all FDA-approved tests, they are only approved for pregnancy applications. Gestational trophoblastic diseases can be considered as pregnancy or gestation-related applications but these cancer-related applications should be considered as "off-label" applications. We have carefully evaluated all 3 tests and demonstrated their particular suitability and accuracy, compared with other commercial hCG tests, for gestational trophoblastic disease applications [15-18].

Data Analysis

In June 2005 all accrued test results from 1998-2005, including dates, ages, diagnoses, antecedent gestation data, and pertinent treatment histories, were digitized by entry into Microsoft Excel 2003 spreadsheet (Microsoft Inc., Redmond WA). Basic mean, range and standard deviation statistics and t statistics were determined in the Excel 2003 spreadsheet. Data groups were ranked and non-parametric centiles were determined, and detection rates

were calculated at corresponding false positive rates. Receiver operating characteristics (ROC) curves were plotted and areas under ROC curves determined as an indicator of test accuracy, and their asymptotic standard errors calculated using AccuROC software, version 2.4 (Accumetric Corp., Montreal, QC).

RESULTS

In the serum from 13 cases with histologic proven PSTT, 4 new cases and 9 at different stages of primary therapy or recurrent disease, the major portion of the total hCG immunoreactivity was due to hCG free β -subunit: mean $60 \pm 19\%$, range 38 – 97% (Table 1). The levels of total hCG (hCG + hCG-H + hCG free β -subunit) were 3.3 - 263 mIU/ml (Table 1). Minimal or no hCG-H was detected (9 cases with no detectable hCG-H, and 4 cases with 5 - 37% hCG-H, mean \pm standard deviation $7.1 \pm 13\%$). Thus, PSTT cases are marked by a middling proportion of hCG immunoreactivity due to hCG free β -subunit.

In the serum from 12 cases with histologic proven non-trophoblastic malignancy, 5 new cases and 7 at different stages of therapy, the total hCG immunoreactivity was due to hCG free β -subunit: mean $91 \pm 11\%$, range 68 – 100% (Table 1). Variable amounts of total hCG were also detected, 2.9 - 474 mIU/ml. Therefore, the majority of non-trophoblastic neoplasm are associated with a high proportion of hCG immunoreactivity due to hCG free β -subunit.

The range of total hCG concentrations and proportions of hCG-H in quiescent GTD cases overlapped with those observed with PSTT and non-trophoblastic hCG malignancy cases (t test: $P > 0.05$, and $P > 0.05$, respectively).

We investigated the usefulness of hCG free β -subunit(%) to differentiate PSTT, non-trophoblastic malignancies, choriocarcinoma/GTN and quiescent GTD (Table 2). This test was $100 \pm 0\%$ accurate in differentiating PSTT from quiescent GTD, $99 \pm 1.7\%$ for PSTT from choriocarcinoma/GTN, $100 \pm 0\%$ for differentiating non-trophoblastic malignancy from quiescent GTD and choriocarcinoma/GTN, and $92 \pm 3.2\%$ accurate for differentiating PSTT and non-trophoblastic malignancy. The results indicate the use of a $>35\%$ hCG free β -subunit cut-off for differentiating PSTT and non-trophoblastic malignancy from quiescent GTD and from choriocarcinoma/GTN, and $>80\%$ hCG free β -subunit cut-off for separating PSTT and non-trophoblastic malignancy.

The usefulness of the free β -subunit(%) test was demonstrated by the Reference Service experience with 12 patients (Table 1), with an uncertain diagnosis. In all 12 cases, non-trophoblastic neoplasm or PSTT was predicted correctly by the finding of predominantly hCG free β -subunit. In all 12 cases, non-trophoblastic neoplasm (5 patients) and PSTT (7 patients) were later confirmed by histology.

DISCUSSION

The finding presented here indicate that hCG free β -subunit(%) determination can be used to definitively differentiate a non-trophoblastic malignancy from a choriocarcinoma/GTN diagnosis, in a patient with a history of pregnancy, hydatidiform mole or choriocarcinoma/GTN. hCG free β -subunit(%) can also point to a non-trophoblastic malignancy in patients presenting with persistent low levels of hCG. hCG free β -subunit(%) can accurately discriminate a PSTT compared with a choriocarcinoma/GTN, and PSTT compared with quiescent GTD in a patient presenting with persistent low levels of hCG or with symptoms that suspect GTD. With less absolute certainty, hCG free β -subunit(%) can also differentiate a PSTT from a non-trophoblastic malignancy. This retrospective analysis was based on stratifying the laboratory values based on the "gold standard" histologic confirmation of PSTT and non-trophoblastic malignancies within the 7-year experience of the Reference Service. It is of note that in 12 of 12 cases, the predicted histologies by the Reference Service from hCG free β -subunit data, were subsequently confirmed to be correct. Most of the data indicated an absolute $100 \pm 0\%$ discrimination. We use the term indicate, however, because of the relatively small number of cases (n=25) analyzed in this study. We invite larger confirmatory studies to confirm these findings.

The optimal use of hCG free β -subunit is as hCG free β -subunit(%), or that expressed as a molar percentage of total hCG [15-18]. Using a cut-off of >35% an absolute (based on n=25) discrimination was made between PSTT plus non-trophoblastic malignancies and other GTD-related diagnoses (choriocarcinoma/GTN and quiescent GTD). Using an alternative cut-off of >80% the discrimination of a non-trophoblastic malignancy from a PSTT can be achieved but with less certainty.

The primary purpose of this study was to identify a reliable means of diagnosing a PSTT other than definitive histology, compared with a choriocarcinoma/GTN, or a quiescent GTD in a patient presenting with persistent low levels of hCG, or symptoms of GTD. Treatment (hysterectomy, chemotherapy or expectant management) decisions are dependent on an accurate diagnosis [1, 4] When endometrial curettage suggests the diagnosis of PSTT in a patient desirous of future fertility, the patient and clinician are confronted by difficult and poignant choices. Hitherto hysterectomy with histology has been recommended as the only means of making a definitive diagnosis. There is pressing need to be able to establish

appropriate diagnosis without sterilizing surgery. Based on the present data, hCG free β -subunit(%) may reliably fill this role. Some non-trophoblastic malignancies, however, also produce hCG free β -subunit [11-14]. Not-surprisingly, production of hCG free β -subunit is also present in a proportion of gonadal and germ cell malignancies [12, 13], which may present with nodules in the uterus like GTN. As such, it is important to exclude non-trophoblastic neoplasms in patients with a history of pregnancy or hydatidiform mole, or among those presenting with persistent low levels of hCG. In our prospective experience with 12 cases suspected of GTN, one with history of hydatidiform mole, PSTT was confirmed by pathology in 7 cases. Ovarian germ cell malignancies were identified in 4 cases (3 dysgerminoma and 1 embryonal malignancy), and one had a parathyroid malignancy. Based upon this experience, it may be as likely to find a germ cell tumor as the origin of the elevated free β -subunit as to find a PSTT.

We conclude that hCG free β -subunit(%) discriminates PSTT and non-trophoblastic malignancies from other GTN possibilities, with extreme sensitivity. The statistical analysis also supports the use of hCG free β -subunit(%) to differentiate PSTT from non-trophoblastic malignancy. Overall, hCG free β -subunit(%) accurately differentiates PSTT from all other GTN and from non-trophoblastic malignancy option. These studies, however, are limited to 25 cases. While larger studies are needed to confirm these results, it is reasonable for clinicians to start evaluating free β -subunit(%) measurements whenever PSTT is considered.

Table 1. Summary of cases with PSTT and non-trophoblastic neoplasms. All cases are those referred to the USA hCG Reference Service, no case was excluded. All cases are those having previously diagnosed disease or those predicted to have disease by the Reference Service and confirmed by histology shortly after referral. Approximately half of the cases were referred to the Reference Service to confirm the nature of the hCG, real vs. false positive, among other investigative alternative. For comparison, we summarize data from cases with quiescent gestational trophoblastic disease (quiescent GTD). These are the 69 cases described in Table 2 of the companion paper [4]; details not repeated. These are also 82 cases with pathology proven choriocarcinoma or GTN described in Table 1 of the companion paper [4]; details not repeated. hCG results, hCG free β (%) and hyperglycosylated hCG (%) are presented, together with the reason for the referral.

	hCG mIU/ml	hCG free β (%)	hCG-H(%)	Reason for referral
1. Cases having histology proven non-trophoblastic malignancy, n=12				
1	119	81%	4%	Myeloma shown, confirm real hCG
2	474	68%	2%	Pancreatic cancer shown, confirm real hCG
3	165	88%	0%	Endometrial Cancer shown, confirm real hCG
4	41	100%	0%	Karposi's sarcoma shown, confirm real hCG
5	8.7	78%	0%	Dysgerminoma shown, confirm real hCG
6	26	100%	0%	Ovarian embryonal shown, confirm real hCG
7	40	100%	0%	Ovarian serous shown, confirm real hCG
8	14	87%	0%	NED, quiescent or false positive hCG or GTD? ^a
9	160	100%	0%	NED, quiescent or false positive hCG or GTD? ^a
10	8.0	100%	0%	NED, quiescent or false positive hCG or GTD? ^a
11	2.9	100%	0%	NED, quiescent or false positive hCG or GTD? ^a
12	4.2	88%	0%	NED, quiescent or false positive hCG or GTD? ^a
Mean \pm SD	95 \pm 140 ^{c,d}	91 \pm 11% ^{c,d}	0.55 \pm 1.3% ^{c,d}	
Range	2.9 – 474	68 – 100%	0 – 4%	
2. Cases having histology proven PSTT, n=13				
13	28	69%	16%	NED, quiescent or false positive hCG or GTD? ^b
14	8.5	47%	34%	NED, quiescent or false positive hCG or GTD? ^b
15	231	38%	37%	NED, quiescent or false positive hCG or GTD? ^b
16	35	50%	0%	NED, quiescent or false positive hCG or GTD? ^b
17	12.8	68%	0%	NED, quiescent or false positive hCG or GTD? ^b
18	94	48%	0%	NED, quiescent or false positive hCG or GTD? ^b
19	13	62%	0%	NED, persistent mole suspected ^b
20	0.77	46%	0%	PSTT history, active disease?
21	3.3	39%	0%	PSTT history, active disease?
22	236	82%	0%	PSTT previously shown, confirm real hCG
23	25	90%	0%	PSTT previously shown, confirm real hCG
24	138	97%	5%	PSTT previously shown, confirm real hCG
25	31	52%	0%	PSTT previously shown, confirm real hCG
Mean \pm SD	65 \pm 84 ^{e,f}	60 \pm 19% ^{e,f,g}	7.1 \pm 13% ^{e,f}	
Range	3.3 – 236	38 – 97%	0 – 37%	
3. Cases with choriocarcinoma/GTN, n=82 [4]				
Mean \pm SD	13380 \pm 30747	9.3 \pm 9.2%	54 \pm 41%	
Range	5.9 – 144627	0 - 35%	2.0 - 100%	
4. Cases with quiescent GTD, n=69 [4]				
Mean \pm SD	54 \pm 103	5.4 \pm 7.8%	0.47% \pm 2.1%	
Range	0.5 - 144	0 - 30%	0 - 12%	

- ^a Non-trophoblastic malignancy or PSTT predicted by presence of significant hCG free β -subunit (%) by USA hCG Reference Service. Feed-back confirmed non-trophoblastic malignancy by histology, one week to 2 months after the referral. In cases 8-12, a new parathyroid malignancy, new embryonal ovarian malignancy, and 3 new dysgerminoma cases identified, respectively.
- ^b Non-trophoblastic malignancy or PSTT predicted by presence of significant hCG free β (%) by USA hCG Reference Service. Feed-back confirmed PSTT by histology following hysterectomy or hysteroscopy within 2 weeks to 2 months after the referral (cases 13-19).
- ^c In a t test, non-trophoblastic malignancy compared with choriocarcinoma/GTN, no significance observed with hCG ($P>0.05$), significant difference observed with hCG free β subunit(%) and hyperglycosylated hCG ($P<0.00000001$, $P<000000001$).
- ^d In a t test, non-trophoblastic malignancy compared with quiescent GTD, no significance observed with hCG or hyperglycosylated hCG ($P>0.05$ and $P>0.05$), significant difference observed with nhCG free β subunit(%) ($P<0.00000001$).
- ^e In a t test, PSTT compared to choriocarcinoma/GTN, no significant difference observed with hCG ($P>0.05$), significant difference observed with hCG free β -subunit(%) and hCG-H (%) ($P<0.00000001$, $P<0.00000001$).
- ^f In a t test, PSTT compared with quiescent GTD, no significance observed with hCG or hyperglycosylated hCG ($P>0.05$ and $P>0.05$), significant difference observed with hCG free β subunit(%) ($P<0.00000001$).
- ^g In a t test, PSTT compared with non-trophoblastic malignancy, no significance observed with hCG or hyperglycosylated hCG ($P>0.05$ and $P>0.05$), significant difference observed with hCG free β subunit (%) ($P=0.000008$).

Table 2. Usefulness for an hCG free β -subunit(%) test. We examined the test at 2 arbitrary cut-off values, >35% and >80%. With each a detection rate is given at a corresponding false positive rate. We also investigated the utility of the test independent of an arbitrary cut-off by receiver operating characteristic (ROC) analysis. This analysis plots infinite cut-off points and their detection rates against the corresponding false positive rate. The area under the ROC curve (AU-ROC) is a direct measure of test accuracy. AU-ROC curve \pm standard error (SE) results are presented.

Test comparison	AU-ROC	Cut off >35%	Cut off >80%
PSTT vs. quiescent GTD	100 \pm 0%	100% @ 0%	
PSTT vs. choriocarcinoma/GTN	99 \pm 1.7%	100% @ 0%	
Non-trophoblastic malignancy vs. quiescent GTD	100 \pm 0%.	100% @ 0%	
Non-trophoblastic malignancy vs. choriocarcinoma/GTN	100 \pm 0%	100% @ 0%	
PSTT vs. non-trophoblastic malignancy	92 \pm 3.2%		77% @ 23%

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PRECIS

A test for hCG free β -subunit is shown to differentiate placental site trophoblastic tumor from other gestational trophoblastic neoplasms