PCR Reagents for Detection of (CAG)$_n$ Repeats in Huntington Disease

To the Editor:
Recently Muglia et al. [1] reported in your journal a nonisotopic detection of (CAG)$_n$ repeats in the Huntington disease (HD) gene. We have read this article with great interest, as we use a similar method for the detection of the above [2, 3].

There are many difficulties in the PCR conditions of examining CAG repeats in the HD gene and in the detection of PCR products on nondenaturating polyacrylamide gel by silver staining. As yet there is no standardized protocol for the detection of CAG repeats in the HD gene. Muglia et al. [1] reported factors that affect the utility of the PCR product from the HD region by using the known HD-1 and HD-3 primers [4]. They used a relatively high MgCl$_2$ concentration (2.0 mmol/L) without dimethyl sulfoxide in 35 cycles. When they applied >35 PCR cycles, they obtained high background of nonspecific bands. We do not see these bands in our method with the lowest possible MgCl$_2$ concentration (0.625 mmol/L), dimethyl sulfoxide (120 g/L) [3] instead of formamide, and 36 cycles.

Figure 1 demonstrates four patients’ results obtained by use of 8% nondenaturating polyacrylamide gel stained by the silver staining method [5] applied by Muglia et al. We found that the amount of mispriming and other nonspecific products mainly depends on the origin of Taq polymerase and other conditions, such as the number of PCR cycles and the use of enhancer components. The latter were investigated by Muglia et al., but the origin of Taq polymerase was not indicated in the article. We found that AmpliTaq (Perkin-Elmer, Norwalk, CT) and Taq polymerase from Promega (Madison, WI) gave sharper bands and less background than some others.

References

Authors of the article referred to reply:

To the Editor:
Töth et al. report a method of detection of (CAG)$_n$ repeats causing Huntington disease. They suggest some technical variations to our procedure. The major differences are the use of a lower MgCl$_2$ concentration (0.625 mmol/L) and the use of dimethyl sulfoxide (DMSO) (12%) instead of formamide. Before deciding to use formamide, we tried performing PCR with DMSO as reported in the published article. However, we achieved the optimum results by using formamide (35 mmol/L). This difference in results may be attributed to the fact that we did not attempt to decrease the MgCl$_2$ concentration while using DMSO. It is possible that the use of DMSO together with a lower concentration of MgCl$_2$ yields similar results to those obtained when using formamide and a MgCl$_2$ concentration of 2 mmol/L.

With respect to the Taq polymerase, we used Taq polymerase from Promega with the incubation buffer specified in our article.

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An Urgent Use for Hemoglobin A$_{1c}$?

To the Editor:
The deciding factor in whether to measure an analyte in the emergency out-of-hours period is whether the result will affect the immediate clinical management. Hemoglobin (Hb) A$_{1c}$ is not included in the list of tests.
usually provided [1, 2], but the unforeseen may occur.

A transplant team was informed that kidneys and pancreas were available in another hospital from a 14-year-old girl who had suffered a cardiac arrest after a grand mal seizure. She had become hypernatremic and was infused with a 50 g/L dextrose solution. The surgeon was informed that the plasma glucose was 21 mmol/L and the question arose whether the hyperglycemia reflected undiagnosed diabetes mellitus. A Hb A1c done on call immediately was 7.1%, indicating a very high probability that the patient had diabetes [3]. Normal oral glucose tolerance was found in only 4% of subjects with a Hb A1c value of at least 7% in a metaanalysis [4]. The pancreas was thus unsuitable, but the heart, liver, and kidneys were successfully transplanted. Decisions regarding the suitability of organs for transplantation must be made quickly. Hb A1c was the appropriate choice in that context.

**Rapid, Highly Sensitive Immunoassay for Determination of Cardiac Troponin I in Patients with Myocardial Cell Damage**

To the Editor:
The aim of this study was to validate a new automated cardiac troponin I (cTnl) assay developed by Sanofi Diagnostic Pasteur (Marnes la Coquette, France) on the Access immunoassay system from the same manufacturer, and to evaluate its diagnostic sensitivity for early detection of myocardial damage. The assay is a two-site sandwich, immunochromeluminometric ELISA using two monoclonal antibodies that recognize different epitopes unique to the human cTnl isoform [1]. Pipetting, incubations, measurements, and data-reduction steps are performed on the Access analyzer, which produces the first test result in 20 min. The minimum detectable cTnl concentration, assessed by 10 replicate measurements in a single run of the zero calibrator serum supplied with the kit and defined as the cTnl value corresponding to the signal 3 SD greater than the mean found for this calibrator, was estimated as 0.01 μg/L. The assay measured cTnl in serum and EDTA-anticoagulated plasma in the same way: Fresh specimens collected at the same time from subjects (n = 24) with an increased concentration of cTnl gave similar results for serum and EDTA-plasma (0.49 ± 0.78 vs 0.46 ± 0.74 μg/L, respectively; P = 0.48). Assay reproducibility was tested by assaying three control materials (from Sanofi) containing human cTnl at 0.28, 6.6, and 25.4 μg/L plus two samples of pooled fresh serum (0.07 and 0.30 μg/L, respectively). Within-run CVs (n = 30) were between 3.8% and 12.5%, and between-run CVs (n = 10) ranged between 4.3% and 15.7%. Correlation studies were conducted with two alternative techniques for cTnl: Sanofi Diagnostics Pasteur ELISA manual assay and Opus immunomasssay (Behring Diagnostics, Westwood, MA), performed according to the manufacturers’ current protocols [2, 3]. Linear regression equations were as follows: Access = 1.43 Pasteur – 0.08 μg/L (S_{xy} = 0.19, r = 0.948, n = 44), and Access = 0.09 Opus + 0.05 μg/L (S_{xy} = 0.48, r = 0.952, n = 81). In particular, the Opus assay led to ~10-fold higher values than the two Sanofi assays.

We used the Access assay to measure concentrations of cTnl in sera from subjects in five groups: (a) 105 apparently healthy people, ages 22–84 years; (b) 44 patients with a typical history of myocardial infarction (MI) of <8 h duration; (c) 8 patients with severe muscular damage [total creatine kinase (CK) values 10 240 to 29 000 U/L] but no apparent cardiac injury; (d) 20 consecutive dialysis patients with no evidence of myocardial injury; and (e) 22 patients with unstable angina (diagnosis based on typical electrocardiogram changes during episodes of chest pain together with coronary arteriography, performed within 72 h of admission). Procedures followed were in accordance with the Helsinki Declaration of 1975, as revised in 1983.

We found that cTnl concentrations in 99% of the apparently healthy subjects were ≤0.03 μg/L and in 88% were ≤0.01 μg/L, the detection limit of the assay as defined above and determined with the zero calibrator. The highest value for cTnl in these samples was 0.063 μg/L. To evaluate the diagnostic sensitivity of the Access cTnl in the early phase of MI, we analyzed a single peripheral venous blood sample obtained in our MI patients immediately after admission to the hospital before any revascularization treatment, e.g., thrombolysis (median time after the onset of chest pain, 210 min; range, 30–450 min). For comparison, we also measured myoglobin and CK-MB mass. All three assays were performed on a single Access analyzer at the same time. The cutoff values were as follows: myoglobin, 60 μg/L; CK-MB, 5.0 μg/L; and cTnl, 0.03 μg/L. In this population, the Access cTnl showed the same diagnostic sensitivity (29 positive of 44 MI patients, 66%) as myoglobin (28 of 44, 64%), the classical early cardiac marker, whereas the sensitivity of CK-MB mass deter-

**References**


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Table 1. Clinical and angiographic data for 22 patients with unstable angina, according to relation to Access cTnI cutoff value.

<table>
<thead>
<tr>
<th></th>
<th>cTnI &lt;0.03 µg/L (n = 15)</th>
<th>cTnI &gt;0.03 µg/L (n = 7)</th>
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<td>Age, years</td>
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<td>56 ± 13</td>
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<td>6/1</td>
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<td>Angiographic findings:</td>
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<tr>
<td>Multivessel disease</td>
<td>7</td>
<td>4</td>
</tr>
<tr>
<td>Mean luminal stenosis, %</td>
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<td>85 ± 12</td>
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<td>Lesion morphology:*</td>
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<tr>
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<td>1</td>
</tr>
<tr>
<td>Type B1 lesions, no.</td>
<td>8</td>
<td>6</td>
</tr>
<tr>
<td>Type B2 lesions, no.</td>
<td>4</td>
<td>7</td>
</tr>
</tbody>
</table>

Data presented are mean value ± SD or number of patients, unless otherwise indicated.

* As defined by the American College of Cardiology/American Heart Association Task Force [4].

Prostate-Specific Antigen is Not Increased in Young Men by Ultraendurance Sport Performances

To the Editor:

Oremek and Sieffert [1] suggested that extensive physical activity increases prostate-specific antigen (PSA) concentrations. They demonstrated the increase after a standardized exercise on a cycloergometer for 15 min at 75–100 W in many healthy men with different ages.

We performed PSA measurements during various sport performances to establish if strenuous exercise increases the serum PSA in young men.

We measured PSA on 30 men with a mean age of 27 years (range 18–45) participating in ultraendurance performances of different sports. Twelve men participated in the Płiné 24-h, an ultraendurance nonstop 24-h speed ice skating competition (February 1994, Italy); three in the Pavia–Venetia, an ultraendurance water ski race of 450 km (April 1995, Italy); 10 in the Fila Sky Marathon, a marathon performed at an altitude of 4300 m (October 1995, Himalaya, People’s Republic of China); and five in the Millegrobbe, a 3-day cross-country ski competition of ~100 km (January 1995, Italy).

Blood was drawn immediately before and immediately after the performances in plain Vacutainer Tubes (Becton Dickinson, Franklin Lakes, NJ) and centrifuged on the field; the serum was stored at −20 °C until analysis and in liquid nitrogen during travel for the Tibetan mountain

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Ciba Corning ACS:180 Direct Total Testosterone Assay Can Be Used on Female Sera

To the Editor:
We were intrigued by the article by Fitzgerald and Herold [1], which compared the fully automated, nonisotopic, direct (i.e., no serum purification step performed before analysis) assay of total testosterone used in the Ciba Corning Diagnostics ACS:180 instrument (Chiron Diagnostics, Medfield, MA) with a chemical ionization GC-MS method and with a manual, coated-tube, direct RIA [Coat-A-Count; Diagnostic Products Corp. (DPC), Los Angeles, CA]. The advantages of an accurate, fully automated, nonisotopic testosterone method over a manual RIA, with or without a purification step, are obvious.

The authors observed excellent correlation ($r = 0.99$) between testosterone values obtained with the ACS:180 vs GC-MS of male sera [1]. However, the poor correlation ($r = 0.56$) between testosterone values obtained with the ACS:180 vs GC-MS of female sera, prompted them to suggest “that Fuqua’s recommendation of a purification step before immunoassay analysis should be extended to include all female specimens, since ACS and DPC immunoassays did not agree with GC-MS” [1].

In women, measurement of the serum testosterone concentration is useful in evaluating hirsutism, alopecia, and menstrual disorders. With assays by the ACS:180 method/instrument, hirsute women have been shown to have testosterone concentrations 0.7–1.4 times the upper limit (2.5 nmol/L) of the reference interval [2].

We obtained good agreement between testosterone values quantified with the ACS:180 vs the DPC method (DPC testosterone = 0.974ACS + 0.357; $r = 0.969$; n = 35) used routinely in our laboratory. Because of the advantages of the fully automated ACS:180 system, we changed to this method. The recommendation by Fuqua, endorsed by Fitzgerald and Herold [1], however, prompted us to report ACS testosterone values on male sera and to send female sera to a referral laboratory (Corning Nichols, San Juan Capistrano, CA) for total testosterone analysis with an extraction-chromatography RIA. The referral laboratory method is a manual, second-antibody RIA method, used after the serum has been extracted with an ethyl acetate/hexane mixture and fractionated by chromatography on a Celite column.

We compared the total testosterone values obtained with the ACS:180 for 38 female serum specimens against those reported by the referral laboratory for aliquots of the same sera sent frozen by overnight delivery. The correlation between these

References
1. Oremek GM, Seiffert UB. Physical activity releases prostate-specific antigen (PSA) from the prostate gland into blood and increases serum

marathon and at –20 °C in Italy until analysis [2, 3]. PSA was immunofluorometrically quantified on the AIA1200 (Tosoh, Tokyo, Japan). The possible modification of the analyte concentration owing to hemococoncentration was controlled by always measuring hematocrit and serum osmolality. We did not observe statistically significant differences between pre- (mean 1.1 μg/L, range 0.4–2.7) and postexercise (1.2 μg/L, 0.4–2.9) PSA values. The endurance performances did not modify the marker concentrations or other endocrinological or hematological variables [3–5] in these professional and amateur athletes in orthostatism in different kinds of effort (resistive in water skiing, aerobic in the marathon, etc.) under various environmental conditions (cold temperature for ice skating, rough terrain for the marathon, etc.). We also performed PSA measurements on a group of 12 elite cyclists. The athletes (mean age 22 years) performed an incremental exercise on the cycloergometer for 24 min starting from 50 W, with increments of 50 W every 3 min until exhaustion. We recruited cyclists for study, as the characteristic position on the bicycle and the possible perineal stimulation from the bicycle seat can release PSA in to circulation, as hypothesized for extremely high values in a patient with adenocarcinoma [6].

We did not observe significant variations due to cycloergometer exercise (means pre- and postexercise 1.8 μg/L).

Our results are consistent with previous studies demonstrating that stressful exercise in nontrained individuals had no effect on serum PSA [7], and bicycle riding for 250 miles did not increase PSA [8].

We examined young men because of a particular kind of strenuous sport performed; it is probable that exercise-induced potential increases in PSA might be greater in older individuals, as reported in ref. 1.

letters
methods was excellent [\( r = 0.966 \); slope = 1.150 (95% confidence interval: 1.05–1.25); intercept = -0.047 (95% confidence interval: -2.00 to 1.91)] (Fig. 1, top) over a wide testosterone concentration range (0.5–50 nmol/L). Moreover, in the clinically important testosterone range for females, 0.5–3.5 nmol/L (Fig. 1, bottom), the average difference (0.031 nmol/L; range: -0.59 to 1.07) between ACS:180 and extraction-chromatography RIA testosterone values was neither statistically (\( P > 0.05 \)) by paired t-test, \( n = 18 \)) nor clinically significant. However, the extraction-chromatography RIA gave testosterone results \( \sim 15\% \) higher than the ACS:180 assay for most of our female sera, an effect that was most pronounced in samples containing testosterone \( > 10.4 \) nmol/L (Fig. 1, top). Two of our specimens gave values (38.3 and 41.6 nmol/L) with the extraction-chromatography RIA that were \( \sim 50\% \) higher than the results (24.8 and 27.6 nmol/L, respectively) of the ACS:180 direct assay (Fig. 1, top).

Interestingly, both Jockenhövel et al. [2] and Wheeler et al. [3] have confirmed the good performance characteristics of the ACS:180 testosterone assay, reported previously by Fitzgerald and Herold [1]. Wheeler et al. [3], however, observed that the ACS:180 assay gave testosterone results greater than an extraction assay for some female sera, and one of their specimens gave an ACS:180 value approximately double the result obtained with their extraction RIA. The differences between their results and ours may be the higher recovery of testosterone and specificity of the extraction (ethyl acetate/hexane)-chromatography RIA assay vs an extraction (ethyl acetate) RIA without a column chromatography purification step, especially in serum samples containing a high concentration of testosterone. In any event, the differences between testosterone values obtained with the ACS:180 direct assay and the extraction-chromatography RIA were not clinically significant.

Moreover, the manufacturers’ reference intervals for total testosterone concentration in female sera were similar between the ACS:180 (0.48–2.63 nmol/L) direct assay and the extraction-chromatography RIA (0.52–2.43 nmol/L). We believe that the ACS:180 total testosterone assay is a clinically useful assay in evaluating testosterone concentration in both female and male sera, thus obviating the need to perform a separate assay on most female sera with either an extraction or an extraction-chromatography RIA.

![Graph](image)

Fig. 1. Comparison of ACS (x) and extraction-chromatography RIA (y) testosterone assays (top) for all female sera \( n = 38 \); \( y = 1.150x - 0.047, r = 0.966 \); and (bottom) for female sera with testosterone concentrations in the clinically important range, 0.5–3.5 nmol/L \( n = 18 \); \( y = 0.943x + 0.087, r = 0.906 \).

References

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The authors of the report referred to reply:

To the Editor:
The letter by Wians and Stuart points out the need for a reference method for the analysis of testosterone. In our original manuscript we reported that the ACS:180 testosterone assay compared very favorably with GC-MS for specimens from men but not women [1]. The difference between the two methods seemed to be gender-specific because both methods agreed for male specimens at low concentrations (e.g., those with concentrations in the reference range for women). Our results also agree with the only other published comparison of the ACS and GC-MS, which concluded that “at female concentrations of testosterone, results by the ACS:180 and extraction methods were significantly higher than GC-MS results (\( P < 0.01 \))” [2].

A pitfall in Wians and Stuarts’ study is the use of one immunoassay to validate another. Immunoassays are based on antibodies’ recognizing and binding to an epitope. Numerous examples in the literature demonstrate that different antibodies have similar cross-reactivities with structurally related compounds. A classic example is immunoassays designed to detect the presence of amphetamines [3]. Virtually all amphetamine immunoassays share some cross-reactivity with other structurally related sympathomimetic compounds such as psuedoephedrine, phenylpropanolamine, and 3,4-methylenedioxymethamphetamine. This shared cross-reactivity has led to the generally accepted laboratory practice that immunoassay drug screens are confirmed by “a second independent chemical technique” because of the potentially adverse consequences of a positive finding. In urine drug testing,
immunoassays do not suffice for qualitative identification, much less quantitative measurement.

We are not suggesting that every test performed by an immunoassay be confirmed by a second independent technique. Clearly this is not needed or required in most clinical situations. Our point is that, whenever possible, all clinical assays should be validated by an independent technique before they are put into widespread use; this was the main focus of our original manuscript.

We compared the same extraction-chromatography RIA assay (Quest Diagnostics, San Juan Capistrano, CA) referenced by Wians and Stuart with our negative chemical ionization (NCI) GC-MS method for female specimens. As shown in Fig. 1R, there was no statistically significant correlation between our GC-MS method and that used by the Quest Diagnostics (slope not significantly different from 0). Over the time period in which these samples were collected (2 months), our serum-based quality-control specimen (target value 0.72 nmol/L) averaged 0.75 nmol/L with a CV of 10% (n = 9), demonstrating the accuracy and precision of the GC-MS method at low concentrations. The lack of correlation between our GC-MS method and the extraction-chromatography RIA is of concern and we are working with Quest Diagnostics to resolve the discrepancy.

The challenge faced by any immunoassay for the analysis of female serum specimens is a difficult one. The sample matrix is complex and known to contain many compounds structurally related to testosterone. The data presented by Wians and Stuart show that the ACS:180 compares reasonably well with that of an extraction-chromatography RIA. However, agreement does not equal accuracy. Discrepancies between various methods will persist until a nationally or internationally recognized reference method for the analysis of testosterone is validated. We are actively pursuing such a method, using isotope-dilution NCI GC-MS.

References

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Oxaprozin and 5-(p-Hydroxyphenyl)-5-phenylhydantoin Interference in Phenytoin Immunoassays

To the Editor:

Rainey et al. [1] recently published their studies on metabolite and matrix interference in Abbott TDx® Phenytoin (TDx) and Phenytoin-II (TDxII) assays (Abbott Labs., Abbott Park, IL). They report that TDx Phenytoin, which uses a polyclonal antibody, demonstrates a substantial positive bias in patients with renal insufficiency because of the assay’s high (15.9%) cross-reactivity to the major metabolites of phenytoin, 5-(p-hydroxyphenyl)-5-phenylhydantoin (HPPH) and its glucuronide ester (HPPG) [1]. They also report that the TDxII assay, which uses a monoclonal antibody, has high (~50%) cross-reactivity to a nonsteroidal anti-inflammatory drug, oxaprozin (Daypro®) [1].

During a recent study, a patient taking oxaprozin demonstrated discrepancy between phenytoin values by the TDxII, which gave the result in the toxic range, and that by Chiron Diagnostics’ (Walpole, MA) new monoclonal assay, ACS:180® Phenytoin, for which the result was in the therapeutic range (GM Lawson, Mayo Clinic, personal communication).

To confirm the effects of oxaprozin in the TDx, TDxII, and ACS:180 Phenytoin assays, I studied the specificity of all three assays to oxaprozin and HPPH. Stock solutions of HPPH (Sigma Chemical Co., St. Louis, MO) and oxaprozin (Searle, Skokie, IL) in methanol were added to two separate serum pools, one containing phenytoin (pool B) and the other without phenytoin (pool A), and the apparent phenytoin concentrations were measured by all three assays according to the manufacturers’ directions. The TDx assays were run on the TDxFix® analyzer, which uses homogeneous fluorescence polarization signals. The ACS:180 Phenytoin assay was run on the fully automated, random-access ACS:180® chemiluminescent system [3].

The concentrations of the added cross-reacting compound and the observed phenytoin concentrations are presented in Table 1. All three assays
have comparable range (up to 40 mg/L) and detection limits (<1 mg/L). The ACS:180 assay agreed well with both TDx and TDxII assays, demonstrating linear regression slopes of 1.02 and 0.94, intercepts of -1.46 and -0.19 mg/L, and correlation coefficients of 0.96 and 0.96, respectively, for 100 samples from patients taking phenytoin.

These results for oxaprozin cross-reactivity in TDxII agree with Rainey et al. (≈50%) [1] when oxaprozin is added to a phenytoin-free pool at 200 mg/L. At higher oxaprozin concentrations, however, the cross-reactivity is much higher (99% and 131% at 300 and 400 mg/L). Such cross-reactivity would result in seriously increased TDxII assay results in samples containing oxaprozin at 300–400 mg/L. Although typical oxaprozin concentrations range from 98 to 230 mg/L [1], there is a good likelihood of encountering patients with oxaprozin concentrations of 300–400 mg/L. Our data also suggest that cross-reactivity increases when phenytoin is present in the sample. The respective apparent phenytoin concentrations are 101 and 121 mg/L in pools containing 0 or 9 mg/L of phenytoin when supplemented with 200 mg/L of oxaprozin. The TDx Phenytoin assay shows much lower cross-reactivity to oxaprozin (0.2–0.5%, depending on the concentrations of oxaprozin added) and is constant whether phenytoin is present in the sample or not. The ACS:180 assay shows no cross-reactivity to oxaprozin.

The data for HPPH cross-reactivity in the two TDx assays also agree with those of Rainey et al. Again, the cross-reactivity does not depend on the presence or absence of phenytoin (8.3% vs 6.8% in the TDx, and 9.2% vs 11.1% in the TDxII assay). The ACS:180 assay has insignificant (<1%) cross-reactivity to HPPH. No HPPG was available for comparing cross-reactivity to this compound in the assays described here.

In summary, the ACS:180 Phenytoin assay does not cross-react with HPPH or oxaprozin. Results of the ACS:180 Phenytoin assay were therefore superior to those of both TDx Phenytoin assays in samples containing HPPH and oxaprozin.

**References**


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