

Medical Evaluation of a Case with Confirmed Positive hCG Test

(Appendix to the WADA Guidelines for Reporting and Management of urinary hCG and LH findings in male athletes)

A confirmed positive urine hCG test in a male Athlete should lead to investigation of a non-doping cause before confirming an Anti-Doping Rule Violation for hCG doping. (Note: hCG is not prohibited in female Athletes).

Testing for hCG

hCG is a heterodimeric glycoprotein comprised of two subunits, α (hCG α) and β (hCG β). hCG occurs in urine in different molecular forms, including the intact and nicked α/β heterodimers as well as the dissociated α - and β -subunits and their degradation products (e.g. the β -core fragments, nicked products, etc.).

Both hCG, its subunits and their fragments may be detected in urine by hCG immunoassays with wide specificity ("total hCG" assays). Anti-doping tests, however, aim to detect only the hCG- α/β heterodimer (*i.e.* by applying so-called "intact hCG" assays, which in addition to the intact α/β heterodimer may also detect the "nicked" α/β heterodimer). Among a variety of available commercial hCG immunoassays, only some have been validated for this purpose.

The heterodimeric hCG is either undetectable or found at very low levels (usually below 2 IU/L) in urine from healthy males. However, heterodimeric hCG may be produced by testicular cancers or extra-testicular germ cell tumors. If such tumors can be excluded, the otherwise unexplained presence of elevated levels of heterodimeric hCG in serum or urine is evidence for pharmacological administration of hCG.

A positive urine "intact hCG" test result (> 5 IU/l) in an athlete may be due to an undiagnosed testicular tumor containing trophoblastic elements that synthesize hCG. Rarely, ectopic hCG secretion can arise from extra-testicular germ cell tumors, typically located in the midline of the mediastinum, retro-peritoneum or pineal gland. These extra- testicular tumors have a significantly worse prognosis than testicular germ cell tumors.

Medical Evaluation

Following an AAF for hCG test, the first step is to promptly exclude a pathological cause by a medical assessment. The importance of this should be communicated to the athlete who should subsequently be reviewed by a doctor, ideally a urologist or an endocrinologist.

The medical assessment of a potential pathological cause of a positive hCG test must include:

1. History (including cryptorchidism, family history);
2. Physical examination (including testes palpation, testis volume, gynecomastia);
3. Laboratory investigations - serum hCG (intact), alpha fetoprotein (AFP), LDH as tumor marker and serum LH, FSH, testosterone, SHBG (to detect hCG bioactivity);
4. Imaging
 - a. Ultrasound of testes (hypoechoic lesions, microlithiasis)
 - b. If serum hCG (intact) assay remains positive AND there is no palpably enlarged testis or presumptive tumor identified by ultrasound, imaging to exclude an extra-testicular germ cell tumor is indicated by CT scan (alternatively MRI or PET scan) of chest, abdomen and brain.

A palpably enlarged testis requires referral to an urologist or oncologist for further evaluations and treatment of a presumed testis tumor.

If serum hCG (intact) remains elevated and no testis or extra-testicular tumor is identified in the original investigation, the athlete should have clinical follow-up with the same serum hCG (intact) immunoassay, including repeat testis ultrasound (to examine for any new or changed hypoechoic testicular lesions) at 3 months. As some of these tumors may be slow growing, follow-up to exclude a testis tumor may need to be prolonged (up to 2 years).

Although the investigation for testicular tumors/cancers should be pursued without delay, further anti-doping testing during the period of investigation is often required to clarify the situation.

See Section 9 - Results Management of the *Guidelines for Reporting and Management of hCG & LH Findings* for further information about follow-up testing and initiating results management.