

WADA Technical Document – TD2019IRMS

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Written by:	WADA Laboratory Expert Group	Approved by:	WADA Executive Committee
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Detection of Synthetic Forms of Endogenous Anabolic Androgenic Steroids by GC/C/IRMS

1.0 Introduction

This Technical Document describes the Analytical Method to detect the presence of synthetic forms of Endogenous Anabolic Androgenic Steroids (EAAS) by Gas Chromatography / Combustion / Isotope Ratio Mass Spectrometry (GC/C/IRMS) in urine *Samples*.

Consideration is also given to boldenone, boldenone *Metabolite(s)* and formestane ¹, which may be found naturally in urine *Samples* at low concentrations.

19-Norandrosterone (19-NA) and 19-noretiocholanolone (19-NE) are considered in a separate Technical Document, TD19NA [1], and the technical recommendations and requirements described herein shall not be applied to their analysis.

1.1 Application of GC/C/IRMS

1.1.1 GC/C/IRMS analysis as a Confirmation Procedure for the exogenous administration of EAAS

GC/C/IRMS analysis shall be conducted as a Confirmation Procedure when the Laboratory receives an “*Atypical Passport Finding (ATPF) Confirmation Procedure Request (ATPF-CPR)*” or a “*Suspicious Steroid Profile (SSP) Confirmation Procedure Request (SSP-CPR)*” notification through *ADAMS*, as described in the Technical Document on the Measurement and Reporting of EAAS (TDEAAS) [2].

In addition, even if the *Markers* of the “steroid profile” are within the normal ranges, the Testing Authority, the Athlete Passport Management Unit (APMU), or *WADA* may request GC/C/IRMS analysis to be performed on any urine *Sample*.

¹ Formestane (4-hydroxyandrost-4-en-3,17-dione) is an aromatase inhibitor but its structure is similar to EAAS and it may also be found naturally in urine *Samples*; therefore, it requires an Analytical Testing approach similar to that described in the TDEAAS [2].

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Furthermore, the Laboratory may at any time advise ² the Testing Authority to perform (or not) the GC/C/IRMS analysis based upon its expertise, for example in the presence of any other *Marker(s)* of administration of EAAS such as 6 α -hydroxy-androstenedione, 3 α ,5-cyclo-5 α -androstan-6 β -ol-17-one, 6 β -hydroxy-androsterone or 6 β -hydroxy-epiandrosterone (sulfates), or an altered ratio of 7 β -hydroxy-dehydroepiandrosterone to 16 α -hydroxy-androsterone (sulfates).

1.1.2 GC/C/IRMS analysis for formestane, boldenone or boldenone *Metabolite(s)*

In *Samples* containing formestane, boldenone or boldenone *Metabolite(s)*, the GC/C/IRMS analysis for these compounds shall be conducted before reporting an *Adverse Analytical Finding* when their estimated specific gravity (SG)-adjusted³ concentrations are determined as follows:

- Concentration of formestane between 50 ng/mL and 150 ng/mL.

[Findings for formestane below 50 ng/mL (SG-adjusted ³, if needed) should be reported as a Negative Finding, unless the result of the GC/C/IRMS analysis, if performed (depending on Laboratory's analytical capacity and following consultation with the Testing Authority), conclusively establishes the exogenous origin of the substance (*Adverse Analytical Finding*).

Findings for formestane above 150 ng/mL (SG-adjusted ³, if needed) shall be reported as *Adverse Analytical Findings*].

² Or as covered by agreement between the Laboratory and the Testing Authority.

³ When the measured SG of the urine *Sample* (SG_{Sample}) is greater than 1.018, the concentrations (free and hydrolyzed glucuroconjugated steroids) shall be adjusted according to the formula:

$$\text{Conc}_{\text{adj}} = \frac{(1.020 - 1)}{SG_{\text{Sample_Max}} - 1} \cdot \text{Conc}_{\text{measured}}$$

[Refer to the effective TD DL for instructions on calculating $SG_{\text{Sample_Max}}$].

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- Concentration of boldenone and/or its *Metabolite(s)* between 5 ng/mL and 30 ng/mL.

[Findings for boldenone and/or its *Metabolite(s)* at concentrations estimated below 5 ng/mL (SG-adjusted³, if needed) should be reported as *Atypical Findings*, unless the results of the GC/C/IRMS analysis, if performed (depending on Laboratory's analytical capacity and following consultation with the Testing Authority), conclusively establish the exogenous origin of the substance (*Adverse Analytical Finding*).

Findings for boldenone and/or its *Metabolite(s)* above 30 ng/mL should be reported as *Adverse Analytical Findings* without the need for GC/C/IRMS analysis, unless it is determined that the *Sample* is substantially degraded due to a high level of microbial contamination (in which case the *Sample* shall be reported as an *Atypical Finding*).

Laboratories that do not have the analytical capacity to perform GC/C/IRMS analysis for formestane, boldenone or its *Metabolite(s)* shall have the *Sample* analyzed by another Laboratory that has such analytical capability.

1.1.3 "B" Sample Confirmation Procedure

When an Adverse Analytical Finding is reported based on the results of a GC/C/IRMS analysis performed on the "A" *Sample*, only the GC/C/IRMS analysis shall be repeated during the "B" Sample Confirmation Procedure, if applicable.

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2.0 GC/C/IRMS analysis

The application of GC/C/IRMS is based on the following:

- The determination of the $\delta^{13}\text{C}$ value of the Target Compound(s) (TCs), *i.e.* the *Marker(s)* of the urinary “steroid profile” [*e.g.* androsterone (A), etiocholanolone (Etio), 5α -androstane- $3\alpha,17\beta$ -diol (5α Adiol), 5β -androstane- $3\alpha,17\beta$ -diol (5β Adiol), testosterone (T), epitestosterone (E)], as well as other target Analytes (*e.g.* boldenone, boldenone *Metabolite(s)*, formestane);
- The determination of the $\delta^{13}\text{C}$ value of the Endogenous Reference Compound(s) (ERC), *e.g.* pregnanediol (PD), 5α -androst-16-en- 3α -ol (16-en), 11β -hydroxyandrosterone (11-OH-A), 11-keto-etiocholanolone (11-oxo-Etio); and
- The calculation of the difference in $\delta^{13}\text{C}$ values, *i.e.* the $\Delta\delta^{13}\text{C}$ value, between the ERC(s) and the TC(s):

$$(1) \quad \Delta\delta^{13}\text{C} = \delta^{13}\text{C}_{\text{ERC}} - \delta^{13}\text{C}_{\text{TC}}$$

The GC/C/IRMS analysis shall be conducted on a single *Sample Aliquot*.

2.1 GC/C/IRMS Method Characteristics

Laboratories shall implement the following into the GC/C/IRMS methodology:

- The system shall be calibrated periodically against a steroid Certified Reference Material (CRM) [*e.g.* CU/USADA-33, CU/USADA-34, or other mixture of certified steroid(s) ⁴] that is traceable to the assigned values of the recognized international Reference Material (RM). Major revisions of the system (*e.g.* change of reference gas, cleaning of the ion source) shall require calibration of the system;
- As part of the method validation, the Laboratory shall determine:
 - the linearity of the ion source using CO₂ pulses of different peak heights/intensities;

⁴ The use of a mixture of certified steroids covering the range of $\delta^{13}\text{C}$ values normally found for TCs and ERCs in urine (*e.g.* -17 ‰ to -34 ‰) is recommended.

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- the linearity of the instrument by the injection of different amounts of RM(s) of underivatized or acetylated, as appropriate, steroid standards [TC(s) and ERC(s)]. The instrumental linearity is defined as the range of intensities (expressed in mV or nA, as appropriate) and/or as amounts (ng) of injected steroids that give a consistent $\delta^{13}\text{C}$ value (within 0.5 ‰ of the mean $\delta^{13}\text{C}$ value, determined within 6 to 10 different peak heights/intensities);
- the linearity of the Analytical Method, *i.e.* the range of TC and ERC concentrations in urine (ng/mL) producing consistent $\delta^{13}\text{C}$ values within the signal linearity range of the instrument;
- the Limit of Quantification (LOQ) for each TC and ERC as the lowest concentration in urine (ng/mL) which produces a measurable signal in the linear range of the instrument with a standard deviation (SD) < 1.0 ‰, $n \geq 3$;
- the estimated combined standard Measurement Uncertainty (u_c) for the determination of the $\delta^{13}\text{C}$ values of each TC -and ERC. In each case, the u_c shall be not greater than 1.0 ‰ (u_{c_Max});
- the $\Delta\delta^{13}\text{C}$ values for each ERC-TC pair (including, at least, A, Etio, 5 α Adiol, 5 β Adiol and T as TCs and using at least two ERCs, one of which shall be PD) analyzed in volunteer urine samples and/or *Athlete negative Samples* (a minimum of 20 male and 20 female urine samples), covering the range of steroid concentrations usually found in *Doping Control Samples*⁵. The analysis of these negative urine samples shall serve to evaluate Analytical Method performance by the Laboratory and shall meet the following criteria:
 - the mean $\Delta\delta^{13}\text{C} + 2\text{SD}$ value for ERC-TC combinations containing A, T or the Adiolis as TCs shall be ≤ 3 ‰;
 - the mean $\Delta\delta^{13}\text{C} + 2\text{SD}$ value for ERC-TC combinations containing Etio or E as TCs shall be ≤ 4 ‰; and

⁵ The requirement to have measurements from a minimum of 20 urine reference samples from females does not apply to T and E determinations. However, a minimum total number of 40 reference determinations is required.

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- for each ERC-TC combination, the SD of all $\Delta\delta^{13}\text{C}$ values shall be ≤ 1.2 ‰.
- The stability of CO₂ pulses shall be tested before the analysis of each batch of *Samples*. The linearity of the signal shall be checked regularly, e.g. monthly;
- The urinary TC(s) and ERC(s) once hydrolyzed shall be further purified by High Performance Liquid Chromatography (HPLC) (recommended), Solid Phase Extraction (SPE) or other equivalent purification step prior to the GC/C/IRMS analysis;
- A negative (NQC) ⁶ and a positive (PQC) urine quality control sample containing all relevant TC(s) and ERC(s) shall be included in each batch of *Samples* analyzed and subjected to the same *Sample* preparation procedure (including hydrolysis of glucuronide conjugates and Analyte derivatization, if applicable). The relevant TC(s) shall meet the positivity criteria in the PQC. The consistency of the $\delta^{13}\text{C}$ determinations of the NQC and PQC shall be monitored through the use of QC-charts;
- An appropriate RM of the relevant free (unconjugated) steroids, underivatized or acetylated TC(s) and ERC(s), as appropriate, with traceable $\delta^{13}\text{C}$ value(s), shall be injected prior to the analysis of each batch of *Samples*. It is recommended that this RM is also injected at the end of each sequence (e.g. after 25-30 injections);
- Laboratories shall be capable of performing GC/C/IRMS analyses on A, Etio, T, 5 α Adiol and 5 β Adiol. When the concentration is sufficient, the TC(s) should be selected/prioritized depending on the *Marker(s)* of the “steroid profile” that prompted the GC/C/IRMS analysis:
 - T, 5 α Adiol and/or 5 β Adiol are the preferred TC(s) to detect the administration of T;
 - Laboratories shall perform GC/C/IRMS analyses on E on those *Samples* in which the concentration of E is abnormally high, i.e. if > 200 ng/mL in males or > 50 ng/mL in females (SG-adjusted³, if needed).

⁶ This does not apply to GC/C/IRMS determinations for formestane, boldenone or boldenone *Metabolite(s)*.

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- The analysis should be based on the use of PD as the principal ERC (if measurable in the *Sample*, *i.e.* if the signal is not suppressed, affected by poor chromatography or by the administration of a precursor, *e.g.* pregnenolone). However, another ERC, either 16-en, 11-OH-A or 11-oxo-Etio, should also be routinely used to replace PD when not measurable in the *Sample*. The same ERC shall be used for the determination of all the $\Delta\delta^{13}\text{C}$ values.
- No value obtained from any peaks of intensity below or above the range of linearity or in the presence of significant co-eluting peaks shall be considered or reported;
- The steroids may be analyzed underivatized or after acetylation, but only values equivalent to underivatized compounds shall be used to determine the $\Delta\delta^{13}\text{C}$ value of the ERC-TC pair. The following mass balance equation for adjustment of the measured $\delta^{13}\text{C}$ values from acetates back to the free form shall be used:

$$(2) \quad \delta^{13}\text{C}_s = (n_{cd} \cdot \delta^{13}\text{C}_{cd} - n_d \cdot \delta^{13}\text{C}_{d_corr}) / n_s$$

where n: number of carbon atoms; s: native steroid (underivatized form); d: derivative group (*e.g.* acetyl), and cd: derivatized compound.

As δ_{cd} is not known, δ_{cd_corr} is estimated empirically by consecutive measurements of a non-acetylated and acetylated steroid (*e.g.* 16-en or 5 α -androstanol).

2.2 Identification of urinary *Metabolites* prior to reporting an *Adverse Analytical Finding*

A GC-MS analysis is required to ensure the identity of the peaks of the relevant TC(s) and ERC(s) and the absence of significant interference prior to reporting an *Adverse Analytical Finding* or an *Atypical Finding* based on GC/C/IRMS results. This is not necessary when the GC/C/IRMS results are negative.

The same mixtures shall be analyzed by GC-MSⁿ under similar chromatographic conditions. Minor differences in retention times (RT) between the two techniques are expected. The provisions of the Technical Document on Identification Criteria (TDIDCR) shall be followed [3]. In addition, a full scan spectrum shall be obtained over the complete width of the steroid chromatographic peak(s) of interest to document the lack of interference.

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2.3 Interpretation of GC/C/IRMS results

The results of the GC/C/IRMS analyses shall be interpreted as follows:

2.3.1 Positive

When $\Delta\delta^{13}\text{C}$ value(s) are consistent with the exogenous origin of the TC(s), *i.e.* if one of the following sets of criteria is fulfilled ^{7, 8} (**Appendix 1**):

- i. The $\Delta\delta^{13}\text{C}$ value of the ERC-T pair and of one of the ERC-5 α Adiol or ERC-5 β Adiol pairs are both > 3 ‰;
- ii. The $\Delta\delta^{13}\text{C}$ values of the ERC-5 α Adiol and ERC-5 β Adiol pairs are both > 3 ‰;
- iii. The concentration of E is > 50 ng/mL in females or > 200 ng/mL in males (SG-adjusted, if needed³) and the $\Delta\delta^{13}\text{C}$ value of the ERC-E pair is > 4 ‰;
- iv. The $\Delta\delta^{13}\text{C}$ value of the ERC-A pair is > 3 ‰ or the $\Delta\delta^{13}\text{C}$ value of the ERC-Etio pair is > 4 ‰;
- v. The $\Delta\delta^{13}\text{C}$ value of the ERC-A pair is between 2 ‰ - 3 ‰ or the $\Delta\delta^{13}\text{C}$ value of the ERC-Etio pair is between 3 ‰ - 4 ‰, and the $\Delta\delta^{13}\text{C}$ value of one of the ERC-5 α Adiol or ERC-5 β Adiol pairs is > 3 ‰;
- vi. The $\Delta\delta^{13}\text{C}$ value of the ERC-5 α Adiol pair is > 4 ‰ and the $\delta^{13}\text{C}$ value of 5 α Adiol is ≤ -27 ‰ (*e.g.* DHT administration);
- vii. The $\Delta\delta^{13}\text{C}$ value of either the ERC-formestane, ERC-boldenone or ERC-boldenone *Metabolite(s)* pairs is greater than 4 ‰.

⁷ It is not expected that all TCs will be affected to the same extent. Decisions based on the $\Delta\delta^{13}\text{C}$ criteria specified in 2.3.1 i) to vii) and Appendix 1 take into account the Measurement Uncertainty associated with the contributing $\delta^{13}\text{C}$ values.

⁸ The Laboratory shall consider all analytical evidence (*e.g.* concentrations of “steroid profile” *Markers*, $\Delta\delta^{13}\text{C}$ values of other ERC-TC combinations, including the use of additional ERC(s) if necessary) in order to properly assess whether there is significant data or information that would cast doubt on or refute the reporting of the finding as an *Adverse Analytical Finding* or *Atypical Finding*.

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2.3.2 Negative

When $\Delta\delta^{13}\text{C}$ values do not confirm the exogenous origin of the TC(s), *i.e.* when the $\Delta\delta^{13}\text{C}$ values of the ERC-TC pairs do not meet any of the criteria specified in section 2.3.1 above.

2.3.3 Inconclusive

- viii. When only one of the combined criteria specified in points i), ii), v) or vi) above is met (*e.g.* the $\Delta\delta^{13}\text{C}$ value for the ERC-T pair is $> 3 \text{ ‰}$ but the $\Delta\delta^{13}\text{C}$ values for the ERC-Adiol pairs are both $< 3 \text{ ‰}$) ⁸;
- ix. Due to technical limitations, *e.g.* when there is insufficient *Sample* volume or very low concentrations of TC(s) or ERC(s), or in the presence of interfering compounds or any other factor preventing a reliable measurement of the relevant diagnostic *Metabolite* or ERC-TC pair ⁹;
- x. The Laboratory may interpret the results as inconclusive when the criteria for reporting an *Adverse Analytical Finding* are not met but, in its opinion, are neither consistent with the endogenous origin of the urinary *Metabolites* (*e.g.* ERC $\delta^{13}\text{C}$ value at -24.5 ‰ and TC at -27.0 ‰).

⁹ Technical limitations in the analysis of specific ERC-TC pair(s) should not necessarily invalidate the reporting of an *Adverse Analytical Finding* based on the reliable measurement of other ERC-TC pair(s) in the *Sample* and consideration of all available analytical evidence for interpretation of results.

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3.0 Reporting GC/C/IRMS Results

The Laboratory shall report the results of the GC/C/IRMS analyses in *ADAMS* as follows:

3.1 Adverse Analytical Finding

Samples for which the results of the GC/C/IRMS analysis were positive:

- Each *Sample* for which an *Adverse Analytical Finding* is reported shall be reported individually;
- The Test Report shall include:
 - The $\delta^{13}\text{C}$ value of all TC(s) and ERC(s) measured, and each associated u_c (expressed in ‰) ¹⁰;
 - A comment indicating that the GC/C/IRMS finding is consistent with the exogenous administration of steroids specifying the identity of the relevant TC(s) that produced a positive GC/C/IRMS finding.

[Example for comment on *Adverse Analytical Finding* in the Test Report:

GC/C/IRMS results are consistent with the exogenous origin of T and 5 β Adiol].

3.1.1 Provision of a Second Opinion for GC/C/IRMS

When the results of the GC/C/IRMS analysis indicate an *Adverse Analytical Finding* for a *Sample*, the Laboratory should seek the opinion, in writing, of an expert from a second Laboratory before reporting the *Adverse Analytical Finding*. If obtained, the second opinion shall be recorded in the Laboratory Documentation Package.

¹⁰ The Laboratory does not have to report the $\Delta\delta^{13}\text{C}$ values, which are automatically calculated in *ADAMS* based on the corresponding $\delta^{13}\text{C}$ values of TCs and ERCs.

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3.2 *Atypical Finding*

Samples for which the results of the GC/C/IRMS analysis were inconclusive:

- Each *Sample* for which an *Atypical Finding* is reported shall be reported individually.
- The Test Report shall include:
 - The $\delta^{13}\text{C}$ value of all TC(s) and ERC(s) measured, and each associated u_c (expressed in ‰) **10**;
 - A comment indicating that the GC/C/IRMS finding is inconclusive specifying the identity of each relevant TC that produced an inconclusive GC/C/IRMS finding.

[Example for comment on *Atypical Finding* in the Test Report:

The results of the GC/C/IRMS analyses for T and the Adioms are inconclusive].

3.3 Negative Finding

Samples for which the results of the GC/C/IRMS analysis were negative:

- Each *Sample* shall be reported individually.
- The Test Report shall include:
 - The $\delta^{13}\text{C}$ value of all TC(s) and ERC(s) measured, and each associated u_c (expressed in ‰) **10**;
 - A comment that the GC/C/IRMS results do not indicate an exogenous administration of steroids.

[Example for comment on Negative Finding in the Test Report:

GC/C/IRMS results do not confirm the exogenous origin of steroids].

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4.0 Interpretation

- The GC/C/IRMS and GC-MSⁿ confirmation methods provide independent and complementary information, but their results must be considered together to arrive at a conclusion that is supported by the scientific literature and knowledge;
- The urinary “steroid profile” may show no major anomaly whilst being excreted following the administration of an EAAS; in such a case, the results of the GC/C/IRMS analysis indicating a synthetic origin of the steroid *Marker(s)* shall prevail;
- Conversely, values for *Marker(s)* of the “steroid profile” may be outside the subject-based longitudinal reference range while still being of endogenous origin (e.g. heavy ethanol drinking leading to an increased urinary excretion of T and 5 β Adiol, microbial formation of free T, or intense, prolonged exercise increasing the excretion of A);
- The “steroid profile” may be altered by the administration of a synthetic preparation of a steroid related to testosterone having a relatively enriched $\delta^{13}\text{C}$ value, which therefore may not be detected by GC/C/IRMS. In such cases, the provisions of the Technical Document on Results Management Requirements for the *Athlete Biological Passport* (TD RMR) shall be followed [4].

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5.0 References

1. WADA Technical Document TD19NA (current version): Harmonization of Analysis and Reporting of 19-Norsteroids related to Nandrolone.

[https://www.wada-ama.org/en/resources/search?f\[0\]=field_resource_collections%3A30](https://www.wada-ama.org/en/resources/search?f[0]=field_resource_collections%3A30)

2. WADA Technical Document TDEAAS (current version): Endogenous Anabolic Androgenous Steroids: Measurement and Reporting.

[https://www.wada-ama.org/en/resources/search?f\[0\]=field_resource_collections%3A30](https://www.wada-ama.org/en/resources/search?f[0]=field_resource_collections%3A30)

3. WADA Technical Document TDIDCR (current version): Minimum Criteria for Chromatographic-Mass Spectrometric Confirmation of the Identity of Analytes for Doping Control Purposes.

[https://www.wada-ama.org/en/resources/search?f\[0\]=field_resource_collections%3A30](https://www.wada-ama.org/en/resources/search?f[0]=field_resource_collections%3A30)

4. WADA Technical Document TDRMR (current version): Results Management Requirements for the *Athlete Biological Passport*. Annex L to the International Standard for Testing and Investigations (ISTI).

<https://www.wada-ama.org/en/resources/world-anti-doping-program/international-standard-for-testing-and-investigations-isti-0>

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Appendix 1. Interpretation criteria for GC/C/IRMS positive test

Positive Criteria Section 2.3.1	$\Delta\delta^{13}\text{C}_{\text{ERC-TC}}$					Formestane, Boldenone, Boldenone <i>Metabolites</i>
	T	E [#]	A	Etio	5 α Adiol, 5 β Adiol	
i.	> 3 ‰				> 3 ‰ (either Adiol)	
ii.					> 3 ‰ (both Adioms)	
iii.		> 4 ‰				
iv.			> 3 ‰			
				> 4 ‰		
v.			2-3 ‰		> 3 ‰ (either Adiol)	
				3-4 ‰	> 3 ‰ (either Adiol)	
vi.					$\Delta\delta(\text{ERC-5}\alpha) > 4 ‰$ and $\delta^{13}\text{C}(5\alpha) \leq -27 ‰$	
vii.						> 4 ‰

Concentration (SG-adjusted, if needed³) > 50 ng/mL in females or > 200 ng/mL in males.