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Testosterone Testing Protocol

Effective Date: September 19, 2018
Revised Date: October 27, 2022

Scope

This protocol reviews the appropriate use of serum testosterone testing in men and women aged ≥ 19 years. This document is intended to direct primary care practitioners and to help constrain inappropriate test utilization, particularly as it pertains to "wellness" and "anti-aging" practices. This protocol expands on the guidance provided in the associated BC Guidelines.ca: *Hormone Testing – Indications and Appropriate Use*.

Testosterone testing for paediatric and transgender patients is out of scope of this protocol. For information and guidance on testosterone testing for transgender people, refer to *Gender-affirming Care for Trans, Two-Spirit, and Gender Diverse Patients in BC: A Primary Care Toolkit*, produced by Trans Care BC at the Provincial Health Services Authority.

Key Recommendations

Symptom Assessment

- Current evidence suggests low testosterone can be a consequence rather than a cause of aging or poor health.
- The decision to test must be guided by medical history and clinical examination.
- Testosterone deficiency in men usually presents with a constellation of symptoms.

Timing and Frequency

- In untreated men, serum total testosterone must be collected in the morning, preferably before 10:00AM, or within three hours of waking up, and preferably in a fasting state.
- Men receiving stable androgen replacement can be tested annually. See *Monitoring Response to Treatment* for appropriate timing.
- Healthy adult males will experience fluctuations in testosterone levels due to biologic variation (10-15%) meaning that two successive measurements on the same individual are expected to differ by up to, but typically not more than, 30%. There is no need to run a follow-up test if a result within the 20 – 30% range would not impact choice of treatment.

Unsupported Indications

- Testing for testosterone deficiency is not recommended in asymptomatic men or women.
- Erectile dysfunction in isolation is not an indication for testosterone testing.
- Testosterone testing is not useful for the investigation of low libido in women.

Tests

In British Columbia the testosterone tests available are:

- serum total testosterone, and
- calculated bioavailable testosterone (cBAT), which includes the sex hormone binding globulin test (SHBG)

MSP Cost of Tests[1]	
Serum Total Testosterone	$15.81
cBAT (includes SHBG)	$29.37

Current to April 1st, 2022.

Circulating testosterone exists in three forms: free, weakly bound to albumin, and strongly bound to SHBG. **Serum total testosterone** measures all three forms. Bioavailable testosterone is the sum of free testosterone and albumin-bound testosterone. In BC, all bioavailable and free testosterone results are calculated rather than directly measured. **Calculated bioavailable testosterone (cBAT)** and **calculated free testosterone** are derived from the same calculation, which utilizes both the measured total testosterone and measured SHBG concentrations. Although the two parameters may be reported separately, cBAT and calculated free testosterone are functionally and diagnostically equivalent (and therefore redundant) – as such, only cBAT will be referenced in the remainder of the guideline. Reference ranges for serum total testosterone and cBAT are method and age dependent and are determined by each laboratory independently.

Patients should use the same laboratory for initial and follow-up testosterone tests because reference ranges are laboratory-dependent,[2] meaning that results from different laboratories may not be comparable. For more information about the different forms of testosterone in plasma and their measurement, refer to BCGuidelines.ca – *Hormone Testing Guideline Appendix A: Testosterone Testing and Measurement in BC*.

Testosterone Deficiency in Men

Routine biochemical screening for testosterone deficiency (hypogonadism) in asymptomatic men is not recommended. A decision to test must be guided by the medical history and clinical examination. In the case of isolated, or non-specific symptoms only, a comprehensive general assessment is required to exclude potential alternative explanations[3] and to guide further investigations.

When an untreated male patient is investigated for hypogonadism and is incidentally discovered to have a high total testosterone, hypogonadism is ruled out. Incidental discovery of a modest elevation total testosterone in the context of an investigation for hypogonadism does not necessarily warrant investigation.

In the case of follow up of a previously ordered, relatively low, testosterone measurement in a minimally symptomatic man, refer to *Appendix A: Differential Diagnosis of Hypogonadism in Men* and *Appendix B: Medications that May Alter Testosterone Levels in Men and Women* for conditions and medications associated with changes in testosterone concentration.

Signs and Symptoms of Testosterone Deficiency in Men

Late onset hypogonadism (LOH), defined as hypogonadal symptoms in a male over 65 years of age, with associated serum testosterone concentrations less than 6-8 nanomoles (nmol) per litre[10], and the symptoms identified in *Table 1: Symptoms and signs of testosterone deficiency in men, in order of specificity*, below.

LOH is frequently associated with obesity and type 2 diabetes mellitus (T2DM).[3] The long-term outcome of treating the hypogonadal symptoms associated with this condition are uncertain, and there are unclear cardiovascular safety concerns. However, addressing the underlying conditions (obesity and T2DM) associated with LOH through significant weight loss (10% of total body weight or greater)[11] will increase the serum testosterone concentration, improve the hypogonadal symptoms, and benefit the long-term cardiovascular outcomes and cognitive function in this patient. Therefore, treatment of the causes of the late onset hypogonadism (which offers the opportunity to improve morbidity and mortality) should be prioritized over the biochemical recognition, and symptomatic treatment, of the hypogonadism itself.[3]

There are many non-specific somatic and psychological symptoms associated with hypogonadism (refer to the "Supportive" and "Not specific" columns in *Table 1: Symptoms and signs of testosterone deficiency in men, in order of specificity*, below). Any one of these findings in isolation, including erectile dysfunction[4], is insufficient grounds to order a testosterone test.

Table 1: Symptoms and signs of testosterone deficiency in men, in order of specificity[5,6]

Specific to testosterone deficiency	Supportive of testosterone deficiency	Not specific to testosterone deficiency
• Loss of body hair (axillary, facial, pubic) • Very small testes (<6 mL)	• Breast discomfort, gynecomastia • Eunuchoidal body proportions • Infertility, low sperm count • Height loss, low-trauma fracture, low bone mineral density • Hot flushes, sweats • Pervasive decrease in sexual desire (libido) and activity • Erectile dysfunction • Decreased frequency of morning erections or spontaneous erections	• Fatigue or decreased energy • Depression or depressed mood • Poor concentration and memory • Sleep disturbance, increased sleepiness • Anemia • Decreased muscle bulk and strength • Increased body fat, body mass index (BMI)

Adapted from Bhasin 2010[6] and Bhasin 2018[5]

Testing for Testosterone Deficiency in Men

Serum total testosterone is the initial test of choice. Specimens must be collected in the morning,[8] preferably before 10:00 AM, or within three hours of waking up, and preferably in a fasting state[5,9]. Testing should occur when the sleep-wake pattern is stable (e.g., not during shift changes or jetlag). Testing of serum total testosterone should be performed when patients are clinically well; do not test during acute illness or hospitalization.

If the total testosterone level is below the lower limit of normal (approximately 8 nmol/L in younger men [<30 years], and 6 nmol/L in older men [> 50 years)[10,12,13], ***and a diagnostic question remains***, cBAT (which includes SHBG) can be used to confirm or rule out hypogonadism. Total testosterone is determined in large part by the carrier protein SHBG, the latter of which can vary markedly between individuals.[10] That is, low SHBG can cause low testosterone, and this situation can be clarified with cBAT. See *Table 2: Conditions associated with alterations in SHBG concentrations in men and women*, for a list of conditions that may impact SHBG.

Table 2: Conditions associated with alterations in SHBG concentrations in men and women[5,6]

Decreased SHBG concentrations	Increased SHBG concentrations
• Diabetes mellitus[α] • Obesity[α] • Nephrotic syndrome[α] • Use of glucocorticoids, some progestins, and androgenic steroids[α] • Hypothyroidism • Acromegaly	• Aging[α] • Cirrhosis and hepatitis[α] • Use of some anticonvulsants[α] • Use of estrogens • HIV infection • Hyperthyroidism • Congenital
[α] **Particularly common conditions associated with alterations in SHBG levels**	

Note that testosterone is characterized by variable secretion. Healthy adult males will experience fluctuations in testosterone levels due to biologic variation (10-15%) meaning that two successive measurements on the same individual are expected to differ by up to, but typically not more than, 30%.

Diagnosis in Men

In BC it has been observed that men frequently receive prescriptions for testosterone replacement without first having a serum testosterone test to confirm low levels.[15] This practice is not appropriate, as biochemical confirmation of a low for age serum total testosterone (or cBAT) is necessary to confirm the clinical impression of hypogonadism. In the absence of this biochemical confirmation, a re-visitation or verification of the original empiric diagnosis will be very difficult since prolonged androgen therapy will result in suppression of the hypothalamic pituitary gonadal axis for as long as 18 months.

While specific investigation is beyond the scope of this protocol, it is important to establish the etiology of hypogonadism, *after* biochemical confirmation of the clinical diagnosis, and *before* initiating testosterone replacement. Refer to *Appendix A: Differential Diagnosis of Hypogonadism in Men* and *Appendix C: Hypogonadism Investigation Algorithm* for guidance on initial investigation and testing.

Prior to initiating testosterone replacement, the following baseline tests are recommended: hematocrit, prostate-specific antigen (PSA), and digital rectal exam (DRE).[7] Other contraindications to testosterone replacement should be considered. These are discussed in detail elsewhere.[5,7]

Occasionally the cause of hypogonadism is congenital/pituitary/hypothalamic in nature and if there are pre-existing risk factors (e.g., cranial irradiation, hemochromatosis), referral to endocrinology is recommended. Refer to *Appendix C: Hypogonadism Investigation Algorithm* for more information.

Consider referral if uncertain. Indications for referral to specialists are outlined in *Table 3: Indications for consideration of referral to an endocrinologist, urologist, or obstetrician/gynaecologist as appropriate* below.

Monitoring of Testosterone-Replacement Treatment in Men

Monitor men receiving androgen replacement by repeating the hematocrit, PSA test, and DRE at three and six months after initiation, then annually if stable.[7] Some recommend that PSA testing after one year is not necessarily obligatory.[5] Men receiving stable androgen replacement can be tested with serum total testosterone testing annually.[5,7]

Blood collection timing by route of administration:[5]

- **Injectable testosterone enanthate or cypionate:** measure testosterone *either* midway between injections *or* at trough
- **Transdermal gels/Intranasal:** measure 2-8 hours after application
- **Transdermal patches:** 3-12 hours after application
- **Oral testosterone undecanoate:** 3-5 hours after ingestion with a fat-containing meal

Testosterone Testing in Prostate Cancer

Total testosterone testing is indicated to confirm adequacy of androgen deprivation therapy (ADT) in men with prostate carcinoma. Only tandem mass spectrometry is sufficiently sensitive to accurately measure the low total testosterone seen in men rendered chemically castrate for treatment of prostate carcinoma.[16] In BC, testosterone analysis by tandem mass spectrometry is available upon request and should be specifically indicated on the requisition. Testosterone should be tested three months after initiating ADT, and in the event of any increase in PSA levels.

Testosterone Testing in Women

Testosterone testing is indicated for investigation of signs and symptoms of hyperandrogenism in women based on medical history and clinical examination. Testosterone testing is not indicated for the investigation of women with low libido.[17]

The upper limit of normal for testosterone in women is approximately 2-3 nmol/L, or slightly higher depending on menstrual phase and use of oral contraceptive medications.[18] In polycystic ovarian syndrome, total testosterone concentrations are within the normal reference interval or slightly higher. Consequently, testosterone concentrations greater than twice the upper limit of normal (i.e., greater than 5 nmol/L) suggest an alternate etiology, such as an androgen-secreting tumour.

Signs and Symptoms of Hyperandrogenism in Women

A range of symptoms and signs from hirsutism to virilisation may occur. The Endocrine Society recommends testing for hyperandrogenism in women with hirsutism that is moderate or severe, of rapid onset, or accompanied by menstrual dysfunction, obesity or clitoromegaly.[19] Other indications for referral are outlined in *Indications for Referral*.

Testing for Hyperandrogenism in Women

Serum total testosterone is frequently normal in women with mild clinical hyperandrogenism (due to androgen suppression of SHBG production). cBAT testing (which includes SHBG) has a better diagnostic yield for testosterone excess in women.[20] Repeat serum testosterone testing is not indicated if cBAT is normal. Testing of other androgens is dependent on clinical findings and is beyond the scope of this protocol; for more information refer to the BC Guideline *Hormone Testing - Indications and Appropriate Use*. For women who have regular menstrual cycles, collection should be performed in the morning on day 4-10.[19]

Diagnosis of the Cause of Hyperandrogenism in Women

The diagnosis of testosterone excess is based on medical history and physical findings, followed by investigational tests. Polycystic ovary syndrome (PCOS) is the most common cause of hirsutism[21] and of excess androgen production in pre-menopausal women.[19] It is important to rule out non-classic congenital adrenal hyperplasia, which occurs in 1.5-6.8% of women with hyperandrogenism.[22] A history of rapid virilization is suggestive of ovarian or adrenal malignancy and such patients should be immediately referred. For more information refer to *Appendix B: Medications that May Alter Testosterone Levels in Men and Women* and *Appendix C: Hypogonadism Investigation Algorithm*. Complete guidance for the investigation and diagnosis of female hyperandrogenism is beyond the scope of this document. Indications for urgent or non-urgent referral are outlined in *Table 3: Indications for consideration of referral to an endocrinologist, urologist, or obstetrician/gynaecologist as appropriate* below.

Monitoring Response to Treatment

Women receiving treatment for hyperandrogenism: Response to treatment of hyperandrogenism in women is clinical. Therefore, testing serum total testosterone and cBAT in patients treated for hyperandrogenism is not recommended unless a concrete cause has been identified, such as non-classical congenital adrenal hyperplasia or an androgen-secreting tumour.

Women receiving androgen therapy for low libido: Testosterone testing is not useful for monitoring women receiving androgen therapy for low libido unless overuse is suspected, or unexpected virilisation has developed.

Indications for Referral

Table 3: Indications for consideration of referral to an endocrinologist, urologist, or obstetrician/gynaecologist as appropriate

Male[5–7]	Female[22,23]
Confirmed or suspected: • Hypothalamic/pituitary tumour* • Cushing syndrome* • Acromegaly* • Hyperprolactinemia* • Hemochromatosis • Idiopathic hypogonadotropic hypogonadism • Cryptorchidism, anorchia • Genetic conditions including Klinefelter syndrome, Kallmann syndrome, myotonic dystrophy • Male factor infertility	**Confirmed or suspected:** • Rapid virilisation/rapid hair loss* • Symptoms consistent androgen-secreting tumour of adrenal or ovarian origin* • Cushing syndrome* • Acromegaly* • Congenital adrenal hyperplasia (CAH) • Polycystic ovary syndrome (PCOS) • Gestational hyperandrogenism • Ovarian hyperthecosis • Exogenous androgen administration

* *Some indications may require urgent referral; these are indicated with an asterisk.*

Resources

Abbreviations

TT	Total testosterone
cBAT	Calculated bioavailable testosterone
SHBG	Sex hormone binding globulin
PSA	Prostate-specific antigen
DRE	Digital rectal examination
LOH	Late-onset hypogonadism
PCOS	Polycystic ovarian syndrome
T2DM	Type 2 diabetes mellitus

Practitioner Resources

- **RACE: Rapid Access to Consultative Expertise Program – www.raceconnect.ca**

  RACE is a telephone consultation line for select specialty services for physicians, nurse practitioners and medical residents.

  If the relevant specialty area is available through your local RACE line, please contact them first. Contact your local RACE line for the list of available specialty areas. If your local RACE line does not cover the relevant specialty service or there is no local RACE line in your area, or to access Provincial Services, please contact the Vancouver Coastal Health Region/Providence Health Care RACE line.

  - **Vancouver Coastal Health Region/Providence Health Care:** *www.raceconnect.ca*
    Available Monday to Friday, 8 am to 5 pm
    ☎ 604-696-2131 (Vancouver area) or 1-877-696-2131 (toll free)
  - **Northern RACE:** ☎ 1-877-605-7223 (toll free)
  - **Kootenay Boundary RACE:** *www.divisionsbc.ca/kb/race* ☎ 1-844-365-7223 (toll free)
  - **Fraser Valley RACE:** *www.raceapp.ca* (download at Apple and Android stores)
  - **South Island RACE:** *www.raceapp.ca* (download at Apple and Android stores) or see *www.divisionsbc.ca/south-island/RACE*
  - Note that endocrinology on Vancouver Island is available through the Royal Jubilee Hospital/Victoria General Hospital on call endocrinologist. The on-call endocrinologist can be reached through intranet.viha.ca or the Royal Jubilee Hospital switchboard.

- **Pathways – PathwaysBC.ca**

  An online resource that allows GPs and nurse practitioners and their office staff to quickly access current and accurate referral information, including wait times and areas of expertise, for specialists and specialty clinics. In addition, Pathways makes available hundreds of patient and physician resources that are categorized and searchable.

Patient and Caregiver Resources

- **ChoosingWisely.ca:** Treatment for Erection Problems: When you need testosterone treatment and when you don't
- **HealthLinkBC.ca:** Testosterone
- **Trans Care BC:** Improving gender-affirming care across B.C. (phsa.ca)

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Appendices

- *Appendix A: Differential Diagnosis of Hypogonadism in Men*
- *Appendix B: Medications that May Alter Testosterone Levels in Men and Women*
- *Appendix C: Hypogonadism Investigation Algorithm*

This draft guideline is based on scientific evidence current as of October 2022.

This guideline was developed by the Guidelines and Protocols Advisory Committee in collaboration with the Provincial Laboratory Medicine Services, and adopted under the *Medical Services Act* and the *Laboratory Services Act*.

For more information about how BC Guidelines are developed, refer to the GPAC Handbook available at *BCGuidelines.ca: GPAC Handbook*.

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- encourage appropriate responses to common medical situations
- recommend actions that are sufficient and efficient, neither excessive nor deficient
- permit exceptions when justified by clinical circumstances

Contact Information:

Guidelines and Protocols Advisory Committee
PO Box 9642 STN PROV GOVT
Victoria BC V8W 9P1

Email: *hlth.guidelines@gov.bc.ca*
Website: *www.BCGuidelines.ca*

Disclaimer

Appendix A: Differential Diagnosis of Hypogonadism in Men

Adapted from Bhasin et al. 2018[1].

Primary hypogonadism	Secondary hypogonadism
Gonadal Disease	**Hypothalamic/pituitary disease**
• **Kallmann syndrome and other congenital hypothalamic - pituitary conditions** • **Cryptorchidism, myotonic dystrophy, anorchia** • **Some types of cancer chemotherapy, testicular irradiation/damage, orchidectomy** • **Orchitis** • **Testicular trauma, torsion** • **Advanced age**	• Hypothalamic/pituitary tumour • Hemochromatosis • Radiation exposure, Infiltrative/destructive disease of hypothalamus/pituitary • Idiopathic hypogonadotropic hypogonadism
Secondary to a distinct illness or medication	
• **Medications (refer to Appendix B)** • **End-stage renal disease**	• Hyperprolactinemia • Medications (refer to Appendix B) • Substance use (alcohol, marijuana, opioids) • Systemic illness • Nutritional deficiency/excessive exercise • Obesity, some sleep disorders, type II diabetes mellitus • Organ failure (liver, heart, and lung) • Comorbid illness associated with aging • HIV • Severe hypothyroidism

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Appendix B: Medications that May Alter Testosterone Levels in Men and Women

Note: Does not represent an exhaustive list.

Medications that May Alter Testosterone Levels in Men[1,2]		
Increase serum testosterone levels	**Decrease serum testosterone levels**	
• **Bicalutamide** • **cimetidine** • **finasteride** • **leuprolide** • **phenytoin** • **rifampin** • **tamoxifen** • **valproic acid**	• anabolic steroids • carbamazepine • corticosteroids • cyclophosphamide • cyproterone • digoxin • estrogens • goserelin • ketoconazole	• leuprolide • nilutamide • opioids*, including opioid agonist treatment • spironolactone • tetracycline • thioridazine • verapamil
* ***Studies indicate opioid-induced testosterone deficiency is likely linked to long term therapy with opioids.***[3] ***Consistent with the evidence, the recommendations from the 2018 Endocrine Society Guideline suggest to only test those who are receiving long-term opioids rather than short-term.***[4]		

Medications that May Increase Testosterone Levels in Women[1,2]
• **barbiturates** • **clomiphene** • **estrogens** • **valproic acid**

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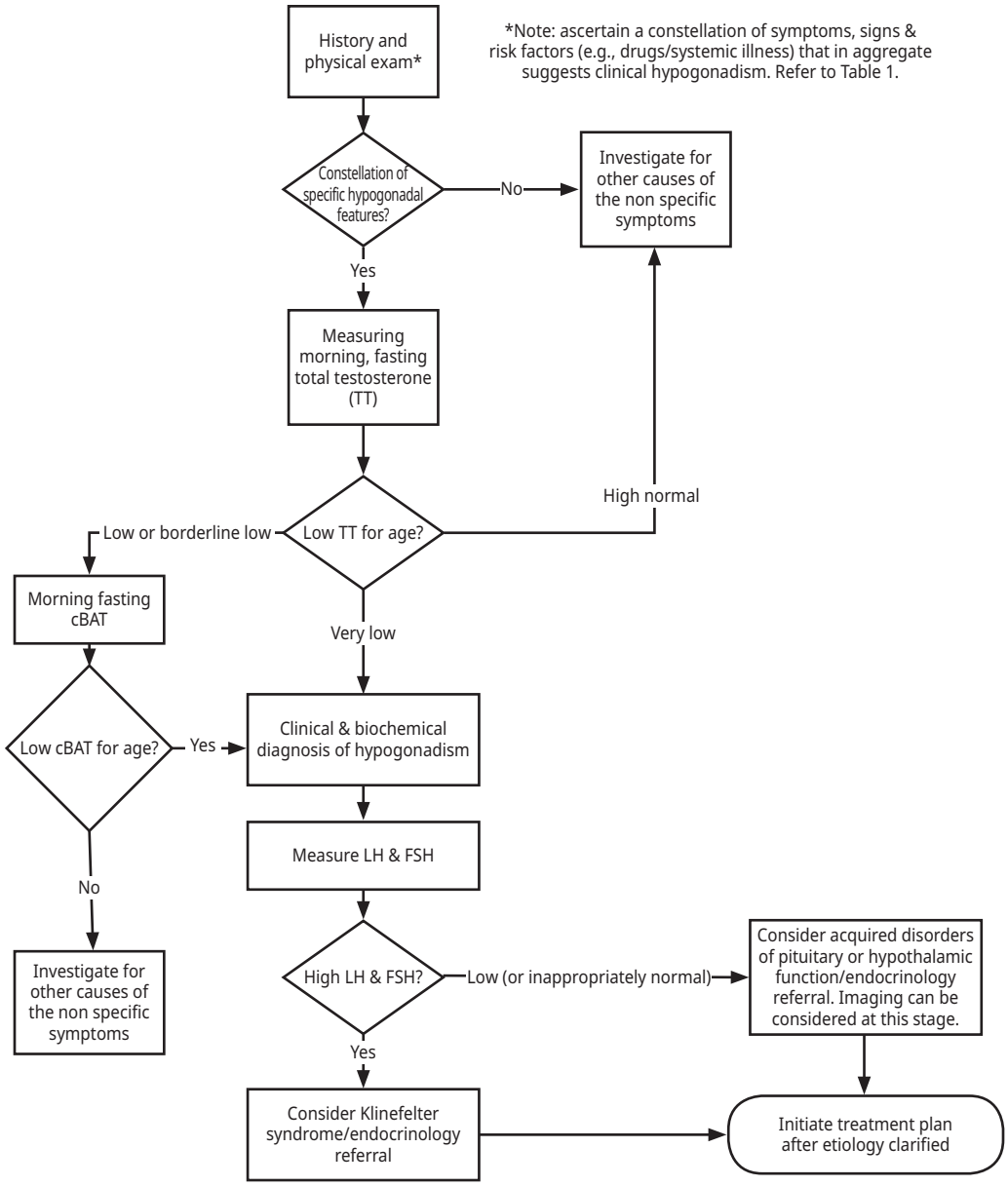
Appendix C: Hypogonadism Investigation Algorithm

Adapted from Bhasin et al. 2018[5].*



* When a patient is investigated for hypogonadism and is incidentally discovered to have hypertestosteronism and does not have symptoms of hyperandrogenism, then this does not need to be pursued diagnostically.