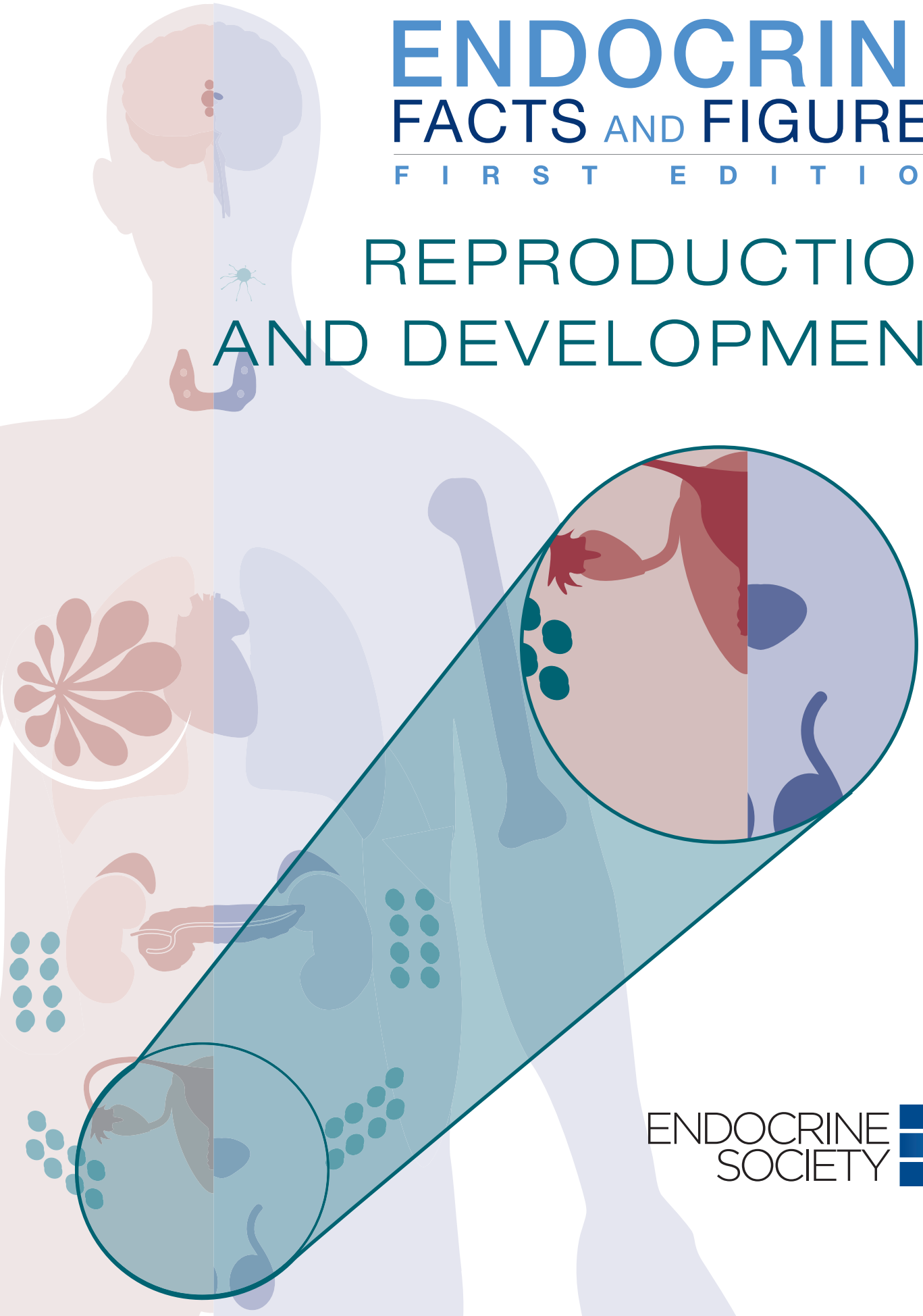
ENDOCRINE FACTS AND FIGURES

FIRST EDITION

REPRODUCTION AND DEVELOPMENT



ENDOCRINE SOCIETY

REPRODUCTION AND DEVELOPMENT

MENOPAUSE

UP TO

80%

OF WOMEN UNDERGOING MENOPAUSE EXPERIENCE **VASOMOTOR SYMPTOMS (VMS).**[1]

VMS LEFT UNTREATED ACCOUNTS FOR

$1,365 USD (DIRECT COSTS) AND

$781 USD (INDIRECT COSTS) PER YEAR.[2]

MALE HYPOGONADISM

2.29%

OF MEN IN THEIR 40S AND

3.75%

OF MEN IN THEIR 60S **TOOK ANDROGEN REPLACEMENT THERAPY** IN 2011.[4]

DISORDERS OF SEXUAL DEVELOPMENT

1:16,000–1:18,000

CONGENITAL ADRENAL HYPERPLASIA HAS AN INCIDENCE IN THE US.[7]

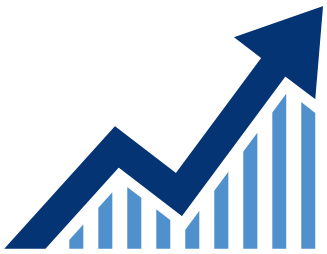
TURNER SYNDROME OCCURS IN ONE IN 2,500 LIVE-BORN FEMALES.[8]

KLINEFELTER SYNDROME IS THE MOST FREQUENT MALE CHROMOSOMAL DISORDER, WITH A PREVALENCE OF APPROXIMATELY 150 PER 100,000 LIVE-BORN MALES.[9]

PCOS

$5.46 BILLION

ASSOCIATED COST OF EVALUATION AND CARE OF PCOS IN 2005 (IN USD).[3]



BETWEEN 2000 TO 2011 GLOBALLY, TESTOSTERONE SALES PER YEAR WENT FROM **$165 MILLION USD TO $2 BILLION USD.**[5]

$5,000–$10,000

ANNUAL COST OF TOPICAL ANDROGEN (IN USD).[6]

Source:

1 Woods *et al.* 2005 and Gold *et al.* 2006
2 Sarrel *et al.* 2013
3 Azziz *et al.* 2005
4 Baillargeon *et al.* 2013
5 Handelsman. 2013
6 Abbvie. 2017
7 Pearce *et al.* 2016
8 Pinsker *et al.* 2012
9 Groth *et al.* 2013

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Mission Statement of the Endocrine Society

The mission of the Endocrine Society is to advance excellence in endocrinology and promote its essential and integrative role in scientific discovery, medical practice, and human health.

About Endocrine Facts and Figures

Endocrine Facts and Figures is a compendium of epidemiological data and trends related to a spectrum of endocrine diseases. The data is organized into nine chapters covering the breadth of endocrinology: Adrenal, Bone and Mineral, Cancers and Neoplasias, Cardiovascular and Lipids, Diabetes, Hypothalamic-Pituitary, Obesity, Thyroid, and Reproduction and Development.

All data is sourced from peer-reviewed publications, with an additional round of review by a group of world-renowned experts in the field. Additional oversight from the Endocrine Facts and Figures Advisory Panel ensured fair and balanced coverage of data across the therapeutic areas.

The first edition of **Endocrine Facts and Figures** emphasizes data on the United States. Future updates to the report will include additional data for other countries.

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For More Information

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Disclaimer

This publication summarizes current scientific information about epidemiology and trends data related to a spectrum of endocrine diseases. It is not a practice guideline or systematic review. Except when specified, this publication does not represent the official policy of the Endocrine Society.

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I. OVERVIEW

This chapter presents data on endocrine and endocrine-related reproductive and developmental conditions and disorders, including: menopause, male hypogonadism, polycystic ovary syndrome (PCOS), premature ovarian failure/primary ovarian insufficiency (POF/POI), congenital adrenal hyperplasia (CAH), and Turner syndrome (TS). In instances when United States (US)-based data are limited, we present data from international studies.

II. MENOPAUSE

2.1 PREVALENCE AND INCIDENCE

Menopause is defined as the time when women have their final menstrual period. Data collected from 3,302 women in the Study of Women's Health Across the Nation suggests that the median age when US women will experience menopause is approximately 52.5 years[1].

2.2 COST BURDEN OF DISEASE

Vasomotor symptoms (VMS) are a main feature of the menopausal transition and can have a significant effect on a person's quality of life[2-4]. VMS primarily include night sweats and hot flashes, and these symptoms are generally moderate to severe[2-5]. Up to 80% of women who are going through the menopausal transition experience VMS[6,7]. VMS are one of the chief menopause-associated issues for which women seek medical treatment in the US[8,9]. VMS may also be associated with greater bone loss, higher bone turnover, and elevated cardiovascular risk[10-12].

Data indicates that most women who have moderate to severe VMS do not receive treatment[13]. The annual direct (inpatient and outpatient visits) and indirect (loss of work productivity [medically related absenteeism and disability]) costs for women with untreated VMS are approximately US $1,365; and $781, respectively[13].

2.3 DEMOGRAPHIC DIFFERENCES

The age of final menopause (when adjusted for other factors) does not vary significantly by race (Table 2)[1].

However, duration of total VMS does vary by race/ethnicity, with Japanese and Chinese women having the shortest total VMS durations (median, 4.8 and 5.4 years, respectively) and African American women having the longest total VMS duration (median, 10.1 years). The total VMS duration for non-Hispanic white women was 6.5 years, and for Hispanic women it was 8.9 years[15].

Table 1

Baseline costs for vasomotor symptom treatment in 2017 US dollars.*	
MODERATE TO SEVERE VMS	COSTS
90-day supply of clonidine	$40
Two physician visits	$172
THERAPY INITIATION	
Two physician visits	$172
DRUG ACQUISITION COSTS	
Norethindrone acetate/ethinyl E2	$465
Conjugated estrogen/medroxyprogesterone	$618
BREAKTHROUGH BLEEDING AT 3 MONTHS (OR CONTINUED SPOTTING AT 6 MONTHS)	
Endometrial biopsy	$258
Pathology and laboratory fees	$191
TELEPHONE CALL TO PHYSICIAN	
Spotting at 3 months	$21
Source: Utian *et al.* 2005[14]	

Abbreviations: VMS, vasomotor symptoms; E2, estradiol.
Notes: *, approximated using and inflation calculator.

Table 2

Age of final menstrual period by race.				
RACE/ETHNICITY	ADJUSTED	P VALUE	UNADJUSTED	P VALUE
Hispanic	53.10	0.653	50.86	0.0009
African American	52.59	0.653	52.17	0.0009
Chinese	52.86	0.653	52.41	0.0009
Japanese	53.24	0.653	53.14	0.0009
Caucasian[b]	52.85	0.653	52.88	0.0009
Source: Gold *et al.* 2013[1]				

Notes: Median age (years) at final menstrual period, adjusted and unadjusted for baseline covariates and time-invariant predictors (Multivariate Cox Proportional Hazards Model);[b], this was the reference group used for covariate adjustments.

2.4

LIFE EXPECTANCY AND MORTALITY

Later age at natural menopause has been associated with numerous positive health outcomes[16-18], such as longer survival, greater life expectancy[19] and reduced rates of: all-cause mortality[20], cardiovascular death[21,22], cardiovascular disease (CVD)[19,23-29], stroke[30], atherosclerosis[31], angina after myocardial infarction[32], osteoporosis[33], and low bone density and fracture[34,35]. However, later age at menopause has also been associated with higher risk of breast, endometrial, and ovarian cancer[19,36-39].

III. MALE HYPOGONADISM

As men age past 30 years, circulating testosterone (T) declines progressively by 0.4 to 2% per year[40-42]. Symptoms of androgen deficiency may include decreased energy, mood, muscle mass and strength, erectile function, bone density, and libido[43]. Erectile dysfunction, low libido, and lack of morning erections are the symptoms that are most specific for male hypogonadism[44].

3.1

PREVALENCE AND INCIDENCE

One US study on osteoporosis and androgens in a cohort of 2,447 men (mean age 73 years) reported that 3.0% had T deficiency (the study defined T deficiency as less than 200 ng/dl)[46].

A study on trends in T prescribing practices in the US, reported that from 2001 to 2011 T use more than tripled among men 40 years or older (0.81% in 2001

Table 3

Symptoms and signs of androgen deficiency in men.
A. MORE SPECIFIC SYMPTOMS AND SIGNS
Breast discomfort, gynecomastia
Incomplete or delayed sexual development, eunuchoidism
Reduced sexual desire (libido) and activity
Inability to father children, low or zero sperm count
Decreased spontaneous erections
Hot flushes, sweats
Loss of body (axillary and pubic) hair, reduced shaving
Very small (especially <5 ml) or shrinking testes
Height loss, low trauma fracture, low bone mineral density
B. OTHER LESS SPECIFIC SYMPTOMS AND SIGNS
Diminished physical or work performance
Decreased energy, motivation, initiative, and self-confidence
Poor concentration and memory
Feeling sad or blue, depressed mood, dysthymia
Increased body fat, BMI
Sleep disturbance, increased sleepiness
Mild anemia (normochromic, normocytic, in the female range)
Reduced muscle bulk and strength
Source: Bhasin *et al.* 2011[45]

Abbreviations: BMI, body mass index.

Table 4

Percentage of men in the United States given androgen replacement therapy by age group and year.											
	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011
N	624,080	670,126	703,738	698,074	724 518	715,546	720 046	761,088	729,965	698,380	698,343
% Given ART	0.54	0.66	0.76	0.75	0.81	0.90	1.05	1.22	1.66	1.99	2.29
AGE 50-59											
N	424,534	457,417	490,381	501,335	562,482	578,941	605,057	675,508	639,073	625,709	643,106
% Given ART	1.02	1.19	1.39	1.36	1.37	1.52	1.69	1.88	2.54	2.98	3.26
AGE 60-69											
N	161,273	182,399	197,578	204,055	234,902	250,808	280,662	331,150	309,766	300,312	317,143
% Given ART	1.32	1.53	1.72	1.68	1.69	1.87	2.06	2.28	3.03	3.51	3.75
AGE ≥70											
N	60,925	69,210	71,445	73,181	93,855	95,678	104,750	113,813	103,342	82,203	84,875
% Given ART	0.77	0.79	0.99	0.99	1.00	1.13	1.20	0.96	1.92	2.10	2.22
ALL AGES											
N	1,270,812	1,379,062	1,463,142	1,476,645	1,615,757	1,640,973	1,710,515	1,881,559	1,782,146	1,706,604	1,743,467
% Given ART	0.81	0.96	1.11	1.10	1.14	1.20	1.45	1.66	2.23	2.63	2.91
Source: Baillargeon *et al.* 2013[47]											

Abbreviations: ART, androgen replacement therapy; N, number of eligible men.

to 2.91% in 2011)[47] (Table 4). In 2011, 2.29% of men in their 40s and 3.75% of men in their 60s were taking androgen replacement therapy. The study looked at four formulations and concluded that men most commonly used topical gels. It also reported that gel use had the highest rate of increase—more than 5-fold[47].
In 2010 (geographically in the US) the South had the highest prevalence of T use (3.77% for men 40 years of age or older), the West had the second highest prevalence (2.61%), followed by the Midwest (1.78%), and the Northeast (1.60%)[47].

A European study that included 3,334 men aged 40-79 years reported that 80% had normal total T (TT) and normal free T (FT), 8% had normal TT and low FT, 3% had low TT and normal FT, and 9% had low TT and low FT[48]. Normal TT and low FT were associated with advanced age and poorer health; whereas, low TT and normal FT were associated with younger age and obesity. Low FT, even in those with normal TT, was associated with classical symptoms of androgen deficiency (such as sexual dysfunction). Therefore, clinicians should assess FT levels in men suspected of having androgen deficiency.

3.2

COST BURDEN OF DISEASE

T gels, patches, buccal tablets, nasal sprays and subcutaneous pellets are quite expensive. For example, the topical gel Androgel© 1% (50 mg to 100 mg/day), costs roughly US $5,000-$10,000/year[49,50]. Intramuscular T esters (cypionate, enanthate) are much more affordable with a maximum recommended dose of 400 mg per month, which equates to an average cost of between US $100-200/year[51,52].

Handelsman *et al.* reported that T purchases increased at a compound global annual growth rate of 25% from 2000 to 2011 (from approximately US $165 million to $2 billion). During the same time period, sales in the US increased at a compound annual growth rate of 23%[53].

3.3

DEMOGRAPHIC DIFFERENCES

Male androgen deficiency increases as men age. The majority of studies have not shown significant difference in T levels or symptom of T-deficiency between races[54,55] (Table 5).

Table 5

Total and free testosterone and sex hormone binding globulin levels overall by race/ethnic group.				
VARIABLE	OVERALL N=1,845	WHITE N=681	BLACK N=523	HISPANIC N=641
TT, ng/dl	437.8 ± 180.1	433.7 ± 171.7	447.3 ± 196.5	439.4 ± 186.8
FT, ng/dl	9.1 ± 3.7	9.0 ± 3.5	9.3 ± 4.0	9.4 ± 3.9
TT < 300 ng/dl	457 (24.3)	179 (24.0)	122 (26.6)	156 (21.2)
FT < 5 ng/dl	218 (10.6)	85 (10.2)	63 (12.4)	70 (8.8)
TT by FT category				
TT <300 ng/dl, FT <5 ng/dl	186 (9.3)	74 (9.2)	49 (10.2)	63 (7.9)
TT >300 ng/dl, FT ≥5 ng/dl	271 (15.0)	105 (14.8)	73 (16.4)	93 (13.3)
TT ≥300 ng/dl, FT >5 ng/dl	32 (1.3)	11 (1.0)	14 (2.2)	7 (0.9)
TT ≥300 ng/dl, FT ≥5 ng/dl	1,356 (74.4)	491 (75.0)	387 (71.2)	478 (77.9)
SHBG, nmol/liter (move to lowest row as T values are the most important)	34.0 ± 17.7	34.0 ± 16.6	35.2 ± 20.7	31.9 ± 16.2
Source: Araujo *et al.* 2007[55]				

Abbreviations: T, testosterone; SHBG, sex hormone binding globulin; FT, free testosterone; TT, total testosterone.

Table 6

Unadjusted and adjusted hazard ratios for all-cause mortality, myocardial infarction, and stroke associated with testosterone treatment for low testosterone in men.									
MODEL	ALL-CAUSE MORTALITY			MYOCARDIAL INFARCTION			STROKE		
	Hazard ratio	95% CI	P value	Hazard ratio	95% CI	P value	Hazard ratio	95% CI	P value
COMPARING NON-NORMALIZED TREATED VERSUS UNTREATED (REFERENCE = UNTREATED)									
Univariate N = 25,701 versus 13,378	0.83	0.79-0.87	<0.001	0.95	0.79-1.15	0.599	0.90	0.61-1.34	0.610
Propensity matched (stabilized inverse probability of treatment weights) N = 23,953 versus 11,957	0.84	0.80-0.89	<0.001	0.98	0.80-1.19	0.811	0.94	0.61-1.44	0.675
COMPARING NORMALIZED TREATED VERSUS UNTREATED (REFERENCE = UNTREATED)									
Univariate N = 43,931 versus 13,378	0.40	0.39-0.43	<0.001	0.70	0.59-0.83	<0.001	0.57	0.40-0.82	0.002
Propensity matched (stabilized inverse probability of treatment weights) N = 40,852 versus 11,957	0.44	0.42-0.46	<0.001	0.76	0.63-0.93	0.005	0.64	0.43-0.96	0.031
COMPARING NORMALIZED TREATED VERSUS NON-NORMALIZED TREATED (REFERENCE = NON-NORMALIZED TREATED)									
Univariate N = 43,931 versus 25,701	0.49	0.47-0.51	<0.001	0.74	0.64-0.85	<0.001	0.64	0.48-0.87	0.004
Propensity matched (stabilized inverse probability of treatment weights) N = 40,852 versus 23,953	0.53	0.50-0.55	<0.001	0.82	0.71-0.95	0.008	0.70	0.51-0.96	0.028
Source: Sharma *et al.* 2015[67]									

Abbreviations: N, number; CI, confidence interval.

Table 7

Association among testosterone status and cardiovascular disease, metabolic syndrome, and all-cause mortality.			
	NORMAL TT LOW CFT OR (95% CI)	LOW TT NORMAL CFT OR (95% CI)	LOW TT LOW CFT OR (95% CI)
BASELINE			
HAVING CVD			
Unadjusted	2.15 (1.67, 2.75)***	1.57 (1.04, 2.36)*	2.44 (1.93, 3.08)***
Age, center, BMI, comorbidities	0.83 (0.60, 1.15)	1.69 (0.94, 3.03)	1.00 (0.73, 1.37)
HAVING METS			
Unadjusted	1.94 (1.48, 2.55)***	4.13 (2.70, 6.33)***	4.02 (3.13, 5.17)***
Age, center, BMI, comorbidities	1.32 (0.94, 1.86)	2.55 (1.54, 4.22)***	1.60 (1.17, 2.18)**
FOLLOW-UP			
DEVELOPING CVD			
Unadjusted	1.72 (1.09, 2.72)*	1.56 (0.83, 2.95)	1.80 (1.18, 2.74)**
Age, center, BMI, comorbidities	1.06 (0.64, 1.73)	1.41 (0.72, 2.76)	1.17 (0.74, 1.85)
DEVELOPING METS			
Unadjusted	1.59 (0.94, 2.70)	2.53 (1.11, 5.76)*	2.39 (1.43, 4.00)**
Age, center, BMI, comorbidities	1.34 (0.74, 2.42)	1.45 (0.59, 3.53)	1.65 (0.93, 2.93)
ALL-CAUSE MORTALITY			
Unadjusted	2.62 (1.93, 3.56)***	1.15 (0.75, 1.75)	2.70 (2.02, 3.60)***
Age, center, BMI, comorbidities	1.24 (0.89, 1.73)	1.21 (0.77, 1.91)	1.63 (1.18, 2.24)**
Source: Antonia *et al.* 2016[48]			

Abbreviations: CI, confidence interval; CVD, cardiovascular disease; OR, odds ratio; BMI, body mass index; MetS, metabolic syndrome; TT total testosterone, cFT, calculated free testosterone.

Notes: Data are reported as hazard ratios (95% CI), with normal TT/normal cFT as the referent group; *, $p < .05$; ** , $p < .01$; ***$P < .001$

3.4

LIFE EXPECTANCY AND MORTALITY

Studies have associated low T levels with metabolic syndrome (MetS), decreased muscle strength, hyperinsulinemia, diabetes mellitus, bone loss and osteoporosis, loss of libido, erectile dysfunction, depression, lethargy, inability to concentrate, sleep disturbance, irritability, depression, regression of secondary sex characteristics, and decreased interest in activities[46,56-66]. These signs and symptoms are associated with low T and not proven to be causative. Thus, low T may be a reflection of overall poor health.

A study by Sharma *et al.*[67] (Table 6) reported that normalizing T levels via T replacement therapy resulted in a significant reduction in all-cause mortality, myocardial infarction, and stroke.

Table 8

Conditions where clinicians should consider measure serum testosterone levels.
Osteoporosis or low trauma fracture, especially in a young man
Sellar mass, radiation to the sellar region, or other diseases of the sellar region
T2DM
End-stage renal disease and maintenance hemodialysis
Treatment with medications that affect T production or metabolism, such as glucocorticoids and opioids
HIV-associated weight loss
Moderate to severe chronic obstructive lung disease
Infertility
Source: Bhasin *et al.* 2010[45]

Abbreviations: T2DM, type 2 diabetes mellitus.

Table 9

General clinical guidelines on testosterone treatments for male androgen deficiency.		
FORMULATION	PHARMACOKINETIC PROFILE	REGIMEN
Transdermal T patch	Treatment restores serum T, DHT, and E2 levels to the physiological male range.	1 or 2 patches, designed to nominally deliver 5-10 mg T over 24 h applied every d on nonpressure areas
T enanthate or cypionate	Depending on the dose, after a single IM injection, serum T levels rise into the supraphysiological range, then decline gradually into the hypogonadal range by the end of the dosing interval.	150-200 mg IM every 2 wk or 75-100 mg/wk
T pellets	Serum T peaks at 1 month and then is sustained in normal range for 3-6 months, depending on formulation.	3-10 pellets implanted SC; dose and regimen vary with formulation
1%, 1.62%, or 2% T gel	Restores serum T and E2 levels to the physiological male range.	Available in sachets, tubes and pumps 5-10 g T gel containing 50-100 mg T every d.
Buccal, bioadhesive, T tablets	It is absorbed from the buccal mucosa.	30 mg controlled release, bioadhesive tablets twice daily
T-in-adhesive matrix patch	It restores serum T, DHT and E2 to the physiological range.	2 × 60 cm2 patches delivering approximately 4.8 mg T/d
Oral T undecanoate	When administered in oleic acid, T undecanoate is absorbed through the lymphatics, bypassing the portal system; there is considerable variability in the same individual on different days and among individuals.	40-80 mg orally, twice daily or three times daily with meals
Injectable long-acting T undecanoate in oil	When administered at a dose of 750 to 1,000 mg IM, serum T levels are maintained in the normal range in a majority of treated men.	European regimen 1,000 mg IM, followed by 1,000 mg at 6 wk, and 1,000 mg every 10-14 wk
Source: Bhasin *et al.* 2011[45]		

Abbreviations: T, testosterone; IM, intramuscular; d, day; wk, week; SC, subcutaneous; DHT, dihydrotestosterone; E2, estradiol; US, United States.

DHT AND E2	ADVANTAGES	DISADVANTAGES
T:DHT and T:E2 levels are in the physiological male range.	There is relative ease of application, and treatment corrects symptoms of androgen deficiency.	Serum T levels in some androgen-deficient men may be in the low-normal range; these men may need to apply two patches daily; skin irritation at the application site occurs frequently in many patients.
DHT and E2 levels rise in proportion to the increase in T levels; T:DHT and T:E2 ratios do not change.	Treatment corrects symptoms of androgen deficiency; it is relatively inexpensive when self-administered; there is dosing flexibility.	Treatment requires IM injection; serum T levels have peaks and valleys; treatment has been associated with erythrocytosis.
T:DHT and T:E2 ratios do not change.	Treatment corrects symptoms of androgen deficiency.	Treatment requires surgical incision for insertions; pellets may extrude spontaneously.
Serum DHT levels are higher and T:DHT ratios are lower in hypogonadal men treated with the T gel than in healthy eugonadal men.	Treatment corrects symptoms of androgen deficiency; there is dose flexibility, ease of application, and good skin tolerability.	There is the potential of transfer to a female partner or child by direct skin-to-skin contact; a small proportion of treated men reported skin irritation; there are moderately high DHT levels.
Treatment normalizes serum T and DHT levels in hypogonadal men.	Treatment corrects symptoms of androgen deficiency in healthy, hypogonadal men.	There are gum-related adverse events in 16% of treated men.
T:DHT and T:E2 are in the physiological range.	Treatment lasts 2 d.	There is some skin irritation.
There is a high DHT:T ratio.	There is the convenience of oral administration.	It is not approved in the US; there are variable clinical responses, variable serum T levels, and a high DHT:T ratio.
DHT and E2 levels rise in proportion to the increase in T levels; T:DHT and T:E2 ratios do not change.	Treatment corrects symptoms of androgen deficiency; requires infrequent administration.	Treatment requires IM injection of a large volume (4 ml); a very small number of men reported coughing immediately after injection.

Table 10

Individual studies on various testosterone therapies for male androgen deficiency.

MEDICATIONS	SUBJECTS	REGIMEN	RESULTS	REFERENCE
Novel transdermal 2% T	220 hypogonadal men with T2DM and/or MetS I	12-month treatment	Over a 6-month period, transdermal TRT was associated with beneficial effects on insulin resistance, total and LDL-cholesterol, Lpa, and sexual health.	H Jones *et al.* 2011[73]
T gel	790 men 65 years of age or older with a serum T concentration of less than 275 ng per deciliter and symptoms suggesting hypoandrogenism	Treated for 1 year	Raising T concentrations for 1 year from moderately low to the mid-normal range for men 19 to 40 years of age had a moderate benefit with respect to sexual function and some benefit with respect to mood and depressive symptoms but no benefit with respect to vitality or walking distance.	Snyder *et al.* 2016[75]
T gel (with goserelin acetate and anastrozole to suppress T and E2)	Group A: 198 healthy men 20 to 50 years of age Group B: 202 healthy men 20 to 50 years of age	Group A. Treatment with goserelin acetate (to suppress endogenous T and E2) and randomly assigned to receive a placebo gel or 1.25 g, 2.5 g, 5 g, or 10 g of T gel daily for 12 weeks Group B: Treatment with goserelin acetate, placebo gel or T gel, and anastrozole (to suppress the conversion of T to E2)	The percentage of body fat increased in subjects receiving placebo or 1.25 g or 2.5 g of T daily without anastrozole (mean T level, 44±13 ng per deciliter, 191±78 ng per deciliter, and 337±173 ng per deciliter, respectively). Lean mass and thigh-muscle area decreased in subjects receiving placebo and in those receiving 1.25 g of T daily without anastrozole. Leg-press strength fell only with placebo administration. In general, sexual desire declined as the T dose was reduced.	Finkelstein *et al.* 2013[74]

Abbreviations: T, testosterone; T2DM, type 2 diabetes mellitus; MetS, metabolic syndrome; E2, estradiol.

In contrast, Araujo *et al.*[66] reported a week association between endogenous sex steroid levels and mortality. In addition, the European Male Aging Study found that having and/or developing CVD was not associated with T levels after adjusting for age, BMI, and comorbidities (Table 7)[48].

There was a great deal of interest when two publications using large pharmacoepidemiologic databases, suggested that T use was associated with an increased risk of having a cardiovascular event. There were many criticisms of these studies, including the fact that approximately one-third did not have documented T levels prior to therapy. However, it did lead to the US Food and Drug Administration changing its labeling to discourage the use of T in men with age-related declines in T. Recently, studies of men older than 65 years with low T levels found that T treatment was associated with improved bone density and hematocrit, without any change in cognition or carotid plaque volume. Larger studies are now being planned which are sufficiently powered for heart disease outcomes[68-71].

3.5 KEY TRENDS ON DIAGNOSIS, TREATMENT, AND HEALTH OUTCOMES

3.5.1 Appropriate Levels

Experts don't agree on what androgen levels are "normal" for healthy, aging men. Mohr *et al.* proposed age-specific thresholds of 251, 216, 196, and 156 ng/dl for men in their 40s, 50s, 60s, and 70s (respectively). These thresholds correspond to the bottom 2.5th percentile of the data in the study[72].

A European study of T and hypogonadism in 3,369 men aged 40 to 79 years defined late-onset hypogonadism as the presence of at least three sexual symptoms associated with a TT level of <3.2 ng per milliliter and a FT level of <64 pg per milliliter: poor morning erection, low sexual desire, and erectile dysfunction[44].

Table 11

Potential adverse effects of testosterone replacement.
ADVERSE EVENTS FOR WHICH THERE IS EVIDENCE OF ASSOCIATION WITH T ADMINISTRATION
Growth of metastatic prostate cancer
Reduced sperm production and fertility
Erythrocytosis
Acne and oily skin
Detection of subclinical prostate cancer
UNCOMMON ADVERSE EVENTS FOR WHICH THERE IS WEAK EVIDENCE OF ASSOCIATION WITH T ADMINISTRATION
Male pattern balding (familial)
Growth of breast cancer
Gynecomastia
Induction or worsening of obstructive sleep apnea
FORMULATION-SPECIFIC ADVERSE EFFECTS
Intramuscular injections of T enanthate, or cypionate
Pain at injection site
Fluctuation in mood or libido
Excessive erythrocytosis (especially in older patients)
Intramuscular injections of T undecanoate[a]
Coughing episodes immediately after the IM injection
Hematocrit
Injection site pain
Transdermal patches
Frequent skin reactions at application site
Transdermal gel
Potential risk for T transfer to partner or another person who is in close contact (need to remind patient to cover application sites with clothing and to wash skin and hands with soap before having skin-to- skin contact with another person)
Skin irritation
Buccal T tablets
Irritation of gums
Alterations in taste
Pellet implants
Infection, expulsion of pellet
Oral tablets[b]
Effects on liver and cholesterol (methyltestosterone)
Source: Bhasin *et al.* 2010[45]

Abbreviations: T, testosterone.

Notes: [a], data on undecanoate from Zitzman et al. 2013[76];[b], liver toxicity has been reported mostly with oral 17-alkylated androgens.

Table 12

Conditions where testosterone administration is a concern for an association with a high risk of adverse outcome and not recommended.
VERY HIGH RISK OF SERIOUS ADVERSE OUTCOMES
Metastatic prostate cancer*
Breast cancer
MODERATE TO HIGH RISK OF ADVERSE OUTCOMES
Unevaluated prostate nodule or induration*
PSA >4 ng/ml (>3 ng/ml in individuals at high risk for prostate cancer, such as African-Americans or men with first-degree relatives who have prostate cancer)*
Hematocrit >50%
Severe lower urinary tract symptoms associated with benign prostatic hypertrophy as indicated by AUA/IPSS >19*
Uncontrolled or poorly controlled congestive heart failure
Source: Bhasin *et al.* 2010[45]

Notes: *, data are poor.

Clinicians should diagnose androgen deficiency only if a patient has unequivocally low serum T levels and consistent symptoms and signs. Initial diagnostic tests should use a reliable assay to measure morning TT levels, and levels should be confirmed by repeating this measurement, along with serum gonadotropin levels to identify an etiology. Clinicians should measure free or bioavailable T levels in some men with TT near the lower limit of normal or in men with suspected sex hormone-binding globulin abnormalities due to age or obesity[45].

3.5.2 Treatment

T therapy is recommended for symptomatic androgen deficiency in men to develop and maintain secondary sex characteristic and improve sense of well-being, muscle mass and strength, bone mineral density, and sexual function[45]. Clinicians treating patients with any of the approved formulations should try to maintain T levels in the mid-normal range[45].

One study reported that treatment with transdermal 2% T gel over a 6-month had beneficial effects on insulin resistance, total and LDL-cholesterol, lipoprotein(a), and sexual health in hypogonadal men with type 2 diabetes (T2DM) and/or MetS[73].

Another study examined combined treatments of various strengths of T gel with medications to suppress endogenous T and/or suppress the conversion of T to estradiol in 198 healthy 20- to 50-year-old men[74]. The study reported that a wide variety of levels of T were needed to maintain lean mass, fat mass, strength, and sexual function and recommended that clinicians should reassess both the evaluation and management of hypogonadism in men[74].

A third study examined 790 men 65 years of age or older who had low T levels and symptoms that suggested hypoandrogenism. The study reported that increasing T concentrations from moderately low to the mid-normal range (corresponding to concentrations in men age 19-40 years) for 1 year had a moderate benefit regarding sexual function, some benefit regarding mood and depressive symptoms, but no benefit regarding vitality or walking distance[75].

Although the data is not consistent, the package insert for T still indicates that clinicians should not start T therapy in patients with breast or prostate cancer; hematocrit greater than 50%, untreated severe obstructive sleep apnea, severe lower urinary tract symptoms, or uncontrolled or poorly controlled heart failure[45].

In summary, T therapy is clearly indicated in younger men with clear etiologies for their hypogonadism. The long-term benefits and risks of increasing T levels in older men are unclear[75].

IV. POLYCYSTIC OVARY SYNDROME

Polycystic ovary syndrome (PCOS) is the most common endocrine abnormality of young women in the US today[77-79].

The currently accepted diagnostic criteria issued by the 2003 Rotterdam PCOS consensus workshop group (sponsored by the European Society of Human Reproduction and Embryology/American Society of Reproductive Medicine) states that PCOS should include two of the following three criteria: oligo-anovulation, hyperandrogenism (clinical or biochemical), and polycystic ovary morphology on ultrasound[80,81].

It is important to note that many studies of PCOS used the previous NIH criteria established in 1990 that required both hyperandrogenism and oligo-anovulation, which included a group of women with PCOS who could have more severe symptoms and metabolic complications[82]. The Androgen Excess and PCOS Society PCOS definition requires the presence of hyperandrogenism (clinical or biochemical) associated with ovulatory dysfunction (either oligo-anovulation or PCOs)[83]. Clinical practices use the Rotterdam criteria for the diagnosis of PCOS. Research studies may use all three criteria (Rotterdam, NIH, and AE-PCOS).

In order to make the diagnosis of PCOS, clinicians must also exclude conditions that could cause symptoms of PCOS, such as thyroid disease, elevated prolactin, estrogen deficiency, CAH, and Cushing's syndrome[80-83]. For the purpose of this Facts and Figures report, we use the Rotterdam criteria to define PCOS.

Table 13

Global prevalence and phenotypes for polycystic ovary syndrome based on 2003 Rotterdam criteria.

	SEVERE PCOS	HYPERANDROGENISM AND CHRONIC ANOVULATION	RESULTS	REFERENCE
Periods	Irregular	Irregular	Normal	Irregular
Androgen concentration	High	High	High	Mildly raised
Risks	Potential long-term	Potential long-term	Unknown	Unknown
Ovaries on ultrasonography	Polycystic	Normal	Polycystic	Polycystic
Insulin concentrations	Increased	Increased	Increased	Normal
Prevalence in affected women*	61%	7%	16%	16%

Source: Table adapted from Norman *et al.* 2007[84]

Abbreviations: PCOS, polycystic ovary syndrome.

Notes: *, *Azziz et al.* 2006[83]

4.1

PREVALENCE AND INCIDENCE

4.2

COST BURDEN OF DISEASE

A 2005 study by Azziz *et al.* reported a cost of approximately US $5.46 billion (in 2017 dollars, estimated using an online inflation calculator) to evaluate and provide care to reproductive-aged PCOS women in the US[85]. Diagnostic evaluation accounted for a minor part of the total costs (roughly 2%). The majority of the costs are attributable to treatment of T2DM, menstrual dysfunction, or abnormal uterine bleeding. Therefore, more widespread screening for PCOS would likely be cost-effective, as it would lead to earlier diagnosis and interventions that can prevent and control symptoms and prevent the development of T2DM. In particular, prevention or early diagnosis and optimal treatment of T2DM prevents future complications, such as CVD and associated morbidity, mortality, and health care-related costs (Table 14)[85].

Table 14

The overall health care-related economic burden of polycystic ovarian syndrome patients during their reproductive years.

PROCEDURE	ANNUAL COSTS IN MILLIONS OF US DOLLARS (% OF TOTAL COSTS, IN 2017 US DOLLARS)*
Initial evaluation	$130 (2.3)
Treatment	
Menstrual dysfunction/AUB	$1,768 (30.9)
Infertility	$698 (12.2)
Type 2 DM	$2,313 (40.4)
Hirsutism	$815 (14.2)
Total cost	$5,725 (100.0)

Source: Azziz *et al.* 2005[85]

Abbreviations: AUB, Abnormal uterine bleeding; DM, diabetes mellitus; US, United States.

Notes: *, costs were updated to 2017 figures using an online inflation calculator.

4.3

DEMOGRAPHIC DIFFERENCES

Several studies have demonstrated or reported significant ethnic differences in the prevalence of cardiovascular risk factors in PCOS. These observations mirror known CVD risk factor differences, such as a higher prevalence of the MetS, insulin resistance, and T2DM in Hispanic women. Whether these ethnic differences will interact with PCOS to greatly increase overall CVD risk factors is not clear. There is no evidence for differences in subclinical tests of atherosclerosis[86,87].

4.4

LIFE EXPECTANCY AND MORTALITY

4.4.1

Cardiovascular Risk Factors

Due to the high prevalence of obesity in PCOS and association of PCOS and androgen excess with insulin resistance[88], several studies have demonstrated a higher prevalence of cardiovascular risk factors in PCOS. Independent of BMI, women with PCOS have higher low-density lipoprotein (LDL) cholesterol ("bad cholesterol") and triglycerides along with lower high-density lipoprotein (HDL) cholesterol ("good cholesterol")[88,89]. Although studies have not consistently reported higher blood pressure in women with PCOS, women with PCOS might be at risk for hypertension, especially later in life[90-94]. Because increases in abdominal adiposity and insulin resistance are characteristic of PCOS, these women also have a high prevalence of the MetS[95]. Asymptomatic women with PCOS have early signs of CVD, such as increased left atrial size, increased left ventricular mass index, lower left ventricular ejection fraction, increased carotid artery intima-media thickness, increased coronary artery calcification, and diastolic dysfunction[96-102].

In spite of evidence that women with PCOS have an increased prevalence of cardiovascular risk factors, there is limited data to make conclusions about any increase in event rates of heart disease, stroke, and death. Smaller studies failed to find an increase in cardiovascular event rates[103,104]. In larger retrospective studies, incidences of stroke and mortality were only increased in women with PCOS who developed T2DM[105,106]. Although some studies suggest that features of PCOS are more common in women with coronary artery disease and cardiovascular events, it is not clear that these women would have been diagnosed with PCOS before menopause[81].

4.4.2

Type 2 Diabetes Mellitus

T2DM is considered a CVD equivalent, conferring the same risk of having a cardiovascular event as a prior cardiovascular event. T2DM also erases the female cardioprotective advantage, resulting in a similar cardiovascular risk for women with T2DM as men. Prediabetes is present in as many as 35% of US women and adolescents with as many as 3-10% with T2DM[81]. T2DM is a clear target for prevention in lowering the risk for morbidity and mortality in women with PCOS.

Table 15

Cardiovascular risk in women with polycystic ovarian syndrome.
AT RISK—PCOS WOMEN WITH ANY OF THE FOLLOWING RISK FACTORS:
Hypertension
Dyslipidemia (increased LDL-cholesterol and/or non-HDL-cholesterol)
Cigarette smoking
Impaired glucose tolerance
Family history of premature CVD (<55 years of age in male relative; <65 years of age in female relative)
Obesity (especially increased abdominal adiposity)
Subclinical vascular disease
AT HIGH RISK–PCOS WOMEN WITH:
MetS
OSA
T2DM
Overt vascular or renal disease, CVD
Source: Table adapted from Legro *et al.* 2013[81]

Abbreviations: CVD, cardiovascular disease; HDL, high-density lipoprotein; LDL, low-density lipoprotein; OSA, obstructive sleep apnea, PCOS, polycystic ovary syndrome, T2DM, type 2 diabetes mellitus.

Notes: According to the Androgen Excess and Polycystic Ovary Syndrome Society, women with PCOS should be stratified as being either at high risk or at risk for CVD based the criteria shown above Wild *et al.* 2010[88].

4.4.3

Cancer

Because less-frequent menses (a symptom of PCOS) is linked to an increased risk for endometrial hyperplasia, two meta-analyses examined whether there is an also an increased risk for endometrial cancer associated with PCOS. The analyses reported that women with PCOS have a 2.7- to 3-fold increased risk for developing endometrial cancer[107,108]. Whether this could be due to other risk factors for endometrial cancer, such as obesity, T2DM, and infertility instead of PCOS itself is not known[81].

PCOS has not been associated with breast cancer, and data are lacking linking PCOS with uterine leiomyosarcoma or vaginal, vulvar, or cervical cancers[108,109].

4.4.4

Psychosocial Issues

Women with PCOS have a higher prevalence of depression and anxiety[110]. Psychosocial issues include: PCOS adolescents facing issues of self-presentation, young adult women with PCOS having fertility concerns, and women of all ages with PCOS having concerns related to eating, weight, and androgen excess[111,112].

One study linked PCOS with bipolar disorder[113]. However, this likely refers to both the disorder and its treatment regime[114]. Valproate treatment is associated with weight gain and the development of polycystic ovaries, relative hyperandrogenemia, and oligomenorrhea[115,116]. In addition, *in vitro* studies have shown that valproate increases androgen production (similar to what is seen in polycystic ovaries)[117].

4.4.5

Long-Term Outcome of Children Born to Mothers with Polycystic Ovary Syndrome

Children of PCOS women have an increased risk for developing PCOS (similar to other first-degree relatives)[118,119], and some studies have reported that offspring of PCOS mothers can experience reproductive and metabolic abnormalities[120,121]. However, current data are limited regarding long-term reproductive and metabolic risks for this group. Furthermore, not all children of PCOS mothers develop PCOS, and for those that do, symptoms may not emerge until puberty[122]. There is currently no test that screens girls for PCOS.

4.5

KEY TRENDS ON DIAGNOSIS, TREATMENT, AND HEALTH OUTCOMES

4.5.1

Diagnosis

Anti-Müllerian Hormone

Developing follicles release Anti-Müllerian Hormone (AMH), and clinicians use AMH to predict ovarian reserve and fertility. PCOS women generally have higher AMH levels than women without PCOS, and these levels correlate with PCOS presentation and follicle numbers[123,124].

It has been difficult to define a threshold for using AMH to diagnose PCOS, largely because there is no international standard for AMH assays. AMH assays would be helpful in diagnosing adolescent girls, as irregular menses occur more frequently during puberty and might normalize later in adolescence. AMH could replace an assessment with transvaginal ultrasound during adolescence in terms of evidence for anovulatory accumulation of multiple immature follicles[123,124].

Ultrasound

A recent task force report (recognizing advances in imaging technology) recommends changes to the polycystic ovarian morphology (PCOM) definition. The task force recommends a threshold of ≥25 follicles when the imaging technology affords maximal resolution (*i.e.,* a transducer frequency ≥8 MHz)[125]. In the absence of such technology, clinicians could still use ovarian volume (OV) rather than follicle number for routine daily practice[125]. Current definitions and recommendations for the diagnosis of PCOS have not been updated to include these criteria.

Diagnosis in Adolescents

Normal adolescents might experience irregular menses during puberty that later normalizes, making PCOS diagnoses challenging. Therefore, effectively diagnosing PCOS in adolescents is an area for future development[81,126].

4.5.2

Treatment

Hormonal Contraceptives

Hormonal contraceptives (HC) (*i.e.,* oral contraceptives, patch, or vaginal ring) treat menstrual abnormalities and hirsutism/acne concurrently in women with PCOS. Therefore, we recommend HCs as first-line management[81].

The benefit of oral HCs versus patch or vaginal ring has not been determined, although there might be different risk-benefit ratios among preparations. Some data suggests that extended-cycle HCs (vs. cyclic therapy) may provide better hormonal suppression and prevent ovarian function from rebounding during the period when patients are not taking oral HCs[127].

Metformin in Adults

We do not recommend metformin as first-line treatment for treating obesity or preventing pregnancy complications or cutaneous manifestations. However, we do recommend metformin for women with PCOS who have impaired glucose tolerance or T2DM and unable to modify their lifestyle. For women with PCOS who cannot take or do not tolerate HCs, we recommend metformin as second-line therapy for menstrual irregularity[81].

In women with PCOS, we also recommend metformin for treating hirsutism[128] and cardiovascular risk factors in patients at metabolic risk to prevent CVD and T2DM[129]. Patients should not use metformin for hirsutism, and evidence is lacking regarding metformin treatment for acne[130,131].

Clinicians should consider lifestyle management and weight loss as first-line therapy for women with PCOS who are at increased metabolic risk[129].

Other Medications

Women with PCOS should not take insulin sensitizers, such as inositols or thiazolinediones, due to lack of benefit and safety concerns (respectively). In addition, clinicians should not prescribe statins for hyperandrogenism and anovulation in women with PCOS, unless these women meet current indications for statin therapy[81].

V. PREMATURE OVARIAN FAILURE/PRIMARY OVARIAN INSUFFICIENCY

POF/POI is defined as menstruation ending before a women reaches the age of 40 years[132].

5.1

PREVALENCE AND INCIDENCE

Studies estimate that between 0.9-1.2% of women will have POF/POI[133,134].

5.2

COST BURDEN

There are limited data on the cost burden of POF/POI, aside from the costs associated with VMS listed above.

5.3

DEMOGRAPHIC DIFFERENCES

Hispanics and Blacks have the highest risk of POF/POI, and Japanese-Americans the lowest. Table 16 lists the demographic differences associated with POF/POI[132].

5.4

LIFE EXPECTANCY AND MORTALITY

Women with POF/POI may be at higher risk of early onset of heart disease[135,136] and mortality[16]. In addition, women with POF/POI are likely to spend more years in an estrogen-deficient state, and thus might be at higher risk for osteoporosis and fracture[16,137].

A study by Luborsky *et al.* reported that there appear to be ethnic variations in the prevalence of and health factors associated with POF/POI. However, the cross-sectional design of the study made it impossible to clarify possible cause and effect relationships. We likely need more studies on the health risks of POF/POI[132].

Table 16

Primary ovarian failure by ethnicity.

	CAUCASIAN	HISPANIC	BLACK	JAPANESE	CHINESE	**TOTAL**
PREMATURE MENOPAUSE (<40 YEARS)						
Number	61	21	40	1	3	126
% in ethnic group	1.0	1.4	1.4	0.14	0.5	1.1
95% CI	0.7-1.4	0.8-2.5	1.0-2.1	0.02-1.1	0.1-1.9	0.9-1.3
EARLY MENOPAUSE (AGE 40-45 YEARS)						
Number	177	60	104	6	13	360
% in ethnic group	2.9	4.1	3.7	0.8	2.2	3.1
95% CI	2.4-3.5	3.0-5.6	2.9-4.7	0.3-2.2	1.1-4.3	2.7-3.5
MENOPAUSE (>45 YEARS)						
Number	791	235	352	76	54	1,508
% in ethnic group	13.0	16.1	12.5	10.5	9.1	12.9
95% CI	12.0-14.2	13.9-18.7	11.0-14.1	7.9-13.6	6.6-12.5	12.2-13.7
PREMENOPAUSAL						
Number	5,034	1,140	2,318	644	522	9,658
% in ethnic group	83.0	78.3	82.4	88.6	88.2	82.9
95% CI	81.8-84.2	75.5-80.9	80.5-84.1	85.3-91.2	84.5-91.1	82.0-83.7
TOTAL NUMBER	6,063	1,456	2,814	727	592	11,652

Source: Luborsky *et al.* 2003[132]

Table 17

Multivariate odds ratios and 95 percent confidence intervals for factors associated with premature ovarian failure. * **

		ALL			CAUCASIAN			AFRICAN AMERICAN		
		OR	(95% CI)	*P* value	OR	(95% CI)	*P* value	OR	(95% CI)	*P* value
BMI (kg/m2)		1.03	(1.01-1.06)	0.011	1.01	(0.98-1.07)	0.3	1.04	(1.0-1.1)	0.028
Hormone (not birth control pills)		2.9	(1.9-4.3)	0.00001	3.0	(1.7-5.2)	0.0001	4.5	(2.3-9.1)	0.0001
Disability	none	1.0	(reference)		1.0	(reference)		1.0	(reference)	
	some	0.9	(0.4-1.9)	0.7	1.0	(0.4-2.7)	0.9	0.8	(0.2-3.3)	0.7
	severe	1.4	(0.8-2.5)	0.1	2.2	(1.1-4.6)	0.04	0.9	(0.3-2.2)	0.7
Smoking	never	1.0	(reference)		1.0	(reference)		1.0	(reference)	
	past	0.9	(0.5-1.5)	0.7	1.2	(0.6-2.4)	0.7	0.7	(0.3-1.9)	0.5
	current	1.8	(1.1-2.8)	0.01	2.2	(1.2-4.1)	0.02	1.7	(0.8-3.6)	0.2
Arthritis		1.3	(0.7-2.0)	0.24	1.2	(0.7-2.2)	0.5	1.7	(0.8-3.5)	0.12
Osteoporosis		3.7	(1.9-7.0)	0.0006	5.6	(2.5-12.8)	0.0004	1.4	(0.3-6.6)	0.7

Source: Luborsky *et al.* [132]

Abbreviations: OR, odds ratio; CI, confidence interval.

Notes: *, there are not enough Asian women with POF/POI so they were not included in the study; **, adjusted for ability to pay for basics, education level, site and age at interview.

Among Caucasian women there were significant associations between POF/POI and hormone use, severe disability, smoking, and osteoporosis. However, among African Americans, POF was not associated with osteoporosis, but was associated with female hormone use and higher BMI (Table 17)[132].

5.5
KEY TRENDS ON DIAGNOSIS, TREATMENT, AND HEALTH OUTCOMES

Clinicians should prescribe hormone therapy for women with premature ovarian failure/premature ovarian insufficiency (POF/POI) up to the age of natural menopause, at which point, clinicians should follow the standard guidelines for age-appropriate menopausal women[138,139].

Hormone therapy can confer an excess risk of mortality in women older than 60 years. Estrogen and progestin in combination can increase the risk of breast cancer in women aged 50-59, but this combination also has been associated with a decrease in overall mortality risk. Those women with prolonged menopausal symptoms who are 60-69 years old can have increased cardiovascular risk with continued hormone therapy. Furthermore, there is an increased risk of stroke in women who have had hysterectomies who take estrogen alone[138,139].

VI. DISORDERS OF SEXUAL DEVELOPMENT

6.1
CONGENITAL ADRENAL HYPERPLASIA

CAH refers to a number of autosomal recessive disorders that are associated with abnormal cortisol production[140].

6.1.1
Prevalence and Incidence

CAH is primarily due to 21-hydroxylase deficiency, which is responsible for roughly 95% of cases[140]. Therefore, this Facts and Figures Report focuses primarily on 21-hydroxylase deficiency-associated CAH.
CAH occurs due to mutations in the CYP21A2 gene, which encodes the adrenal steroid 21-hydroxylase enzyme[141]. This enzyme converts 17-hydroxyprogesterone

to 11-deoxycortisol (the precursor for cortisol) and progesterone to 11-deoxycorticosterone (the precursor for aldosterone)[140]. Therefore, CAH results in the inability to make cortisol and aldosterone, leading to adrenal insufficiency and the accumulation of cortisol precursors that, in turn, lead to an excess of T-like hormones (androgens) in both sexes.

The global incidence of CAH in newborns is roughly 1:16,000 to 1:20,000[142]. The incidence in the US is approximately 1:16,000 to 1:18,000[143,144].

There are two types of Classic (or Classical) CAH, salt-wasting (SW) and simple virilizing. The SW form represents 70% of the classic CAH[145]. Untreated infants with SW CAH are at risk for developing life-threatening adrenal crisis from severe cortisol and aldosterone deficiency. Because newborn females with classic CAH undergo prenatal virilization, resulting in sexual ambiguity at birth, they are more likely to get diagnosed in the early days after birth, before the development of an adrenal crisis. In milder or simple virilizing forms of enzyme deficiency, classic CAH might not be recognized and treated early because patients do not develop adrenal insufficiency. Symptoms often occur later, when increased androgen production in affected girls and boys results in rapid growth or early signs of puberty[140].

There is a non-classic form of CAH that is less severe because affected and/or unaffected enzymes are capable of producing enough cortisol and aldosterone to avoid adrenal insufficiency, but the affected enzymes cause a backup of the precursors that result in an excess of T-like hormones. Girls or women present with symptoms of excess T-like hormones, such as unwanted hair growth and severe acne. They might also develop early puberty and/or irregular periods and infertility[140].

While girls with classic CAH usually have ambiguous genitalia (as noted above), boys appear normal. Therefore, in the US and many other countries, clinicians usually screen newborn babies for classic CAH[142]. Screening can greatly reduce morbidity and mortality by identifying the severe, SW classical form of the disease before patients develop adrenal crises, particularly among affected boys[142]. Males with mild CAH, even those with the SW form, might not be diagnosed until later childhood, when they experience growth problems (or when clinicians diagnose CAH in a younger sibling)[146].

6.1.2

Cost Burden of Disease

Precise data is lacking regarding the cost of classic CAH. However, it has been estimated that adults with classic CAH would implement "sick day rules" 171 times over their lifetime, doubling or tripling the use of glucocorticoid and/or injectable steroid therapy. These patients might also need hospital treatment for adrenal crisis approximately 11 times over a lifetime[147]. It has also been estimated that 20% of patients will die of complications associated with adrenal crisis, resulting in loss of 7 years of life on average[147].

Additional health-related complications are associated with excess corticosteroid use over a lifetime[148]. Those with CAH might also experience more illness associated with CVD. In addition, CAH patients using glucocorticoid therapy have nearly twice the risk of bone fractures. Over a lifetime, this will result in an additional 0.8 fractures per CAH patient[147].

6.1.3

Demographic Differences

Classical Congenital Adrenal Hyperplasia

Table 18 shows the estimated incidence of classical CAH for various populations around the world. In the US, based on New York newborn screening program data, the incidence of CAH in the US is lower in black infants and higher in Hispanic infants than non-Hispanic infants[143] (Table 19).

CAH is an autosomal recessive disorder. Therefore, males and females are affected equally. However, in the absence of screening, there are reports of CAH diagnosed

Table 18

Incidence of classical congenital adrenal hyperplasia in various populations.	
REGION	INCIDENCE
US	1:16,000 – 1:18,000
Southwestern Alaska (Yupik Eskimos)	1:282
Italy/France	1:10,866
La Reunion, France	1:2,141
Scotland	1:17,098
New Zealand	1:14,500
Japan	1:15,800
Source: Adapted from Pang *et al.* 1988[149]	

Table 19

Incidence of classical congenital adrenal hyperplasia in various populations.				
	CAH INCIDENCE	TOTAL TESTED (%)	REFERRED (%)	CONFIRMED (%)
Total	1:18,170	1,962,433	2476	108*
Male	1:18,280	1,005,444 (51.2)	1,432 (57.8)	55 (50.9)
Female	1:18,050	956,856 (48.8)	1,044 (42.2)	53* (49.1)
White	1:15,610	874,066 (44.5)	767 (31.0)	56* (51.9)
Native American	–	3,009 (0.2)	1 (0.04)	0
Asian	1:15,250	137,269 (7.0)	104 (4.2)	9 (8.3)
Black	1:24,840	298,057 (15.2)	618 (25.0)	12 (11.1)
Hispanic	1:17,450	331,589 (16.9)	552 (22.3)	19 (17.6)
Source: Pearce *et al.* 2016[143]				

Notes: *, includes false negative cases.

Table 20

Mortality due to salt-wasting congenital adrenal hyperplasia.					
STUDY	SCREENING	BIRTH YEARS	PREVALENCE SW-CAH	F-M RATIO	DEATHS
Sweden					
Thilen and Larson, 1990	No	1969-1986	1:18,600*	2	2.2
Thilen, 2001	Yes	1989-1994	1:12,800*	0	0
Netherlands					
Van der Kamp *et al.* 2001	No	1988-1999	1:13,100	0	0
Van der Kamp *et al.* 2001	Yes	1988-1999	1:13,600	0	0
US					
Brosnan *et al.* 1999	No	1989-1994	1:20,000	0	0
Brosnan *et al.* 1999	Yes	1989-1994	1:21,800	1	1.4
Source: Grosse *et al.*[146]					

Abbreviations: SW, salt wasting; CAH, congenital adrenal hyperplasia.

Notes: *, the two studies from Sweden used different criteria for SW-CAH, with a much stricter criterion used in the earlier study. The overall prevalence of classical CAH was not significantly different.

in more female than male infants (due to ambiguous genitalia present at birth in females). The higher female-to-male ratio of CAH infants without newborn screening is thought to result from unrecognized male infants with CAH who died from adrenal crisis before CAH could be diagnosed[146].

Non-Classic Congenital Adrenal Hyperplasia

Non-classic CAH occurs more frequently in the population, affecting as many as 0.1 to .2 % of Caucasians and 1 to 2% of Ashkenazi Jews[150].

6.1.4

Life Expectancy and Mortality

The SW form affects 70% of cases of classic CAH identified by newborn screening programs. These cases are at risk for failure to thrive, and potentially fatal hypovolemia and shock within the first 4 weeks of life[142,145].

Without newborn screening for CAH, it is estimated that the infant mortality rate for the SW classic CAH is as high as 11.9%, 5-fold higher than the general population[151].

A review by Grosse and Vliet reported that the infant SW CAH mortality rates are estimated between 0 to 1.5% in cohorts with newborn screening[146]. However, due to a lack of global screening, undiagnosed cases, and unrecognized deaths from CAH, the actual SW CAH mortality rate could be higher[146].

6.1.5

Key Trends on Diagnosis, Treatment, and Health Outcomes

Treatment

Feminizing Surgery

Clinicians still debate the optimal timing of surgical procedures, such as vaginoplasty, perineal reconstruction, and clitoroplasty. Vaginal reconstruction might be technically easier in the neonatal period with recent estrogen exposure from the placenta during pregnancy. However, delayed surgery results in a possible lower risk of vaginal stenosis and the need for vaginal dilation[140]. For patients and their families, considerations include the effects on their mental health and the patient's mental health if surgery is delayed; although, the delay would allow for patient participation in decision-making about surgery that might impair sexual function. Currently, pediatric endocrinologists work with families, and also (ideally) with a team of mental health professionals, social workers, and experienced surgeons[152]. There is a great need for studies of outcomes for techniques and other issues, such as optimal timing and how to individualize the approach to the patient.

Pharmacology

Targeted areas for improvement in the treatment of CAH include therapies that will limit the risks associated with exposure to excess corticosteroids. There are current clinical trials of drug therapies for CAH, such as Chronocort®[153] and a solucortef cortisol pump[154]. Both of these medications attempt to limit side effects of excess corticosteroids by utilizing different corticosteroid formulations or delivery methods that are more physiologic.

A second group of drugs reduce the androgen production precursor backup before the enzyme block. In addition to avoiding the use of excess corticosteroids usually needed to treat or control elevated androgens in children, adolescents, and adult women, these new treatments could avoid the need for expensive treatments, such as GnRH agonists to delay early puberty and/or growth hormone treatments to help optimize height potential for children. These drugs include orally administered ATR-101[155] and abiraterone. A recent study reported that 100-250 mg/day of abiraterone acetate combined with replacement hydrocortisone normalized several measures of androgen excess in women who had classic CAH and elevated serum androstenedione[156]. Currently, abiraterone acetate is in the first Phase 1 trial for pre-pubescent children with classic CAH[157].

Prenatal Treatment

For women who have previously had a child born with CAH and become pregnant again with the same partner, the fetus has a one in four chance of also having CAH. Because of the significant impact of ambiguous genitalia for the patient and their families, researchers have studies and developed experimental use of dexamethasone during pregnancy to normalize fetal androgens. The earliest time to perform a genetic test for CAH via chorionic villus sampling would be after excess fetal androgens have already affected fetal genital development in a female (10- to 12-weeks). Therefore, while early dexamethasone treatment is necessary as soon as pregnancy is diagnosed, it introduces the risk of unnecessary fetal and maternal steroid-exposure in infants without CAH and male infants with CAH who would not benefit from this treatment.

There are a few small cohort studies regarding outcomes of prenatal treatment for CAH. Although they generally agree that virilization is reduced in 80-85% of treated pregnancies, future studies are needed before prenatal treatment can be recommended 140.

Fetal dexamethasone treatment could be associated with reduced birth weight or other cognitive or behavioral problems. However, no studies (to date) regarding children with CAH treated with dexamethasone during pregnancy have reported any significant adverse outcomes[140,158-161]. Maternal exposure to dexamethasone steroid treatment can also increase the risk for pregnancy-associated weight gain, hypertension in pregnancy, preeclampsia, and gestational diabetes. Although studies do not report that prenatal dexamethasone steroid treatment is associated with serious health risks for pregnant mothers, there have been reports of side effects that could be attributed to dexamethasone and weight gain; although the reports often did not include a control group[140,158-161].

Health Outcomes

Height

In patients with CAH, elevated androgens in early puberty and prematurely advanced bone age results in lower achieved height than predicted (based on parental heights). Excess corticosteroid exposure might also be responsible for impaired growth[140].

According to a meta-analysis that included data from patients with classic CAH at 18 centers worldwide, mean adult height of was 1.37 SD (10 cm) below the mean. The meta-analysis also reported that patients diagnosed before reaching 1 year of age had increased adult height (0.54 SD)[162]. Adolescents with classic CAH have an attenuated pubertal growth spurt[163]. In spite of this, patients with classic CAH who strictly adhere to thrice-daily medication and monitoring every 3 months can reach approximate target heights[163-165]. Therefore, vigilance regarding treatment is important during the first 2 years of life and during puberty to optimize height. Patients who have NCCAH can also experience reduced adult height, but the height deficit is not as severe as with classic CAH.

Important to note, there is limited evidence that initiation glucocorticoid treatment before puberty will improve adult height in those with NCCAH[166,167]. Similarly, there are limited studies evaluating drugs that enhance growth in children with classic CAH.

We need studies of newer agents that limit androgen excess and/or new strategies utilizing currently available agents to promote growth or delay puberty to help optimize height potential.

Fertility

Studies on fertility in CAH males are inconclusive[168-171]. One study reported substantially reduced fertility (243) and another reported normal fertility[168].

As males with CAH age, there is an increase in testicular adrenal rest tumors, which impairs fertility. Depending on the study population, the reported prevalence of these tumors ranges from 0-94%[168,169,172].

The suppression of gonadotropin secretion by adrenal steroids may also impair fertility in males with CAH if they do not receive adequate doses of glucocorticoids[171]. In addition, men with CAH had fewer steady heterosexual relationships, compared to age-matched controls, which might point to psychosocial factors that affect fertility[170].

In a fertility study of women with CAH conducted by Hagenfeldt et al., pregnancy and delivery rates are significantly lower, despite fertility treatments[173]. The percentage of women with CAH who tried to become pregnant was 30% compared to 66% of controls,; in addition, 50% of women with NCCAH, 30% of women with simple virilizing CAH, and 7% of women with SW CAH had children[173].

Cardiometabolic Risk

A study by Finkielstain *et al.* reported the adolescents and adults with CAH had a high prevalence of overweight, obesity, insulin resistance, high body mass index, and hypertension (elevated blood pressure was more present in classical CAH than non-classical CAH patients). In addition, 18% of adults had MetS[174].

The UK cohort study of adults with CAH (referenced above) reported that CAH patients had a higher body mass index in comparison with matched controls[175]. The reported prevalence of comorbidities included obesity (41%), hypercholesterolemia (46%), and insulin resistance (29%), but there was no comparison to a matched control group for the latter two conditions[175].

Future studies should examine how types of treatment or adjusting treatment protocols could prevent the development of cardiometabolic conditions and risk factors.

Additional Comorbidities

Finkielstain *et al.* reported that 61% of CAH patients had low vitamin D and 37% of CAH adults had low bone mineral density[174]. The UK cohort noted the osteopenia was present in 40% of adults and osteoporosis in 7%[175]. Thirty-two percent of classical CAH and 59% of non-classical CAH women had hirsutism, and 33% of boys and 44% of adult men with classical CAH had testicular adrenal rest tumors (which can impair fertility)[174].

Women with non-classic CAH were more likely to have irregular periods and insulin resistance (similar to women with PCOS)[174]. Insulin resistance is also common in both children with classical CAH (27%) and adults with classical (38%) and non-classical CAH (20%)[174].

Future studies are needed to characterize both the risk factors for co-morbidities and the best treatment regimens to lower the risk for developing health conditions.

Table 21

Anxiety and depression scores as assessed by Hospital Anxiety and Depression Score in patients with congenital adrenal hyperplasia compared with normative data.						
	MALE CLASSICAL CAH (N = 33/62, 51%)	AGE- AND SEX- MATCHED CONTROLS (N = 165)	FEMALE CLASSICAL CAH (N = 65/103, 63%)	AGE- AND SEX- MATCHED CONTROLS (N = 325)	FEMALE NON-CLASSICAL CAH (N = 31/31, 100%)	AGE- AND SEX- MATCHED CONTROLS (N = 155)
HADS ANXIETY SCORE						
Median (IQR)	6.5 (3.3-8.0)	3.0 (2.0-4.3)	9.0 (6.0-12.5)	4.0 (2.0-6.0)	8.0 (5.0-11.0)	4.0 (2.0-7.0)
P [a]		<0.001		<0.001		<0.001
HADS DEPRESSION SCORE						
Median (IQR)	2.0 (1.0-5.5)	2.0 (0.8-4.0)	5.0 (1.0-7.0)	2.0 (1.0-5.0)	4.0 (1.5-9.0)	3.0 (1.0-6.0)
P [a]		0.397		<0.001		0.086
Source: Arlt *et al.* 2010[175]						

Abbreviations: CAH, congenital adrenal hyperplasia; HADS, Hospital Anxiety and Depression Score; IQR, interquartile range.

Notes: For every patient, five sex- and age-matched controls were selected from the normative group (n = 2043). Data are given as mean ± SEM, median, and interquartile range (IQR, 25th–75th percentile). The higher the score, the worse is the perceived impairment of mood.[a], *P* for comparison CAH subgroup vs. sex- and age-matched controls.

Mental Health

Depression

The study of 203 United Kingdom UK adults with CAH (referenced above) also measured anxiety and depression. Scores for anxiety and depression ranged from normal (0-7) to mild (8-10), moderate (11-14), and severe (15-21). Only females with classical and non-classical CAH suffered mild anxiety; neither males nor females suffered from depression (see Table 21)[175].

Psychosocial Problems Specific to Disorders of Sexual Development

The recommendation of existing clinical guidelines[152,176-180] is that patients with psychosocial problems specific to disorders of sexual development (DSD) receive care from interdisciplinary teams that include mental health staff with expertise in managing DSD.

CAH, while a subtype of DSD[180], is not equal to other forms of DSD that have less well-defined outcomes. Mental health clinicians can manage those general psychosocial and psychiatric problems that are not specific to CAH. However, patients who have CAH and are 46,XX are may also have to cope with problems that are more specific to DSD, such as 1) gender assignment at birth when there is marked genital virilization; 2) decisions concerning gender-confirming genital surgery in infancy and early childhood (that is not medically necessitated); 3) medical education and counseling regarding psychosocial prognosis and managing parental distress; and 4) referral to experts for psychological gender evaluation and counseling regarding potential gender reassignment of 46,XX CAH patients seeking gender change[181].

Additional issues specific to DSD that require patient/family counseling include: gender-atypical behavior, preparation for surgery, bisexual and homosexual attractions (increased in 46,XX CAH women, however limited to a minority)[182], social fit, sexual functioning, general quality of life, and concerns about inappropriate curiosity or frank stigmatization by family/peers/lovers regarding gender-atypical features. Ideally, mental health staff with DSD expertise should manage these DSD-related problems using educational websites[183], clinical guidelines[152,176-180,184,185], and long-distance consultation with specialists by e-mail or phone.

6.2 TURNER SYNDROME

6.2.1 Prevalence and Incidence

TS occurs in one in 2,500 live-born females and is defined as the loss of all or part of the X sex chromosome[186].

Roughly half of individuals with TS are of the 45,X karyotype, and do not have the full complement of 46 chromosomes. The other half can have other genetic alterations, including ring X-chromosome formations, deletions along the short or long arm of the X chromosome, or mosaic cell lines comprised of 45,X cells and various combinations of 46,XX, 47,XXX, or other karyotypes. Some individuals have cell lines with Y chromosome material[187].

These chromosomal abnormalities are thought to occur because of the nondisjunction of sex chromosomes during the process of meiosis or during early post-zygotic stages of embryonic development[187].

Girls with TS usually experience ovarian failure, which can occur prior to puberty. This results in decreased sex hormone production and can directly affect neurodevelopment[187].

6.2.2 Life Expectancy and Mortality

There is higher morbidity and mortality seen in TS versus the non-TS population[186]. Some studies suggest that early medical intervention may decrease this higher risk of morbidity and mortality and improve the quality of life of women with TS[188-191]. However, other data indicate that current treatments and detection have little impact on the high morbidity and mortality rates associated with TS, leading to controversy regarding how to best manage several aspects of the disease[186].

Women with TS also display a higher susceptibility to hypertension and stroke, autoimmune thyroiditis, ischemic heart disease, renal and gastrointestinal disease, auditory problems, osteoporosis, and fractures[188,189,191].

A multidisciplinary team of physicians with an interest in the disorder should follow up with all women diagnosed with TS following discharge from pediatric care[188,189,191].

6.2.3 Key Trends on Diagnosis, Treatment, and Health Outcomes

Diagnosis

Features associated with TS (and to what extent they are visible) relate to an individual's specific karyotype and can vary among those with TS[187].

However, common features can include: gastrointestinal issues, diabetes, webbed neck, short stature, hearing loss, lymphedema, POF/POI, hypothyroidism, renal abnormalities, orthopedic disorders, and structural cardiac abnormalities[187].

Table 22

Screening at diagnosis in children and adults with Turner syndrome.
ALL PATIENTS
Hearing evaluation by an audiologist
Cardiovascular evaluation by specialist
TS knowledge evaluation; referral to support groups
Renal ultrasound
Scoliosis/kyphosis evaluation
Growth and pubertal development evaluation
AGES 0–4 YEAR
Hip dislocation evaluation
Eye exam by pediatric ophthalmologist (if age ≥ 1)
AGES 4–10 YEAR
Orthodontic evaluation (if age ≥ 7)
Thyroid function tests (T4, TSH) and celiac screen (TTG Ab)
Educational/psychosocial evaluations
AGE >10
Orthodontic evaluation
Thyroid function tests (T4, TSH) and celiac screen (TTG Ab)
Educational and psychosocial evaluations
BMD (if age ≥ 18 year)
Evaluation of ovarian function/estrogen replacement
LFTs, FBG, lipids, CBC, Cr, BUN
Source: Bondy *et al.* 2007[192]

Abbreviations: BUN, Blood urea nitrogen; CBC, complete blood count; Cr, creatinine; FBG, fasting blood glucose; LFTs, liver function tests; T4, thyroxine; TTG Ab, tissue transglutaminase antibody; TSH, thyroid-stimulating hormone.

Table 23

Ongoing monitoring in Turner syndrome.
ALL AGES
Blood pressure annually
Cardiological evaluation as indicated
ENT and audiology every 1-5 year
GIRLS <5 YEAR
Social skills at age 4-5 year
SCHOOL AGE
Celiac screen every 2-5 year
Liver and thyroid screening annually
Dental and orthodontic as needed
Educational and social progress annually
OLDER GIRLS AND ADULTS
Liver and thyroid screening annually
Age-appropriate evaluation of pubertal development/ psychosexual adjustment
Fasting lipids and blood sugar annually
Celiac screen as indicated
Source: Bondy *et al.* 2007[192]

Table 24

Cardiovascular screening and monitoring algorithm for girls and women with Turner syndrome.
SCREENING: ALL PATIENTS AT TIME OF DIAGNOSIS
Blood pressure annually
Cardiological evaluation as indicated
ENT and audiology every 1-5 year
Comprehensive exam including blood pressure in all extremities
Evaluation by cardiologist with expertise in congenital heart disease
Clear imaging of heart, aortic valve, aortic arch, and pulmonary veins
• Echocardiography is usually adequate for infants and young girls
• MRI and echo for older girls and adults
MONITORING: FOLLOW-UP DEPENDS ON CLINICAL SITUATION
For patients with age-appropriate blood pressure and an apparently normal cardiovascular system
• Reevaluation with imaging at timely occasions (e.g., at transition to adult clinic, before attempting pregnancy, or with appearance of hypertension). Girls that have only had echocardiography should undergo MRI when old enough to cooperate with the procedure
• Otherwise, imaging about every 5-10 year
For patients with cardiovascular pathology, treatment and monitoring determined by cardiologist
Source: Bondy *et al.* 2007[192]

Abbreviations: MRI, magnetic resonance imaging.

There are many areas of uncertainty regarding the diagnosis and management of TS. However, clinicians routinely use detailed healthcare checklists and screening guidelines to detect known complications associated with TS[186].

Treatment

Clinicians should treat growth failure as early as possible. However, puberty should not be delayed to promote statural growth[186,192].

Clinicians should also collect baseline cardiac and serial magnetic resonance imaging data to identify any findings that are unique to TS and that might point to an increased risk of aortic dissection[186,192].

Clinicians should advise patients with defined cardiovascular defects in regards to pregnancy and exercise[192].

Clinicians should start administering hormone replacement therapy at the normal age of puberty and counsel patients regarding long-term health risks associated with TS (Table 25). After 1-2 years, clinicians should add progesterone compounds in order to prevent unopposed estrogen stimulation of the uterus[186].

Clinicians should evaluate TS individuals in early childhood to identify potential learning disorders. Caregivers should discuss POF/POI and advise on the importance of estrogen treatment for both feminization and bone health during teen and adult years. Clinicians

Table 25

Age of final menstrual period by race.		
AGE (YEAR)	AGE-SPECIFIC SUGGESTIONS	COMMENTS
10-11	Clinicians should monitor for spontaneous puberty by Tanner staging and FSH levels.	Low-dose estrogen treatment may not inhibit GH-enhanced growth in stature.
12-13	If no spontaneous development and FSH elevated, clinicians should begin low-dose E2.	Equivalent initial E2 doses include: 0.2-0.4 mg/month, depot (IM); 6.25 µg daily, transdermal; 0.25 mg daily, by mouth.
12.5-15	Clinicians should gradually increase E2 dose over about 2 year (e.g., 14, 25, 37, 50, 75, 100, 200 µg daily via patch) to adult dose.	Usual adult daily doses include: 100-200 µg transdermal E2, 2-4 mg oral E2, 1.25-2.5 mg CEE.
14-16	Clinicians should begin cyclic progesterone treatment after 2 year of estrogen or when breakthrough bleeding occurs.	Oral micronized progesterone is the best option at present; the usual adult dose is 200 mg/d on d 16-25 of monthly cycle or 100 mg on a daily of 3-month cycle.
14-35	Clinicians should continue full doses at least until age 30 because normally estrogen levels are highest between age 15-30 years.	Some women may prefer using oral or transdermal contraceptive for HRT; Clinicians should monitor endometrial thickness.
35-50	Clinicians should administer the lowest estrogen dose that provides full protection against osteoporosis or vasomotor instability—0.625 mg CEE, 1 mg E2, or equivalent.	Clinicians should monitor osteoporosis risk factors, diet, exercise; obtain BMD and begin regular screening mammography by age 45 years.
>50	Clinicians should make decisions on estrogen use based on same considerations as for other postmenopausal women.	New HRT options are appearing, and these recommendations may need updating in near future.
Source: Bondy *et al.* 2007[192]		

Abbreviations: CEE, conjugated equine estrogens; d, day; E2, estradiol; EE2, ethinyl estradiol; HRT, hormone replacement treatment; BMD, bone-mineral density; GH, growth hormone.

should also advise TS patients of the broad phenotypic spectrum regarding the disease and that TS individuals have experienced good quality of life in recent years[192].

All TS patients should be regularly monitored for hearing aortic enlargement, hypertension, dyslipidemia, diabetes, and thyroid function[192].

There are no recommendations for preserving fertility in TS patients due to the reduced follicle pool. Thus, TS women might consider egg donation, gestational surrogacy, or adoption[193].

Future research might make it possible for TS women to conceive with their own oocytes. However there is still a high risk of maternal and fetal morbidity and mortality associated with TS and pregnancy[194].

Clinicians should provide counseling and screening for all TS women who are considering pregnancy[194].

Table 26

Studies on growth hormone treatments and adult height in Turner syndrome.						
REFERENCE	HGH-TREATED PATIENTS	INITIAL HGH DOSE (MG/KG/WK)	MEAN TREATMENT DURATION (Y) (MEAN +/- SD/ MEAN)	MEAN AGE OF START (Y) (MEAN +/- SD)	HEIGHT SDS AT BASELINE (MEAN +/- SD)	HEIGHT SDS GAIN (FROM BASELINE TO ADULT HEIGHT)
Ross *et al.* 2011[195]	382	0.357[g]	4.54	8.62 +/- 4.03	-2.58 +/-0.9	(0.43. 0.89, 0.92)[h]
Linglart *et al.* 2011[196]	43[b] 18[c]	0.245 0.35	4 4	2.6 +/- 0.6 2.6 +/- 1.3	-2.6 +/- 0.6 -1.6 +/- 0.4	0.98[d] 0.98[d]
Stephure *et al.* 2005 [197a]	61	0.30[f]	5.7 +/- 1.6	10.3 +/- 1.8	-.02 +/- 0.9	1.6 +/- 0.6[e]
Davenport *et al.* 2007[198]	45	0.35	2.0	1.98 +/-1.01	-1.42 +/-1.0	1.1 +/- .06
Blum *et al.* 2009[199]	158	0.31 +/- 0.09	5.6 +/- 2.3	10.9 +/-3.1	-2.9 +/-0.8	1.2 +/- .08
Source: Table adapted from Chacko *et al.* 2012[200]						

Abbreviations: SDS, standard deviation score; SD, standard deviation; hGH, human growth hormone; y, year.

Notes: [a], The Canadian Growth Hormone Advisory Committee;[b], standard-dose group (0.035 mg/kg/d);[c], low-dose group (0.05 mg/kg/d);[d], height SDS at start of GH treatment - 2.33 +/- 0.73 and height SDS at end of study - 1.35 +/- 0.86;[e], age-specific TS;[f], GH dose was given 6 days per week;[g], GH dose 0.051 +/- 0.0098,[h], duration of hGH therapy: 1 year, <3 years, and >3 years, respectively.

6.3

KLINEFELTER SYNDROME

Klinefelter syndrome (KS) is a sex chromosome abnormality characterized by supernumerary sex chromosomes. Those who have KS typically possess additional X chromosome, which result in a 47,XXY karyotype. As is true with TS, there are a number of variations on this karyotype, such as those including additional X chromosomes (e.g., 48,XXXY) and mosaicism with 46,XY[187].

Data suggests that boys with KS have similar sex hormone concentrations as normal boys until puberty beings, although some researchers have recently challenged this notion[187].

T production decreases midpuberty, resulting in various degrees of hypergonadotropic hypogonadism, which might contribute to some characteristics observed in KS patients, which include small testes, tall stature, azoospermia, and symptoms related to hypogonadism (including female habitus and body-hair distribution and gynaecomastia[187].

6.3.1

Incidence and Prevalence

The first paper on KS, published in 1942, called it "not uncommon"[223]. Later, after technology made it possible for large-scale chromosome analyses in newborns, the actual prevalence surfaced with a wide range of variation.

A 2013 review by Groth *et al.*[222] reported that KS is the most frequent male chromosomal aberration, with a prevalence of approximately 150 per 100,000 live-born males[222,224].

Morris *et al.* proposed that the prevalence of KS is increasing[225], and also that the prevalence may differ between populations.

6.3.2

Life Expectancy and Mortality

Data from epidemiological studies in KS in the UK and Denmark indicate that KS individuals will live approximately 1.5 to 2 years less than comparable non-KS individuals. Increased mortality in KS results from a range of disorders, including: cerebrovascular disease, diabetes, epilepsy, lung diseases, and intestinal vascular insufficiency[210,211,213,217,220,221,226].

Table 27

Studies on combined estrogen and growth hormone therapy and adult height gain in Turner syndrome.					
STUDY	ORAL ESTROGEN TREATMENT	N	COHORT	CHRONOLOGICAL AGE) BASELINE (Y) (MEAN +/- SD)	ADULT HEIGHT ATTAINED IN SD (AVERAGE GAIN OVER PROJECTED HEIGHT, CM)
Ross *et al.* 2011[201]	Ultralow dose E2: Age 5-8 y; 25 ng/kg/d Age 8 y: 50 ng/kg/d Age >12 y: escalating doses of 100 ng/kg/d - 800 ng/kg/d	A; 33 B: 37 C: 34 D: 33	A: Double PL B: E2 + PL C: hGH (.01 mg/kg x 3/wk) + PL D: E2+ hGH	A: 7.5 +/- 2.3 B: 8.5 +/- 2.7 C: 8.2 +/- 2.6 D: 9.3 +/- 2.5	A: -2.81 +/- 0.85 B: -3.39 +/- 0.74 C: -2.29 +/- 1.10 D: -2.10 +/- 1.02
Quigley *et al.* 2002[202]	Childhood low dose E2: Age 8 - <10 y: 25-50 ng/kg/d Age 10 - <12 y: 67-100 ng/kg/d Age >12 y: 160-200 ng/kg/d	A: 15 B: 24 C: 38 D: 22	A: hGh (0.27 mg/kg/wk) + PL B: hGH (0.27 mg/kg/wk) + E2 C: hGH (0.36 mg/kg/wk) + PL D: hGH (0.36 mg/kg/wk) + E2 E: Double PL	A: 9.7 +/- 2.7 B: 9.6 +/- 2.7 C: 9.8 +/- 2.9 D: 9.9 +/- 2.9	A: -2.2 +/- 1.0 B: -2.7 +/- 1.0 C: -1.9 +/- 1.0 D: -2.2 +/- 1.0
Van Pareren *et al.* 2003[203]	Childhood low dose E2: 5 µg of 17b-E2 (roughly 0.05 µg/kg/d) in 1st 2 y, 7.5 µg/kg/d in 3rd y, 10 µg/kg/d thereafter	A: 19 B: 20 C: 21	A: hGH (4 IUm2) B: hGH (1st y 4 IUm2; thereafter 6 IUm2) C: hGH (1st y 4 IUm2, 2nd y 6 IUm2, thereafter 6 IUm2) (E2 treatment in each group [A-B] was started after the subject reached age 12 y)	A: 6.5 +/- 1.9 B: 6.9 +/- 2.3 C: 6.5 +/- 2.4	A: -1.6 +/- 1.0 B: -0.7 +/- 1.0 C: -0.6 +/- 1.0
Chernausek *et al.* 2000[204]	Conjugated E2: .03 mg/d x 6 mo, then increased to 0.625 mg/d	A: 26 B: 29	hGH (0.375 mg/kg/wk) A: E2 starts at 15 y B: E2 starts at 12 y	A: 9.54 +/- 0.9 B: 9.6 +/- 1.0	A: (8.4 +/- 4.3 cm) B: (5.1 +/- 3.6 cm)
Source: Table adapted from Chacko *et al.* 2012[200]					

Abbreviations: d, day; E2, estradiol; mo, month; N, number; SD, standard deviation; TS, turner syndrome; PL, placebo; y, year.

In Danish populations, the risk of breast cancer in KS individuals was not increased. However there was a large increase in the risk of mediastinal tumors 219. In addition, there was a 70% increased risk of being hospitalized, with the highest risk of hospitalization associated with congenital malformations and psychiatric, endocrine, and metabolic disorders[210,213].

In the UK study mentioned above, 163 deaths occurred among 646 KS patients with a 47,XXY constitution. Diabetes and diseases of the cardiovascular, respiratory and digestive systems were primarily responsible for the increased mortality. In addition, this cohort saw a significantly increased risk of lung cancer and breast cancer incidence and mortality[191].

Table 28

Reported physiological and cognitive–behavioral features of Turner syndrome, Klinefelter syndrome, and XYY syndrome.	
	KLINEFELTER SYNDROME
CARDIOVASCULAR	Deep vein thrombosis, mitral valve prolapse
REPRODUCTIVE	Micro-orchidism, gynaecomastia, hypogonadism, infertility
ONCOLOGICAL	Breast cancer, mediastinal germ-cell tumors
NEUROLOGICAL	Seizures; tremor; non-specific motor impairments, including hypotonia
PULMONARY	Risk of pulmonary embolism
INTELLIGENCE	Normal FSIQ* (5-10 points below siblings), PIQ higher than VIQ
VISUOSPATIAL	Data not available
SOCIAL	Impairments in assessment of trustworthiness of faces and classification of emotions and difficulties with social withdrawal, communication, and emotion regulation
EXECUTIVE FUNCTION	Similar to findings for KS, particularly response- inhibition impairments
OTHER ENDOCRINE	Insulin resistance or diabetes, MetS, hypothyroidism
ORTHOPEDIC	Tall stature, osteoporosis (related to hypogonadism)
IMMUNOLOGICAL	Systemic lupus erythematosus
RENAL	Data not available
LYMPHATIC	Data not available
LANGUAGE	Deficits in oral fluency, written language, reading comprehension, verbal memory
SPEECH	Delay in early childhood
ARITHMETIC	Mixed evidence: some reports of arithmetic problem-solving deficits by contrast with normal mathematic-achievement scores compared with controls
PSYCHIATRIC	Increased risk for ADHD, reading disability or dyslexia, autism- spectrum disorders, depression, schizophrenia
	Source: Hong *et al.* 2014[187]

Abbreviations: KS, Klinefelter syndrome; FSIQ, full-scale intelligence quotient; MetS, metabolic syndrome; VIQ, verbal intelligence quotient. PIQ; performance intelligence quotient; ADHD, attention-deficit hyperactivity disorder.

Notes: *, Normal FSIQ is defined as around 100.

TURNER SYNDROME	ADULT HEIGHT ATTAINED IN SD (AVERAGE GAIN OVER PROJECTED HEIGHT, CM)
Aortic coarctation, bicuspid aortic valve, increased risk of aortic dissection, hypertension	Data not available
Gonadal dysgenesis, delayed or absent pubertal development, infertility	Possible macro-orchidism
Data not available	Data not available
Conductive hearing loss (childhood), sensorineural hearing loss (adulthood)	Seizures, tremor, hypotonia
Data not available	Risk of asthma
Normal FSIQ* (5-10 points below siblings), VIQ higher than PIQ	Similar to findings for KS
Deficits in visuomotor skills, mental rotation, spatial orientation	Data not available
Impairments in face recognition and classification of negative emotions, parent-rated difficulties with social reciprocity and communication (for children)	Similar to findings for KS
Impairments in attention, processing speed, working memory, cognitive flexibility, and sequencing or planning	Similar to findings for KS
Hypothyroidism	Data not available
Short stature, characteristic craniofacial features, scoliosis, osteoporosis (related to hypogonadism)	Tall stature, macrocephaly
Autoimmune thyroiditis, coeliac disease	Data not available
Collecting system malformations, horseshoe kidney	Data not available
Lymphoedema in infancy and early childhood	Data not available
Reports of hyperlexia	Similar to findings for KS, although deficits can be more severe
Possible speech issues related to hearing loss	Similar to findings for KS
Difficulties with calculation and subitising	Similar to findings for KS
Risk for ADHD and dyscalculia; equivocal evidence of autism-spectrum disorders	Risk of ADHD, reading disability or dyslexia, and autism-spectrum disorders; case reports of schizophrenia

6.3.3

Key Trends on Diagnosis, Treatment, and Health Outcomes

KS tend to present with language-related disorders. Speech delays can exist in early development, and by early school age (roughly 5-13 years), KS children can exhibit prominent language-related learning disabilities, such as difficulties with writing and reading. Up to 80% of those with KS meet learning disorder criteria (related mainly to language). School-age children often need special-needs education and speech therapy services, and usually experience persistent difficulties throughout adulthood[187].

There are mixed results regarding treatment for neurocognitive and psychiatric symptoms. Most data come from studies examining T-replacement therapies. Some studies suggest T treatment might improve verbal fluency, concentration, motor function, and general wellbeing. However, we need more placebo-controlled prospective studies to better address this question[187].

Table 29

Abnormalities associated with Klinefelter syndrome and their frequencies.

FEATURE	FREQUENCY
Infertility (adults)[205,206]	91-99
Small testes (bi-testicular size <6 ml)[205]	>95
Increased gonadotropin levels[206]	>95
Azoospermia (adults)[206]	>95
Learning disabilities (children)[207]	>75
Decreased T levels[206]	63-85
Decreased facial hair (adults)[206]	60-80
Decreased pubic hair (adults)[206]	30-60
Gynecomastia (adolescents, adults)[205,207,208]	38-75
Delay of speech development (children)[207]	40
Increased height (prepubertal, adults)[207,209]	30
Abdominal adiposity (adults)[210]	~50
MetS (adults)[210]	46
Osteopenia (adults)[211,212]	5-40
T2DM (adults)[210,213]	10-39
Cryptorchidism[205,207]	27-37
Decreased penile size (children)[207]	10-25
Psychiatric disturbances (children)[207]	25
Congenital malformations, cleft palate, inguinal hernia[214]	~18
Osteoporosis (adults)[212]	10
Mitral valve prolapse (adults)[215,216]	0-55
Breast cancer (adults)[217,218]	Increased risk (~50 fold)
Mediastinal cancers (children)[219]	Increased risk (~500 fold)
Fractures[220,221]	Increased risk (2-40 fold)

Source: Groth *et al.* 2013[222]

Abbreviations: T, testosterone; MetS, metabolic syndrome, T2DM, type 2 diabetes mellitus.

Table 30

Prevalence of Klinefelter syndrome (47,XXY) in studies of newborns, spontaneous abortions, prenatal diagnoses, and perinatal deaths.			
	YEARS OF DATA COLLECTION	NUMBER OF CASES 47,XXY	PREVALENCE PER 1,000 (95% CI) 47, XXY
NEWBORN STUDIES			
Early	1967-1971	41	1.09 (0.80-1.47)
Late	1971-1988	58	1.72 (1.33-2.23)
PRENATAL DIAGNOSES SERIES			
Amniocentesis series all women >35	1976-1981	112	3.08 (2.54-3.71)
CAD series	1980-2006	542	
SPONTANEOUS ABORTIONS			
Culture	1975-2005	17	4.2 (2.4-6.7)
CVS	1987-2005	10	13.1 (6.3-24.0)
PERINATAL DEATHS		3	4.6 (0.9-13.4)
Source: Morris *et al.* 2008[225]			

Table 31

Some available testosterone preparations and suggested dosages for adults with Klinefelter syndrome.				
SUBSTANCE	BRAND NAME (MANUFACTURER)	SUGGESTED DOSE	ROUTE OF ADMINISTRATION	FORMAT
T-undecanoate	Andriol© (Organon: Oss, The Netherlands)	120-160 mg/d TID	Oral	40-mg capsule
T-undecanoate	Nebido© (Schering: Berlin, Germany)	750 mg every 9-16 wk	Intramuscular	750 mg injection
T	Androgel©[1] 1% (Abbvie Pharmaceuticals)	50 mg to 100 mg, daily	Skin	Gel
T	Androgel©[2] 1.62% (Abbvie Pharmaceuticals)	20.25 mg to 81 mg, daily	Skin	Gel
T	Testim©[3] (Endo Pharmaceuticals, Malvern, PA)	50 mg/d	Skin	Gel
T	Axiron©[4] (Lilly, Indianapolis IN)	30-120 mg/d	Skin	Gel
T	Fortesta©[5] (Endo Pharmaceuticals, Malvern, PA)	10-70 mg/d	Skin	Gel
T	Implants© (Organon: Oss, The Netherlands)	400-800 mg every 4-6 mo	Subcutaneous	Pellets
T	Striant© (Columbia Laboratories: Livingston, NJ)	60 mg/d	Buccal	Buccal adhesive
T	Androderm©[6] (Allergan USA, Inc. Irvine, CA)	2-6 mg/d	Skin	Transdermal patch
Source: Table adapted from Groth *et al.* 2012[222]				

Abbreviations: d, day; wk, week; TID, three times a day; mo, month; UK, United Kingdom. T, testosterone.

Notes: [1], Abbvie[49]; [2], Abbvie[49]; [3], Endo[227]; [4], Lilly[228]; [5], Endo[227]; [6], Allergan[229]

Table 32

Outpatient program for patients with Klinefelter syndrome.
AT BASELINE
Fasting glucose, lipids, and HbA1c
Thyroid status, hemoglobin, hematocrit
Information about the syndrome
Physical examination including BP, height, weight, waist, testes, gynecomastia, and varicose veins
Sex hormones: T, estrogen, SHBG, FSH, and LH
Confirmation of karyotype, if necessary
Initiation of androgen treatment (injections, transdermal, or oral)
Questions about well-being, physical activity, energy, sexual activity, libido, socioeconomic situation
Bone densitometry (DEXA scan) and vitamin D status, p-calcium
Echocardiography if deemed necessary
Discussion of fertility issues often resulting in referral to a fertility clinic
Consider referral to plastic surgeon for correction of gynecomastia
Consider referral to psychologist
ANNUAL (EVERY 3 MONTHS INITIALLY)
Questions about well-being, physical activity, energy, sexual activity, libido
Physical examination including BP, height, weight, waist, and gynecomastia
Fasting glucose, lipids, and HbA1c
Sex hormones: total or FT, estrogen, SHBG, FSH, and LH (nadir values)
Thyroid status, hemoglobin, hematocrit
EVERY 2ND YEAR OR UP TO EVERY 10TH YEAR
Bone densitometry (DEXA scan) and vitamin D status, p-calcium
Source: Groth *et al.* 2012[222]

Abbreviations: HbA1c, glycosylated hemoglobin; BP, blood pressure; DEXA, dual-energy x-ray absorptiometry; SHBG, sex hormone-binding globulin; FSH, follicle-stimulation hormone and LH, luteinizing hormone; T, testosterone; FT, free testosterone.

Table 33

Major issues in Klinefelter syndrome and potential solutions.	
PROBLEM	POTENTIAL SOLUTION
Late diagnosis and nondiagnosis	Examination of dried blood spots with new molecular genetic techniques
Will early diagnosis lead to better outcome?	Prospective screening studies with health technology assessment with reference to medical ethics
Poor learning in school	Early diagnosis leading to better learning schemes and perhaps early treatment with T
Effect of T	Randomized clinical trials with T and placebo with study of numerous variables
Poor socioeconomic outcome	Improvements in schooling and possibly early treatment
T2DM	Randomized clinical trials with T and placebo
Increased morbidity	Improvements in adult care with multidisciplinary approach
Infertility	Improved understanding of pathophysiology of germ cell loss through animal models; better testicular sperm extraction techniques
Source: Groth *et al.* 2012[222]	

Abbreviations: T, testosterone; T2DM, type 2 diabetes mellitus.

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