Testosterone Testing in Adult Men

G. Steven Hammond, PhD, MD, MHA
Chief Medical Officer
WA Department of Corrections
March 20, 2015

Background

- Testicular function is normally regulated by the hypothalamo-pituitary-testicular (HPT) axis
- Measurement of serum testosterone levels in men has been used for many years in clinical evaluation of HPT function
- Pathological conditions that disrupt HPT function may result in hypogonadism and androgen deficiency
Hypogonadism - Classic vs. Putative

- Most well-defined clinical conditions of hypogonadism result in frank androgen deficiency with markedly decreased androgen levels
  - Primary hypogonadism such as with congenital abnormalities, destructive orchitis, or trauma
  - Secondary hypogonadism such as occurs with panhypopituitarism or mass effect of pituitary or suprasellar tumor
  - In these syndromes testosterone levels are often very low, (i.e., ½ to 1/10 of the lower limit of normal)
- In syndromes marked by severe androgen deficiency, testosterone replacement therapy yields well recognized benefits
  - Improvement in libido and sexual function
  - Maintenance/improvement of muscle strength and lean body mass
  - Maintenance/improvement of bone density and strength

Hypogonadism - Classic vs. Putative, cont.

- In recent years research has been conducted to study “late onset hypogonadism”, i.e., a putative state of androgen deficiency associated with aging, characterized by lower testosterone levels, decreased libido and sexual function, and physical frailty
  - No clear etiology or pathogenesis of “late onset hypogonadism” has been established – other than simply an effect of aging and association with chronic illness
  - Benefits of testosterone therapy are less well established in the setting of “late onset hypogonadism”
  - Signals of risk, particularly for cardiovascular morbidity, of testosterone replacement therapy in older men have emerged

Testosterone Treatment - New and Old

- For many years, standard testosterone replacement therapy (TRT) was by intramuscular injection of depot-form testosterone every 1-4 weeks
- In the past 15 years transdermal testosterone gel preparations have been marketed; the price of the newer transdermal testosterone gel preparations is 10-20-fold (or more) higher than the older depot forms for intramuscular injection
- Since the transdermal gels have been marketed, mass media has been used to publicize “low T”, a putative health condition characterized by lower testosterone levels, particularly in middle-aged and older men
  - Health benefits of testosterone treatment for age-related “low T” have not been demonstrated
  - Testosterone treatment of age-related “low T” is not FDA-approved and pharmaceutical companies are not allowed to claim benefits of testosterone treatment for age-related “low T”
  - However, pharmaceutical companies are allowed to support “Disease Awareness Campaigns” about “low T” that include encouraging men to talk to their doctors about it and have their testosterone level checked
Recent Trends in Testing & Treating

In this setting there has been marked increase in testosterone testing and prescribing of testosterone products in the USA and to a much lesser extent in the United Kingdom (see next slide).
Serum testosterone levels in men decline with age, such that if “normal” levels are determined on the basis of the distribution of serum testosterone levels in younger men, a substantial proportion of older men will be reported by clinical laboratories as having “low” testosterone levels (see following slides), and thus may be uncritically diagnosed with “hypogonadism”

- The serum total testosterone level is an imprecise test, the value being subject to inter-individual variability of sex hormone binding globulin levels, reducing signal-to-noise ratio in and near the normal range
- Age-related decline in serum testosterone levels is particularly pronounced for free testosterone levels
- Compounding the problem, when serum testosterone levels are measured later in the day than 10 AM they are lower than at the ~8 AM diurnal peak
- “Low T” is not an accepted medical diagnosis
What Is the Clinical Significance of Lower Testosterone Levels in Older Men?

- Without clinical correlates of known hypogonadal syndromes, low testosterone levels in older men are unlikely to be diagnostic of a known clinico-pathological condition
  - Given the known decline in testosterone levels in older men it may be more appropriate to develop age-related reference ranges
- Late onset hypogonadism is not a well-established clinical diagnosis; it is a putative diagnosis in the research setting
  - Neither ICD-9 nor ICD-10 recognize a specific diagnosis of “late onset hypogonadism”
- Given growing concerns about safety of testosterone treatment in older men, caution is warranted in diagnosing and treating late onset hypogonadism
Testosterone Testing

Evidence of Cardiovascular Risk of Testosterone Treatment in Older Men

- An RCT on testosterone replacement therapy (TRT) for men over 65 with mobility limitations was terminated early because of increased CV adverse events associated with TRT – Basaria et al., NEJM 2010
  - TRT treatment course was 6 months, or less if terminated due to early termination of the trial
  - TRT raised hematocrit and thromboxane levels and decreased HDL cholesterol levels

- A retrospective national cohort study of 8709 US veterans with low testosterone levels showed a hazard ratio of 1.29 (1.04-1.58) for all-cause mortality or hospitalization for MI or CVA – Vigen et al., JAMA 2013

Evidence of Cardiovascular Risk of Testosterone Treatment in Older Men, cont.

- A retrospective cohort study of 55,593 men in a large healthcare database showed an increased incidence of MI within 90 days after TRT was prescribed, compared to the year prior to the prescription, ratio 1.36 (1.03-1.81) - Finkle et al., PLOS ONE 2014
  - Effect progressively greater in older men (> 65)
  - Effect also seen in men < 65 with history of heart disease
  - No increase in MI among 167,279 patients prescribed sildenafil or tadalafil
Testosterone Testing

Evidence of Cardiovascular Risk of Testosterone Treatment in Older Men, cont.

- A systematic review and meta analysis of 27 placebo controlled RCTs of TRT lasting >12 weeks that reported CV events, including 2994 subjects, mostly middle-aged or older, showed OR 1.54 (1.09-2.18) for all CV events and OR 1.61 (1.01-2.56) for serious CV events – Xu et al., BMC Medicine 2013
  - Pharmaceutical industry-funded RCTs (13 of 27) showed OR 0.89 (0.50-1.60) vs. non-pharmaceutical industry-funded RCTs (14 of 27) showing OR 2.06 (1.34-3.17)
  - Funnel plot suggested publication bias (i.e. less reported results of increased CV events with TRT)
  - Trim and fill adjustment for publication bias raised the calculated OR
  - Previous, smaller meta analyses that did not show statistically significant increase in CV events with TRT did show trends in this direction

Testosterone Testing

Concerns Voiced at FDA

- Safety concerns prompted the FDA to convene an advisory panel in September, 2014 to address concerns about CV risks of testosterone treatment in older men
  - “There was overwhelming support that the use of TRT should exclude men with age-related testosterone decline. The panel voted 20 to 1 in favor of revising the current indication by limiting TRT to those with classic hypogonadism, and including in the label the potential for cardiovascular risk... and a statement that both the safety and efficacy of TRT in age-related hypogonadism had not been established.” – Garnick, JAMA 2/10/15
  - As of 3/1/15 the FDA has not added a warning about increased CV risk associated with TRT
G. Steven Hammond, Chief Medical Officer
WA – Department of Corrections

March 20, 2015

Testosterone Testing

PEBB/UMP

Testosterone Tests & Treatments, 2010-2013

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<th></th>
<th>2010</th>
<th>2011</th>
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Testosterone Supplementation

|     | Paid $ Injections | $12,862     | $14,497    | $21,807    | $24,623           | $73,789         |
|     | Paid $ Testosterone Pharmaceuticals | $782,150   | $972,202   | $896,193   | $1,153,242        | $3,744,245      |
|     | Total Paid for Treatments (PEBB Prim.) | $794,972   | $987,199   | $853,988   | $1,177,865        | $3,818,034      |
|     | Avg Paid per pt (PEBB Primary) | $744       | $841       | $636       | $749              | $1,460          |
|     | Avg Paid per pt (PEBB Primary - Men) | $754       | $812       | $642       | $754              | $1,438          |

Testosterone Test Patients by Age & Gender, 2010-2013

Testosterone Treatment Patients by Age, Men only, 2010-2013
Testosterone Testing

Agency Medical Director Concerns

- Safety = High
- Efficacy = High
- Cost = High

Testosterone Testing

Agency Medical Director Concerns

- Testosterone testing without additional clinical findings of hypogonadism is highly vulnerable to false positive findings of “hypogonadism”, especially in older men, especially when reference ranges appropriate to men in their 20s are used for older men
  - Such testing exposes patients to risk of inappropriate diagnosis of “hypogonadism” and prescribing of testosterone therapy with attendant risks, particularly of adverse cardiovascular events
  - Efficacy of testosterone treatment in the absence of clear signs and symptoms of hypogonadism is unproven
  - Inappropriate testosterone testing is wasteful in itself and also likely leads to wasteful (and risky) prescribing
Current State Agency Policy

- Medicaid and PEBB – covered without restrictions
- L&I and DOC – prior authorization required

Agency Recommendation

Cover with Conditions:

- In setting of clinical findings well correlated with definable HPT axis pathology (objective physical examination or laboratory/imaging evidence of pituitary or primary gonadal dysfunction; osteoporosis; sexual dysfunction)
  - E.g., gynecomastia or testicular atrophy; hyperprolactinemia; laboratory evidence of hypopituitarism; pituitary macroadenoma; osteoporosis; sexual dysfunction
  - Agencies can further delineate
- “Fasting” (8 AM – 10 AM) blood draw for initial assessment of possible hypogonadism
Questions?

More Information
www.hca.wa.gov/hta/Pages/testosterone.aspx
Order of Scheduled Presentations:

Testosterone Testing

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No requests to provide public comment on the technology review were received.
Testosterone Testing

Clinical Expert

Alvin M. Matsumoto, MD, FACP

Professor, Department of Medicine, University of Washington School of Medicine,
Acting Head, Division of Gerontology & Geriatric Medicine, Department of Medicine, University of Washington School of Medicine
Acting Chief, Gerontology Section, Department of Veterans Affairs Puget Sound Health Care System
Director, Board of Directors, Seattle Institute for Biomedical and Clinical Research
Director, Special Fellowship Program in Advanced Geriatrics, Department of Veterans Affairs Puget Sound Health Care System
Director, Clinical Research Unit, Department of Veterans Affairs Puget Sound Health Care System
Associate Director for Clinical, Geriatric Research, Education and Clinical Center, Department of Veterans Affairs Puget Sound Health Care System
Disclosure

Any unmarked topic will be considered a "Yes"

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<td>2. Equity interests such as stocks, stock options or other ownership interests.</td>
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<td>3. Status or position as an officer, board member, trustee, owner.</td>
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<td>4. Loan or intellectual property rights.</td>
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<td>5. Research funding.</td>
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If yes, list name of organizations that relationship(s) are with and for #6, describe other relationship:

AbbVie - Testosterone and placebo gel for multi-center study

GlaxoSJKline - Dutasteride and placebo, and research support for investigator-initiated study

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<td>funding sources (e.g. member dues, governmental/taxes, commercial products or services, grants from industry or government).</td>
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If yes to #7, provide name and funding sources:

________________________________________________________________________________________

________________________________________________________________________________________

If you believe that you do not have a conflict but are concerned that it may appear that you do, you may attach additional sheets explaining why you believe that you should not be excluded.

I certify that I have read and understand this Conflict of Interest Form and that the information I have provided is true, complete, and correct as of this date.

[Signature] [Date 8/18/2014] [Print Name]

For questions contact: Christine Masters
Health Technology Assessment
PO Box 42712
Olympia, WA 98504-2712
360-725-5126
CURRICULUM VITAE

ALVIN M. MATSUMOTO, MD, FACP

1. PERSONAL DATA
   Date of Birth: March 22, 1949
   Place of Birth: Honolulu, Hawaii, United States
   Citizenship: United States
   Marital Status: Married, 3 Children

2. EDUCATION
   Medical School:
   1971-75 University of Washington School of Medicine, Seattle, WA, M.D., June, 1975
   College:
   1967-71 University of Washington, Seattle, WA, B.S., Chemistry, with Distinction, Magna Cum Laude, June, 1971

3. POSTGRADUATE TRAINING
   Fellowship:
   1979-82 Senior Fellow in Medicine/Endocrinology and Metabolism, University of Washington School of Medicine, Veterans Administration Medical Center, Seattle, WA
   Residency:
   1978-79 Chief Resident in Internal Medicine, United States Public Health Service Hospital, University of Washington School of Medicine, Seattle, WA
   1976-78 Resident in Internal Medicine, University of Washington Affiliated Hospitals, Seattle, WA (Traditional Program)
   Internship:
   1975-76 Intern in Internal Medicine, University of Washington Affiliated Hospitals, Seattle, WA (Traditional Program)

4. FACULTY POSITIONS HELD
   1997- Professor, Department of Medicine, University of Washington School of Medicine, Seattle, WA
   1989-97 Associate Professor, Department of Medicine, University of Washington School of Medicine, Seattle, WA
   1983-89 Assistant Professor, Department of Medicine, University of Washington School of Medicine, Seattle, WA
   1978-79 Acting Instructor of Medicine, University of Washington School of Medicine, Seattle, WA

5. DEPARTMENTAL AND HOSPITAL POSITIONS HELD
   2012- Acting Head, Division of Gerontology & Geriatric Medicine, Department of Medicine, University of Washington School of Medicine, Seattle, WA
2010- Acting Chief, Gerontology Section, Department of Veterans Affairs Puget Sound Health Care System, Seattle, WA
2007- Director, Board of Directors, Seattle Institute for Biomedical and Clinical Research (SIBCR), Seattle, WA
2001- Director, Special Fellowship Program in Advanced Geriatrics, Department of Veterans Affairs Puget Sound Health Care System, Seattle, WA
2000- Director, Clinical Research Unit, Department of Veterans Affairs Puget Sound Health Care System, Seattle, WA
1993- Associate Director for Clinical, Geriatric Research, Education and Clinical Center, Department of Veterans Affairs Puget Sound Health Care System Seattle, WA
1993-00 Chief, Gerontology, Department of Veterans Affairs Puget Sound Health Care System, Seattle, WA
1993-98 Associate Chief of Staff for Geriatrics and Extended Care, Department of Veterans Affairs Puget Sound Health Care System, Seattle, WA
1993-00 Director, Geriatric Evaluation and Management Unit, Department of Veterans Affairs Puget Sound Health Care System, Seattle, WA
1986- Staff Physician, Geriatric Research, Education and Clinical Center, Department of Veterans Affairs Medical Center, Seattle, WA
1983-86 Research Associate, Veterans Administration Medical Center, Seattle, WA
1981-83 Associate Investigator, Veterans Administration Medical Center, Seattle, WA
1978-79 Staff Physician, Primary Care Department, United States Public Health Service Hospital, Seattle, WA

6. HONORS AND AWARDS
2015 Chair, Laureate Awards Committee, The Endocrine Society
2014-18 Associate Editor, Journal of Clinical Endocrinology and Metabolism
2014- Appointed, Chair-Elect, Laureate Awards Committee, The Endocrine Society
2013- Appointed, Co-Chair, Partnership for the Accurate Testing of Hormones (PATH)
2013 Outstanding Reviewer Recognition Award, The Journal of Clinical Endocrinology & Metabolism, The Endocrine Society
2012 Sidney H. Ingbar Distinguished Service Award, The Endocrine Society
2010- Appointed, Member, Partnership for the Accurate Testing of Hormones (PATH) (previously known as Coalition for Quality Testing), The Endocrine Society, American Society for Bone and Mineral Research Representative
2008- Appointed, Member, Scientific Advisory Board, Partnership for Clean Competition (United States Anti-Doping Agency, United States Olympic Committee, National Football League, Major League Baseball and other professional sports leagues)
2008 Elected as Fellow, American College of Physicians
2008-10 Appointed as Clinical Science Chair, Bridge Grant Review Committee, The Endocrine Society
2007-11 Appointed as Chair, Hormone Foundation Committee, The Endocrine Society
2007- Member, Board of Directors, Seattle Institute for Biomedical and Clinical Research
2006 Robert G. Petersdorf Teaching Award, VA Puget Sound Health Care System
2005-11 Appointed as Chair of the Men’s Health Task Force, The Endocrine Society
2005-07 Appointed as Program Chair, American Society of Andrology, 32nd Annual Meeting 2007
2005 The Endocrine Society & Pfizer, Inc. International Award for Excellence In Published Clinical Research in The Journal of Clinical Endocrinology & Metabolism in 2004
2000-01 Appointed as Clinical Chair, The Endocrine Society Annual Meeting 2001
1999 Elected to Western Association of Physicians
1997-00 Elected to Executive Council, American Society of Andrology
1995 Elected to Western Society for Clinical Investigation
1988 Endocrine Society Travel Award to attend 8th International Congress of Endocrinology, Kyoto, Japan, July 17-23, 1988.
1983-86 Veterans Administration Research Career Development Award: Research Associate
1981-83 Veterans Administration Research Career Development Award: Associate Investigator
1974 Alpha Omega Alpha (Medical Honorary)
1971-72 Medical Scientist Training Fellowship (Institutes of General Medical Sciences, National Institutes of Health)
1971 Phi Beta Kappa
1971 Phi Lambda Upsilon (National Chemistry Honorary)
1970-71 Dow Chemical Company Scholarship, University of Washington
1970-71 University Students Club Scholarship, University of Washington
1970 President's Certificate of High Scholarship, University of Washington
1970 National Science Foundation Summer Fellowship-Undergraduate Research Participation Program, Department of Chemistry, University of Washington
1969-70 Dow Chemical Company Scholarship, University of Washington
1969 National Science Foundation Summer Fellowship-Undergraduate Research Participation Program, Department of Chemistry, University of Washington
1968-69 Dow Chemical Company Scholarship, University of Washington
1967-68 Seattle Japanese American Citizens League Scholarship

7. BOARD CERTIFICATION
Nov 1981 Diplomate, American Board of Endocrinology and Metabolism (64276)
Sep 1978 Diplomate, American Board of Internal Medicine (64276)
May 1976 Diplomate, National Board of Medical Examiners

8. CURRENT LICENSE TO PRACTICE MEDICINE
Mar 1977 State of Washington (0015733)

9. PROFESSIONAL ORGANIZATIONS
Western Association of Physicians
Western Society for Clinical Investigation
American Federation for Clinical Research
Chairman, West Coast Endocrine Club 1986
The Endocrine Society
Associate Editor, Journal of Clinical Endocrinology and Metabolism, 2014-2018
Chair, Laureate Awards Committee, 2015
Chair-Elect, Laureate Awards Committee, 2014
Co-Chair, Partnership for the Accurate Testing of Hormones (PATH) (previously known as Coalition for Quality Testing), 2013-present
Member, Laureate Awards Committee, 2013-2017
Working Group, Primary Care Clinical Practice Guidelines for Testosterone Therapy in Men with Androgen Deficiency Syndrome, 2013- present
Working Group, Guys’ Guide to Testosterone (formerly the Testosterone Tour): an Interactive Online Tool for Men Interested in Testosterone Therapy, Hormone Health Network, 2012-2013
Working Group, Myth vs. Fact: Male Menopause, Hormone Health Network, 2012-2013
Partnership for the Accurate Testing of Hormones (PATH) (previously known as Coalition for Quality Testing), American Society for Bone and Mineral Research Representative, 2010-present
Task Force, Androgen Deficiency Performance Improvement Module, 2011-2013
Task Force, Evidence-Based Guidelines for Testosterone Therapy in Adult Men with Androgen Deficiency Syndromes, Revision 2010
Member, Testosterone Therapy Performance Measure Set Committee, 2008-2010
Clinical Science Chair, Bridge Grant Review Committee, 2008-2010
Chair, Hormone Foundation Committee, 2007-2011
Chair, Men’s Health Task Force, 2007-present
Hormone Foundation Committee, 2005-2007
Task Force, Evidence-Based Guidelines for Evidence-Based Guidelines for Testosterone Therapy in Adult Men with Androgen Deficiency Syndromes, 2004-2006
Meetings & Educational Programs Committee, 2002-2005
Program Committee, Clinical Endocrinology Update, 2002
Annual Meeting Steering Committee, 1998-2001
Clinical Chair, Annual Meeting Steering Committee ENDO 2001
American College of Physicians
Fellow, 2008
Society for the Study of Reproduction
American Society of Andrology
Member, Awards Committee 2012-2014
Member, Program Committee 2006-2008
Chair, Program Committee 2005-2007
Member, Program Committee 2003-2005
Chair, Local Arrangements Committee 2002
Member, Program and Post-Graduate Course Committee 2001-2002
Member, Executive Council 1997-2000
Member, Post-Graduate Course Committee 1999-2000
Member, Program Committee 1997-1999
Chair, Nominating Committee 1997-1998
Nominating Committee 1995-1997
Chairman, Post-Graduate Committee 1992-1993
Program Committee 1992-1993
Awards Committee 1992-1994
American Society for Bone and Mineral Research
Representative, Partnership for the Accurate Testing of Hormones (PATH) (previously known as Coalition for Quality Testing), The Endocrine Society, 2010-present
Representative, CDC Testosterone Measurement Consensus Conference, 2010
American Geriatrics Society
Gerontological Society of America
King County Medical Society

10. TEACHING RESPONSIBILITIES
A. Students
Fourth-Year Students:
Teach clinical geriatric medicine while attending on Transitional Care Unit (TCU) at VAPSHCS (Chronic Care Clerkship-Geriatrics, Conjoint 694). 4 weeks yearly. August 1-15, 2014
Transitional Care Unit (TCU) Teaching Conferences on Core Topics at VAPSHCS. August 1-15, 2014
“Vitamin D deficiency”, August 4, 2014
“Osteoporosis in older adults: not just a problem in older postmenopausal women”, August 12, 2014

B. Housestaff/Fellows
Teach clinical geriatrics to R-l's while attending on Transitional Care Unit (TCU) at VAPSHCS. 4 weeks yearly. August 1-15, 2014
Transitional Care Unit (TCU) Teaching Conferences on Core Topics at VAPSHCS. August 1-15, 2014
“Vitamin D deficiency”, August 4, 2014
“Osteoporosis in older adults: not just a problem in older postmenopausal women”, August 12, 2014
Present at Geriatric Grand Rounds, “Osteoporosis in men: not just a problem in postmenopausal women”, Harborview Medical Center, August 30, 2013
Present at Chief of Medicine Rounds, VAPSHCS, Seattle, WA, “Male hypogonadism”, October 9, 2013
Present at Geriatric Medicine/Psychiatry Fellows Conference, VAPSHCS, Seattle, WA, “Thyroid disorders in older adults”, January 29, 2014
Present at GRECC, Associate Directors for Clinical Teleconference, “VA Clinical Demonstration Projects at VA Puget Sound Healthcare System, GRECC”, February 10, 2014
Present at GRECC Research Seminar, VAPSHCS, Seattle, WA, “Testosterone treatment in older men: where are we now?”, February 10, 2014
Present at SPORE Clinical Studies Seminar, Fred Hutchinson Cancer Research Center, “Important issues and state of knowledge in male hormone hormone replacement therapy: whoa T for low T”, February 27, 2014
Present at Northwest Geriatric Education Center (NWGEC), Geriatric Health Series, Seattle, WA, “Thyroid disorders in older adults”, May 13, 2014
C. Mentorship of Research Trainees (last 5 years)
Mara Roth (Lang), MD, 7/07-6/10, Assistant Professor, Division of Metabolism, Endocrinology and Nutrition, Department of Medicine, University of Washington School of Medicine, Seattle, WA
Christin Snyder, MD, 7/07-6/10, Private Practice, Endocrinology & Metabolism, Portland, OR
Lianne Hirano, MD, 7/09-6/10, Acting Instructor, Division of Gerontology & Geriatric Medicine, University of Washington
Serena Lo, MD, 7/10-6/12, Special Fellowship Program in Advanced Geriatrics, Senior Fellow, Division of Gerontology & Geriatric Medicine, Department of Medicine, University of Washington School of Medicine, School of Medicine, Seattle, WA
Katya Rubinow, MD, 7/11-6/13, Assistant Professor, Division of Metabolism, Endocrinology and Nutrition, Department of Medicine, University of Washington School of Medicine, Seattle, WA
Lori Cooper, MD, 7/12-6/14, Senior Fellow, Division of Metabolism, Endocrinology and Nutrition, Department of Medicine, University of Washington School of Medicine, Seattle, WA
Katherine Ritchey, DO, 7/14-present, Senior Fellow, Division of Gerontology & Geriatric Medicine, Department of Medicine, University of Washington School of Medicine, Seattle, WA
Beverly Kocarnik, MD, 9/14-present, Senior Fellow, Division of Metabolism, Endocrinology and Nutrition, Department of Medicine, University of Washington School of Medicine, Seattle, WA

D. Director, Department of Veterans Affairs, Special Fellowship Program in Advanced Geriatrics. This is a national two-three year fellowship for research training in gerontology, geriatric medicine and geriatric psychiatry. As Director, I serve as academic career mentor for these fellows.

Serena Lo, MD, 7/10-6/12, Senior Fellow, Division of Gerontology & Geriatric Medicine, Department of Medicine, University of Washington School of Medicine
Deborah Huang, MD, 8/10-7/13, Senior Fellow, Division of Gerontology & Geriatric Medicine, Department of Medicine, University of Washington School of Medicine
Lori Cooper, MD, 7/13-present, Senior Fellow, Division of Metabolism, Endocrinology and Nutrition, Department of Medicine, University of Washington School of Medicine, Seattle, WA
Katherine Ritchey, DO, 7/14-present, Senior Fellow, Division of Gerontology & Geriatric Medicine, Department of Medicine, University of Washington School of Medicine, Seattle, WA
Beverly Kocarnik, MD, 9/14-present, Senior Fellow, Division of Metabolism, Endocrinology and Nutrition, Department of Medicine, University of Washington School of Medicine, Seattle, WA

E. Continuing Medical Education
Present at Geriatric Grand Rounds, “Osteoporosis in men: not just a problem in postmenopausal women”, Harborview Medical Center, August 30, 2013
Present at Northwest Geriatric Education Center (NWGEC), Geriatric Health Series, “Thyroid disorders in older adults”, University of Washington, Seattle, WA, May 13, 2014

Present at Skyline at First Hill [Resident Lecture Series], “Testosterone and aging”, Seattle, WA, June 26, 2014


Present at Endocrine Essentials Live for Primary Care, The Endocrine Society, “Low testosterone: when to treat”, Manhattan Beach, CA, November 15, 2014

Present at Endocrine Essentials Live Pro, The Endocrine Society, “Diagnosis and management of hypogonadism”, Manhattan Beach, CA, November 15, 2014


Present at Controversies in the Diagnosis and Treatment of Male Hypogonadism Symposium, “Testosterone measurements to confirm the diagnosis of male hypogonadism”, The Endocrine Society 97th Annual Meeting, San Diego, CA, March 7, 2015

Present at Meet-the-Professor Session, “Assessing and managing testosterone abnormalities in all your patients”, American College of Physicians Annual Meeting Internal Medicine 2015, Boston, MA, April 30, 2015

11. EDITORIAL RESPONSIBILITIES

Associate Editor, Journal of Clinical Endocrinology and Metabolism, January, 2014-December, 2018


Outstanding Reviewer Recognition Award, The Journal of Clinical Endocrinology & Metabolism, The Endocrine Society 2013

Editor, UpToDate, Male Reproductive Endocrinology, January, 2007-present

Member, Faculty of 1000 (F1000) Biology, June, 2006-present

Editorial Quality Review Board, UpToDate, Endocrinology, January, 2003-December, 2006

Editorial Board, American Journal of Medicine, January, 2002-December, 2004


Editorial Board, Endocrine Reviews, January, 1999-December, 2002


12. SPECIAL NATIONAL RESPONSIBILITIES

Member, New Geriatric Research, Education and Clinical Center Review Committee, Office of Geriatrics and Extended Care, Department of Veterans Affairs, March 13-14, 2014, Washington, DC.

Member, Laureate Awards Committee, The Endocrine Society, 2013-2017; Chair-Elect, 2014-2015; Chair, 2015-2016

Member, Task Force, Primary Care Clinical Practice Guidelines for Testosterone
Therapy in Men with Androgen Deficiency Syndrome, The Endocrine Society, 2013-present

Co-Chair, Steering Committee, Partnership for the Accurate Testing of Hormones (PATH), formerly the Coalition for Quality Testing, The Endocrine Society, 2013-2015

Working Group, Guys’ Guide to Testosterone (formerly the Testosterone Tour): an Interactive Online Tool for Men Interested in Testosterone Therapy, Hormone Health Network, 2012-2013

Working Group, Myth vs. Fact: Male Menopause, Hormone Health Network, 2012-2013

Member, Androgen Deficiency Performance Improvement Module Task Force, The Endocrine Society, 2011-2013

Member, Expert Working Group, World Anti-Doping Agency, “Medical Information to Support Therapeutic Use Exemption Committees Decision on Androgen Deficiency/Male Hypogonadism”, 2011

Member, Steering Committee, Partnership for the Accurate Testing of Hormones (PATH), formerly the Coalition for Quality Testing, The Endocrine Society, American Society for Bone and Mineral Research Representative, 2010-present

Member, Scientific Advisory Board, Partnership for Clean Competition (United States Anti-Doping Agency, United States Olympic Committee, National Football League, Major League Baseball and other professional sports leagues), 2008-present

Member, Therapeutic Use Exemption Review Committee, United States Anti-Doping Agency, 2008-present

Clinical Science Chair, Bridge Grant Review Committee, The Endocrine Society, 2008-2010

Chair, Hormone Foundation Committee, The Endocrine Society, 2007-2011

Chair, Men’s Health Task Force, The Endocrine Society, 2005-present

Member, Hormone Foundation Committee, The Endocrine Society, 2005-2007

Chair, Program Committee, American Society of Andrology, 32nd Annual Meeting 2007

Member, US Anti-Doping Agency (USADA), Research Policy Advisory Committee (RPAC), 2005-2008

Member, NICHD Reproductive Medicine Network (RMN) Review Committee, NICHD, NIH, 2004-2005

Member, The Endocrine Society Guidelines Committee, Task Force: Evidence-Based Guidelines for the Use of Testosterone Therapy in Adult Men with Androgen Deficiency Syndromes, 2004-2006

Planning Committee, VA Cooperative Study Program CSP #561 entitled “Evaluation of an Electronic Chart Reminder for Prevention and Treatment of Glucocorticoid-Induced Osteoporosis” (Principal Proponent, RA Adler, Richmond VA Medical Center) 2005

Member, Meetings & Educational Programs Committee, The Endocrine Society, 2002-2005

Clinical Chair, The Endocrine Society Annual Meeting, ENDO 2001

Member, Population Research Subcommittee, NICHD Initial Review Group, NICHD, NIH, July 1, 1996-June 30, 2000

Member, Executive Council, American Society of Andrology, 1997-2000

Member, NICHD Special Review Committee, NIH, September 4-6, 1996

Member, Reproductive Endocrinology Study Section, NIH, July 1, 1990-June 30, 1994

Chairman, Special Reproductive Endocrinology/Biology Study Section, October 6, 1991

Member, Special Reproductive Endocrinology/Biology Study Section, June 18, 1991; October 4, 1992
13. SPECIAL LOCAL RESPONSIBILITIES

VAPSHCS Chair, Research Education Committee, Seattle Institute of Biomedical and Clinical Research (SIBCR), 2012-present
VAPSHCS Member, Clinical Executive Board, 2010-present
VAPSHCS Member, VAPSHCS Research Task Force, 2010
VAPSHCS Member, Research Space Subcommittee, 2009-2012
VAPSHCS Director, Board of Directors, Seattle Insitute for Biomedical and Clinical Research (SIBCR), 2007-present
VAPHSCS Chair, Research Conflict of Interest Subcommittee, 2006-2013
VAPHSCS Chair, Clinical Research Unit Advisory Committee, 2000-present
UW Member, General Clinical Research Center Education Committee, 2005-2009
VAPSHCS Member, Research Space Committee, 2005-2007
UW Senator, University of Washington Faculty Senate, 2003-2005
VAPSHCS Member, Research and Development Education Committee, 2003-2009
VAPSHCS Chair, Institutional Animal Care and Use Committee, 2001-2002
VAPSHCS Member, Research and Development Committee, 2001-2002
VAPSHCS Director, VA Special Fellowship Program in Advanced Geriatrics, 2000-present
VAPSHCS Member, Geriatrics and Extended Care Operations Committee, 1998-2000
VAPSHCS Member, Primary Care Council, 1997-2000
VAPSHCS Chairman, Geriatrics and Extended Care Advisory Board, 1995-1998
VAPSHCS Member, Clinical Executive Board, 1994-1998
VAPSHCS Chairman, Research and Development Committee, 1998-1999
VAPSHCS Member, Research and Development Committee, 1997-1998
VAPSHCS Member, Research Space Subcommittee, 1997-1999
VAMC Member, Health Care Reform Advisory Committee, 1994-1995
VAMC Chairman, Extended Care Committee, 1994-1995
VAMC Member, Research Space Subcommittee, 1993-1995
VAMC Chairman, Research and Development Committee, 1992-1993
VAMC Member, Research Space Subcommittee, 1988-1990
VAMC Chairman (1988) and Member, Scientific Review and Evaluation Committee, 1986-1988
VAMC Member, Research and Development Committee, 1984-1986
VAMC Member, Animal Studies Subcommittee, 1983-1985

14. RESEARCH FUNDING

A. ACTIVE GRANT SUPPORT

1. National Institutes of Health

Co-Investigator, Executive Committee, Cognitive Function Working Group Leader (11.5% effort, PI Peter Snyder) NIA/NINDS grant proposal entitled, “Testosterone Trial”, $30,701,066 (5/15/09-4/30/15) UO1 AG030344.

Site PI, Alvin M. Matsumoto (8% effort), $2,178,864 5/15/09-4/30/15)

The aim of this grant is to investigate the effects of testosterone treatment
on physical function and performance, sexual function, cognitive function and vitality/quality of life in older men with clinical manifestations of hypogonadism and unequivocally low serum testosterone levels, in a multicenter, randomized, double-blind, placebo-controlled study.

Site PI, Alvin M. Matsumoto, Cardiovascular Sub-Study, $136,480 (5/15/10-4/30/15)

This a sub-study of The Testosterone Trial to investigate the effects of testosterone treatment on coronary artery calcification by CT angiography and cardiovascular risk factors, including visceral adiposity.

Co-Investigator (2.5% effort) of project entitled, “Male hormonal contraception and metabolic health” (Project 4, Project Leader, Stephanie T. Page), $1,948,298 (7/1/12-6/30/17), $428,488 (7/1/12-6/30/13) in NICHD Cooperative Contraceptive Research Center (U54 HD42454) grant entitled, “Male contraception research center grant”, P.I. William J. Bremner, University of Washington School of Medicine, $9,624,759 (9/17/12-6/30/17) U54 HD42454.

The aim of this project is to investigate the effects of hormonal contraceptive regimens on risk factors for cardiovascular disease in healthy normal men.

Co-Investigator (5% effort, PI Molly Shores) of project entitled, “Adverse Events Associated with Testosterone Treatment in Hypogonadal Men”, $360,000 (8/12/12-7/31/14) RO1 AG 042934.

The aim of this project is to assess the effects of testosterone treatment of hypogonadal men on combined cardiovascular events and incident aggressive prostate cancer using the national VA database.

Consultant (0% effort, PI Stephanie Page) of project entitled “Dose-response relationships between circulating and intraprostatic androgens in men”, $1,621,917 (7/1/10-6/30/15), $215,962 (7/1/12-6/30/13) R01 AG037603.

The aim of this grant is to determine the dose-response effects of testosterone administration alone or in combination with a 5 alpha-reductase inhibitor (to block conversion of testosterone to dihydrotestosterone) and adrenal androgen precursors on intraprostatic androgen concentrations and cell-specific gene expression in older men.

2. Other

P.I. (10% effort) of GlaxoSmithKline Investigator-Initiated Grant entitled, “Testosterone Replacement and Dustasteride Effectiveness (TRADE)” $474,900 (6/1/04-12/31/14) GSK #000272.

The aim of this study is to determine the effect of testosterone in combination with the 5 alpha-reductase inhibitor, dutasteride, compared to testosterone alone on prostate size, symptoms of benign prostatic hyperplasia (BPH), intraprostatic steroid hormone concentrations and global prostate gene expression in hypogonadal men with mild to moderate BPH.
B. **PENDING GRANT SUPPORT**

None

15. **BIBLIOGRAPHY (**5 most significant publications**)

A. **PEER REVIEWED PUBLICATIONS OF ORIGINAL WORK**


23. Sheckter CB, McLachlan RI, Tenover JS, Matsumoto AM, Burger HG, deKretser DM, Bremner WJ. Stimulation of serum inhibin concentrations by gonadotropin releasing-


32. Gruenewald DA, Matsumoto AM. Age-related decrease in serum gonadotropin levels and gonadotropin-releasing hormone gene expression in the medial preoptic area of male rats is dependent upon testicular feedback. Endocrinology 1991;129:2442-2450. PMID: 1935778


38. Bagatell CA, Matsumoto AM, Christensen RB, Vale WW, Rivier JE, Bremner WJ. Comparison of a gonadotropin releasing hormone antagonist plus testosterone versus testosterone alone as potential male contraceptive regimens. J Clin Endocrinol Metab 1993;77:427-432. PMID: 8345047


46. Gruenewald DA, Marck BT, Matsumoto AM. Fasting-induced increases in food intake and neuropeptide Y gene expression are attenuated in aging male Brown Norway rats. Endocrinology 1996;137:4460-4467. PMID: 8828508
47. Abkowitz JL, Hume H, Yancik SA, Bennett LG, **Matsumoto AM**. Stem cell factor serum levels may not be clinically relevant. Blood 1996;87:4017-4018. PMID: 8611739


51. Tian H, Hammer RE, **Matsumoto AM**, Russell DW, McKnight SL. The hypoxia-responsive transcription factor EPAS1 is essential for catecholamine homeostasis and protection against heart failure during embryonic development. Genes Dev 1998;12:3320-3324. PMID: 9808618


53. Rasmussen DD, Boldt BM, Wilkinson CW, Yellon SM, **Matsumoto AM**. Daily melatonin administration at middle age suppresses male rat visceral fat, plasma leptin, and plasma insulin to youthful levels. Endocrinology 1999;140:1009-1012. PMID: 9927336


55. Anawalt BD, Bebb RA, Paulsen CA, Bremner WJ, **Matsumoto AM**. Lower dosage levonorgestrel and testosterone combinations effectively suppress spermatogenesis and circulating gonadotropin levels with fewer metabolic effects than higher-dosage combinations. J Androl 1999;20:407-414. PMID: 10386821


58. Wolden-Hanson T, Mitton DR, McCants RL, Yellon SM, Wilkinson CW, **Matsumoto AM**, Rasmussen DD. Daily melatonin administration to middle-aged rats suppresses body
weight, intra-abdominal adiposity, and plasma leptin and insulin independent of food intake and total body fat. Endocrinology 2000;141:487-497. PMID: 10650927


72. Sohn EH, Wolden-Hanson T, Matsumoto AM. Testosterone-induced changes in arcuate nucleus cocaine-amphetamine regulated transcript (CART) and NPY mRNA are attenuated in old compared to young male Brown Norway rats: contribution of testosterone to age-related changes in CART and NPY gene expression. Endocrinology 2002;143:954-963. PMID: 11861518


79. Brot MD, Szczypka MS, Reavell R, Marck BT, Matsumoto AM, Palmiter RD. Neonatal 6-hydroxydopamine administration to mice is fatal. Dev Neurosci 2002;24:531-538. PMID: 12697991


83. Herbst KL, Anawalt BD, Amory JK, Matsumoto AM, Bremner WJ. The male contraceptive regimen of testosterone and levonorgestrel significantly increases lean mass in healthy young men in 4 weeks but attenuates a decrease in fat mass induced by testosterone alone. J Clin Endocrinol Metab 2003;88:1167-1173. PMID: 12629101


113. Page ST, Amory JK, Anawalt BD, Irwig MS, Brockenbrough AT, Matsumoto AM, Bremner WJ. Testosterone gel combined with depomedroxyprogesterone acetate is an effective male hormonal contraceptive regimen and is not enhanced by the addition of a GnRH antagonist. J Clin Endocrinol Metab 2006;91:4374-4380. PMID: 16940442


121. Travison TG, O'Donnell AB, Araujo AB, Matsumoto AM, McKinlay JB. Cortisol levels and measures of body composition in middle aged and older men. Clin Endocrinol (Oxf) 2007;67:71-77. PMID:17466009

123. Brambilla DJ, O'Donnell AB, **Matsumoto AM**, McKinlay JB. Lack of seasonal variation in serum sex hormone levels in middle-aged to older men in the Boston area. J Clin Endocrinol Metab 2007;92:4224-4229. PMID: 17684044


129. Shores MM, Kivlahan DR, Sadak TI, **Matsumoto AM**. A randomized, double-blind, placebo-controlled study of testosterone treatment in hypogonadal older men with subthreshold depression (dysthymia or minor depression). J Clin Psychiatry 2009;70:1009-1016. PMID: 19653976


133. Bhasin S, Cunningham GR, Hayes FJ, **Matsumoto AM**, Snyder PJ, Swerdloff RS, Montori VM. Testosterone therapy in men with androgen deficiency syndromes: an


143. Rubinow KB, Vaisar T, Tang C, Matsumoto AM, Heinecke JW, Page ST. Testosterone replacement therapy in hypogonadal men alters the HDL proteome but does not affect


B. INVITED REVIEWS, BOOK CHAPTERS AND EDITORIALS


27. Matsumoto AM. "Andropause"-Are reduced androgen levels in aging men physiologically important? West J Med 1993;159:618-620. PMID: 8279174


68. Bhasin S, **Matsumoto AM**. Patient information page from The Hormone Foundation. Patient guide to testosterone therapy in adult men with androgen deficiency syndromes. J Clin Endocrinol Metab, 2010;95:2p following 3085. PMID: 20540171


76. Shores MM, **Matsumoto AM**. Testosterone, aging and survival: biomarker or deficiency. Curr Opin Diabetes Endocrinol Metab 2014;21:209-216. PMID:24722173


C. OTHER PUBLICATIONS (NON-REFEREED JOURNALS AND LETTERS, BOOKS PUBLISHED, VIDEOS, SOFTWARE.

1. **Matsumoto AM**. Clinical studies using luteinizing hormone releasing hormone [Video]. University of Washington Instructional Media Services, 692829, 3/8/88.

2. **Matsumoto AM**. Use and abuse of anabolic steroids [Video]. University of Washington Instructional Media Services, Master #C66-79-68, 10/24/90.


D. MANUSCRIPTS SUBMITTED


E. PUBLISHED ABSTRACTS [# accepted for presentation]


34

#18. Gross KM, Matsumoto AM, Southworth MB, Bremner WJ. The pattern of luteinizing hormone releasing hormone (LHRH) administration controls the relative secretion of follicle stimulating hormone (FSH) and luteinizing hormone (LH) in man. Clin Res 1984;32:74A.


#20. Gross KM, Matsumoto AM, Southworth MB, Bremner WJ. The pattern of luteinizing hormone releasing hormone (LHRH) administration controls the relative secretion of follicle stimulating hormone (FSH) and luteinizing hormone (LH) in man. Clin Res 1984;32:266A.


#32. Myers JS, Matsumoto AM, Bremner WJ. Basal and clomiphene citrate (CC) stimulated secretion of luteinizing hormone (LH) and testosterone (T) in healthy young and elderly men. Clin Res 1986;34:430A.


#44. **Matsumoto AM**. Is high dosage testosterone enanthate an effective male contraceptive agent? Clin Res 1988;36:125A.


#51. Haley NR, **Matsumoto AM**, Eschbach JW. Low testosterone (T) levels increase in male hemodialysis patients (HDP) treated with recombinant human erythropoietin (rHuEpo). Kidney Int 1989;35:193.

#52. Dahl KD, **Matsumoto AM**. High dosage testosterone (T) administration increases bioactive/immunoreactive (B/I) ratio and alters molecular heterogeneity of circulating

#54. **Gruenewald DA, Matsumoto AM.** Age-related decrease in gonadotropin-releasing hormone (GnRH) gene expression in the medial preoptic area (MPOA) of the male rat. Clin Res 1990;38:97A. (Western Society for Clinical Investigation Travel Award)

#55. **Gruenewald DA, Matsumoto AM.** Age-related decrease in number of neurons expressing the gonadotropin-releasing hormone (GnRH) gene in the medial preoptic area (MPOA) of the male rat. Abstract No. 475. The Endocrine Society, 72nd Annual Meeting, Atlanta, GA, June 20-23, 1990. (Endocrine Society Travel Award)

#56. **Matsumoto AM, Bremner WJ.** Hormonal regulation of spermatogenesis in man. International Conference on Perspectives in Primate Reproductive Biology, Bangalore, India, February 3-7, 1990, Proceedings, p. 21. (Oral presentation in Symposium on Regulation of Testicular Function by AM Matsumoto)


#58. **Matsumoto AM, Dahl KD.** Evidence for relative baseline testicular dysfunction men who become azoospermic versus oligospermic during high dosage testosterone (T) administration. Xith North American Testis Workshop, Montreal, Canada, April 24-27, 1991. Abstract No. 92 (Poster presentation by A.M. Matsumoto)


#62. **Bagatell CJ, Christensen RB, Matsumoto AM, Bremner WJ.** Comparison of a gonadotropin releasing hormone antagonist plus testosterone (T) versus T alone as potential male contraceptive regimens. Clin Res 1992;40:94A.

#63. **Gruenewald DA, Hess DL, Wilkinson CW, Matsumoto AM.** Altered testicular steroidogenesis in aged male F344 rats: a potential confounding pathological variable in


#84. Anawalt BD, Bebb RA, Bremner WJ, Matsumoto AM. Lower dosage levonorgestrel (LNG) and testosterone enanthate (TE): equally effective spermatogenic suppression and fewer metabolic side effects. J Invest Med 1997;45:94A.

#86. Meriggiola MC, Costantino A, Anawalt BD, Di Cintio G, Valdiserri A, Matsumoto AM, Flamigni C, Bremner WJ. Testosterone enanthate 100 mg/week (TE) plus cyproterone acetate (CPA) induces a similar gonadotropin decrease but a more profound spermatogenic suppression compared to levonorgestrel (LNG) plus TE. VIth International Congress of Andrology, Salzburg, Austria, May 25-29, 1997.


#114. Sohn EH, Wolden-Hanson T, Marck BT, **Matsumoto AM**. Testosterone (T)-induced increase in neuropeptide-Y (NPY) gene expression is attenuated in old compared to young male Brown Norway rats: contribution of T to age-related decline in NPY gene expression. J Invest Med 2000;48:62A.


#132. Wolden-Hanson T, Sohn E, Marck BT, Matsumoto AM. Testosterone (T)-induced changes in arcuate nucleus (ARC) cocaine-amphetamine regulated transcript (CART) and NPY mRNA are attenuated in old (O) compared to young (Y) male Brown Norway (BN) rats: contribution of T to age-related changes in CART and NPY gene expression. Abstract OR24-4, p. 100. The Endocrine Society 83rd. Annual Meeting, Denver, CO, June 20-23, 2001 [The Endocrine Society Travel Award to T. Wolden-Hanson].


#147. Amory JK, Watts NB, Easley KA, Sutton PR, Anawalt BD, Matsumoto AM, Bremner WJ, Tenover JL. Testosterone (T) plus finasteride for 3 years increases bone mineral


maintains intratesticular testosterone in normal men with testosterone induced
gonadotropin suppression. Abstract No. OR41-2. The Endocrine Society 86th Annual

#158. Page ST, Herbst KL, Amory JK, Coviello AD, Matsumoto AM, Bremner WJ.
Testosterone suppresses adiponectin levels in men. Abstract No. P1-347. The

#159. Araujo AB, O'Donnell AB, Brambilla DJ, Simpson WB, Matsumoto AM, McKinlay JB.
Androgen deficiency in middle-aged and older men: prevalence, incidence, projections
from the Massachusetts Male Aging Study. Abstract No. P3-462. The Endocrine Society

AM, Weber T, McWhirter C, Brennan JJ. Frequency of dose adjustment for AndroGel
during a three-year clinical trial in hypogonadal men. Abstract No. P2-558. The

#161. Herbst KL, Sarkissian A, Wolden-Hanson T, Marck BT, Bhasin S, Matsumoto AM.
Long-term administration of testosterone decreases myostatin expression in the levator
ani muscle of the male Sprague Dawley rat. Abstract No. P2-133. The Endocrine

#162. Wolden-Hanson TH, Marck BT, Matsumoto AM. Supraphysiologic testosterone
decreases body weight and increases food intake in aging male Brown Norway (BN)
rats. Abstract No. OR3-2. The Endocrine Society 86th Annual Meeting, New Orleans,

#163. Page ST, Amory JK, Bowman ED, Anawalt BD, Matsumoto AM, Bremner WJ, Tenover
JL. Exogenous testosterone alone or with finasteride improves physical performance
and increases lean body mass in older men with low serum testosterone. 12th
International Congress of Endocrinology, Lisbon, Portugal, August 31-September 4,

#164. Page ST, Amory JK, Bowman ED, Anawalt BD, Matsumoto AM, Bremner WJ, Tenover
JL. Exogenous testosterone alone or with finasteride increases physical performance,
grip strength, and lean body mass in older men with low serum testosterone. J Invest

#165. Page ST, Lin D, Nelson PS, Amory JK, Matsumoto A, Bremner WJ. The effect of short-
term medical castration on hormones, PSA and prostate size in normal middle-aged

#166. Page ST, Lin DW, Hess D, Amory JK, Nelson PS, Matsumoto AM, Bremner WJ.
Prostate tissue dihydrotestosterone, but not testosterone, levels are decreased by
medical castration in normal, middle-aged men. Abstract No. OR57-6. The Endocrine

#167. Coviello AD, Herbst KL, McGuinness DM, Anawalt BD, Matsumoto AM, Bremner WJ.
The circulating testicular peptide hormone INSL-3 decreases in men in response to
treatment with a hormonal contraceptive regimen but does not account for failure to achieve azoospermia. Abstract No. OR57-5. The Endocrine Society 87th Annual Meeting, San Diego, CA, June 4-7, 2005.


#179. Matsumoto AM, Marck BT, Tolliver JM. The commonly abused anabolic steroid, bolandiol, may be a selective androgen receptor modulator (SARM) because it increases muscle mass and bone mineral density without affecting prostate weight in castrated male Sprague Dawley rats. Abstract No P3-212. The Endocrine Society 89th Annual Meeting, Toronto, CA, June 2-6, 2007.


16. INVITED LECTURESHIPS AND CONSULTANT

April 2015 Invited Speaker, Meet-the-Professor Session, “Assessing and managing testosterone abnormalities in all your patients”, American College of Physicians Annual Meeting Internal Medicine 2015, Boston, MA, April 30, 2015


Nov 2014 Invited Speaker, Endocrine Essentials Live Pro, The Endocrine Society, “Diagnosis and management of hypogonadism”, Manhattan Beach, CA, November 15, 2014

Nov 2014 Invited Speaker, Endocrine Essentials Live for Primary Care, The Endocrine Society, “Low testosterone: when to treat”, Manhattan Beach,


June 2014  Invited Chair and Consultant, Scientific Advisory Board Meeting, Clarus Therapeutics, Chicago, IL, June 25, 2014

June 2014  Invited Consultant, Testosterone Undecanoate R&D Scientific Advisory Board Meeting, Endo Pharmaceuticals, Chicago, IL, June 19, 2014


May 2014  Invited Speaker, Northwest Geriatric Education Center (NWGEC), Geriatric Health Series, “Thyroid disorders in older adults”, University of Washington, Seattle, WA, May 13, 2014


Feb 2014  Invited Speaker, SPORE Clinical Studies Seminar, Fred Hutchinson Cancer Research Center, “Important issues and state of knowledge in male hormone hormone replacement therapy: whoa T for low T”, February 27, 2014

Dec 2013  Invited Participant, Testosterone Replacement Therapy Advisory Board Meeting, Arlington, VA, December 8, 2013


May 2013 Invited Speaker, “Diagnosis, evaluation and management of hypogonadism”, University of Washington Department of Medicine Grand Rounds, Seattle, WA, May 9, 2013

Apr 2013 Invited Speaker, “Testosterone replacement therapy and mortality”, Innovations in Men’s Health, ASA Special Symposium, San Antonio, TX, April 13, 2013

Apr 2013 Invited Speaker, “Diagnosis, evaluation and treatment of hypogonadism in older men: in search of a patient-centered hole in one”, Medicine Grand Rounds, Boise VA Medical Center, Boise, ID, April 4, 2013

Apr 2013 Invited Speaker, “Osteoporosis: not just a problem in older women”, Internal Medicine Residents Teaching Conference, Boise VA Medical Center, Boise, ID, April 4, 2013

Feb 2013 Invited Participant, Program for Accurate Testing of Hormones (PATH) Steering Committee Strategic Planning Meeting, Reston, VA, February 12-13, 2013

Feb 2013 Invited Speaker, “Why is measuring free testosterone better than total?”, GTx Roundtable on Free Testosterone and Prostate Cancer Treatment, Memphis, TN, February 2, 2013

Dec 2012 Invited Participant, Lilly Consultants Meeting on Diabetes and Hypogonadism, Indianapolis, IN, December 14, 2012


Jul 2011 Invited Participant, Oral testosterone treatment of male hypogonadism meeting, Abbott Pharmaceuticals, Chicago, IL, July 21, 2011


May 2011 Invited Speaker, Endocrine Grand Rounds, University of Pittsburgh, “Use and abuse of androgens”, Pittsburgh, PA, May 20, 2011

May 2011 Invited Participant, Selective Androgen Receptor Modulator Advisory Board, Ligand Pharmaceuticals, Chicago, IL, May 5, 2011


Apr 2011 Invited Speaker, CME Symposium, American College of Medicine Internal Medicine 2011, “Male Hypogonadism: Diagnostic and Therapeutic Strategies”, San Diego, CA, April 7, 2011

Mar 2011 Invited Speaker, Biology of Aging Lecture, Huffington Center of Aging, Baylor College of Medicine, “Testosterone and the aging male: clinical practice and research challenges”, Houston, TX, March 16, 2011

Feb 2011 Invited Participant, Hypogonadism Advisory Board, Abbott Pharmaceuticals, Dallas, TX, February 12, 2011

Dec 2010 Invited Participant, Testosterone Replacement Therapy Advisory Board, Endo Pharmaceuticals, Philadelphia, PA, December 11, 2010


Apr 2010 Invited Speaker, ASA 2010, 35th Annual Meeting, American Society of Andrology, Houston, TX, April 10-13, “Testosterone and the aging male”, April 13, 2010


Feb 2010 Invited Participant, Center for Disease Control Testosterone Measurement Consensus Conference, Atlanta, GA, February 11-12, 2010

Jan 2010 Invited Speaker, Update in Internal Medicine, 33rd Annual Winter Conference, Idaho ACP, “Challenges in the diagnosis and treatment of male hypogonadism”, McCall, ID, January 16, 2010


Jun 2009 Invited Speaker, Merck Research Laboratories, “The Testosterone Trial” and “Importance of active metabolism of testosterone and selective androgen receptor modulators”, Rahway, NJ, June 29, 2009

June 2009 Invited Participant, Endo Pharmaceuticals Regional Advisory Board Meeting, Marina Del Rey, CA, June 26-27, 2009


Mar 2008 Invited Reviewer, Merck Bone, Respiratory, Immunology, Endocrine (BRIE) Research Strategy Review Committee (RSRC), Upper Gwynedd, PA, March 11, 2009


Aug 2008 Invited Participant, “AndroGel DEMAND trial and PRO development”, Dallas, TX, August 20-21, 2008


Mar 2008 Invited Speaker, “Evaluation and treatment of male hypogonadism in primary care. Do we need a Men's Health Initiative?” Department of Internal Medicine Grand Rounds, University of Kansas School of Medicine, Kansas City, KA, March 19, 2008

Mar 2008 Invited Speaker, “Diagnosis and evaluation of male hypogonadism for the endocrinologist”, University of Kansas School of Medicine, CME,
Kansas City, KA, May 19, 2008

Mar 2008  Invited Participant, CDC Workshop on Improving Steroid Hormone Measurements in Patient Care and Research Translation, Centers for Disease Control and Prevention, National Center for Environmental Health, Division of Laboratory Sciences, CDC Chamblee Campus, Atlanta, GA, March 17-18, 2008

Mar 2008  Invited Participant, 1st Annual Conference on Improving Clinical Outcomes in Hypogonadism, Western Region, Los Angeles, CA, March 15, 2008


Feb 2007  Invited Speaker, “The role of androgens in the ageing male”, Society for Endocrinology, British Endocrine Society 2007 Meeting,
March 5-8, 2007, Birmingham, United Kingdom, March 6, 2007.


Feb 2006 Invited Speaker, From Frail to Fit after Fifty Conference, International Conference on Aging, Disability and Independence, University of Florida, St. Petersburg, FL, “How can we avoid the adverse effects of androgens?”, February 1, 2006.


Oct 2005  Invited Consultant, GTx Renal Failure Advisory Board, Chicago, IL, October 8, 2005


Sept 2005  Invited Speaker, 33rd Annual Advances in Family Practice & Primary Care, Continuing Medical Education, University of Washington School of Medicine, “Hypogonadism in men”, Seattle, WA, September 14, 2005.

Aug 2005  Invited Consultant, GTx SARM Phase 1 Clinical Trial Data Evaluation, Seattle, WA, August 24, 2005.


April 2005  Invited Consultant, GTx SARM Advisory Board, Memphis, TN, April 30-May 1, 2005.


Jan 2005  Invited Consultant and Participant, SARMs: Novel Approaches to Frailty, Osteoporosis and Sexual Dysfunction Meeting, TAP and Ligand Pharmaceuticals, Chicago, IL, January 3-4, 2005.

Dec 2004  Invited Participant, Evidence-Based Guidelines for the Management of Androgen Deficiency Syndrome in Men Task Force, Endocrine Society, Philadelphia, PA, December 7, 2004


Sept 2004  Invited Participant, Evidence-Based Guidelines for Management of Androgen Deficiency Syndrome in Men Task Force, Endocrine Society, Chicago, IL, September 17, 2004


July 2004  Invited Consultant, ICOS Selective Androgen Receptor Modulator, Seattle, WA, July 1, 2004

June 2004  Invited Speaker, Endocrine Society CMES, “Screening and Diagnosis of Hypogonadism in Men, Including Selection of Appropriate Patients for Therapy and Benefits of Therapy”, New Orleans, LA, June 19, 2004

June 2004  Invited Speaker, Medicine Grand Rounds, Boise VA Medical Center, “Androgen Replacement in Older Men”, Boise, ID, June 10, 2004

May 2004  Invited Speaker and Discussion Leader, VA Special Fellowship Program in Advanced Geriatrics Annual Meeting, “How Prepare and Write a Grant”, Las Vegas, NV, May 17, 2004


Apr 2004  Invited Consultant, GlaxoSmithKline SARM Advisory Board Meeting, Baltimore, MD, April 17, 2004

Mar 2004  Invited Speaker, Auxilium National Advisory Board Meeting, “Current Research Topics in Androgen Therapy”, Phoenix, AZ, March 20, 2004

Mar 2004  Invited Speaker, Division of Gerontology & Geriatric Medicine, Geriatric Grand Rounds, “Erectile dysfunction in the elderly: diagnosis and treatment”, March 19, 2004


Oct 2003  Invited Consultant, Solvay AndroGel Lifecycle Advisory Panel, San
Antonio, TX, October 29-30, 2003.


Apr 2003 Invited Consultant, GlaxoSmithKline Selective Androgen Receptor Modulator Program, Research Triangle Park, NC, April 21, 2003


Dec 2002 Invited Speaker, 22nd Annual St. Louis Geriatric Research, Education and Clinical Center Conference on Health Promotion and Disease
<table>
<thead>
<tr>
<th>Month</th>
<th>Event Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dec 2002</td>
<td>Invited Consultant, Investigators/Speakers Bureau Development Meeting, Auxilium Pharmaceuticals, Chicago, IL, December 2, 2002</td>
</tr>
<tr>
<td>Nov 2002</td>
<td>Invited Speaker, Special Fellowship Program in Advanced Geriatrics 2nd Annual Meeting, “Career Pathways in Academic Geriatrics”, Boston, MA, November 22, 2002</td>
</tr>
<tr>
<td>Aug 2002</td>
<td>Invited Consultant, Expert Meeting on Org 538 Andriol® Testocaps™, Salt Lake City, UT, August 24-25, 2002</td>
</tr>
<tr>
<td>Aug 2002</td>
<td>Invited Consultant, Postgraduate Institute for Medicine Roundtable Meeting on the “Role of DHT in Prostate Health”, Dallas, TX, August 3, 2002</td>
</tr>
<tr>
<td>May 2002</td>
<td>Invited Speaker, International Longevity Center-USA, Kronos Longevity Research Institute, and NIA, Masculine Vitality Conference, “Biochemistry and Physiology of Male Hormones”, Canyon Ranch, AZ, May 16-19, 2002</td>
</tr>
<tr>
<td>Year</td>
<td>Title</td>
</tr>
<tr>
<td>------</td>
<td>----------------------------------------------------------------------</td>
</tr>
<tr>
<td>Apr 2002</td>
<td>Invited Consultant, Selective Androgen Receptor Modulators, Bristol Myers Squibb</td>
</tr>
<tr>
<td>Apr 2002</td>
<td>Invited Consultant, AndroGel Advisory Board, Solvay Pharmaceuticals</td>
</tr>
<tr>
<td>Apr 2002</td>
<td>Invited Speaker, Department of Medicine Grand Rounds, University of Washington School of Medicine</td>
</tr>
<tr>
<td>Mar 2002</td>
<td>Invited Speaker, Geriatrics Grand Rounds, University of Washington School of Medicine</td>
</tr>
<tr>
<td>Mar 2002</td>
<td>Invited Speaker, Uniform Services Urology Research Group Annual Meeting</td>
</tr>
<tr>
<td>Dec 2001</td>
<td>Invited Speaker, Endocrine Society CMES Ancillary Symposium on Aging Men and Women: Does Sex Steroid Therapy Improve Quality of Life</td>
</tr>
<tr>
<td>Nov 2001</td>
<td>Invited Consultant, GTx Medical Advisory Board for GTx-007 and SARMs</td>
</tr>
<tr>
<td>July 2001</td>
<td>Invited Speaker, Primary Care for the Disabled Seminar Series</td>
</tr>
<tr>
<td>May 2001</td>
<td>Invited Consultant, Dutasteride Spermatogenesis Study (ARIA 1009) and Gonadal Effects of SB223412, GlaxoSmithKline</td>
</tr>
<tr>
<td>Apr 2001</td>
<td>Invited Speaker, Endocrinology &amp; Metabolism Grand Rounds</td>
</tr>
<tr>
<td>Date</td>
<td>Event</td>
</tr>
<tr>
<td>----------</td>
<td>----------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Dec 1999</td>
<td>Invited Speaker, Department of Medicine Grand Rounds, &quot;Androgens and Aging&quot;, Emory University School of Medicine, Atlanta, GA, December 7, 1999.</td>
</tr>
<tr>
<td>Nov 1999</td>
<td>Invited Speaker, GRECC Symposium, &quot;The Brown Norway (BN) rat as a model to study age-related alterations in the neuroendocrine regulation of food intake (FI) and body weight (BW) and body composition&quot;, The Gerontological Society or America, 52nd. Annual Meeting, San Francisco, CA, November 21, 1999.</td>
</tr>
<tr>
<td>Feb 1999</td>
<td>Invited Speaker, Seminars in Reproductive Medicine, Department of Obstetrics and Gynecology, Division of Reproductive Endocrinology,</td>
</tr>
</tbody>
</table>
Feb 1999 Invited Speaker, Endocrinology Grand Rounds, Baylor College of Medicine, "Hormone Replacement in the Elderly", Houston, TX, February 18, 1999.


Aug 1998 Invited Speaker, Drew University of Medicine, Endocrinology, Metabolism and Molecular Medicine Division Seminar, "Rat Models of Age-Related Sarcopenia", Los Angeles, CA, August 28, 1998.


June 1997 Invited Speaker, Endocrine Society Annual Meeting Symposium on Androgen Use in Men, "Androgen replacement in hypogonadal men", 67
Minneapolis, MN, June 11, 1997

May 1997  Invited Speaker, 25th. Annual Spring Update, Advances in Internal Medicine, University of Michigan Medical School, Department of Internal Medicine, "Benefits and Risks of Hormone Replacement Therapy for Older Adults", Ann Arbor, MI, April 30, 1997.

May 1997  Invited Speaker, Division of Geriatric Medicine Research Conference, University of Michigan Medical School, "Alteration in Food Intake and Body Weight Regulation with Aging in a Rat Model", Ann Arbor, MI, April 29, 1997.

May 1997  Invited Speaker, Geriatrics Section, Ann Arbor V.A. Medical Center, "Geriatrics and Extended Care at the V.A. Puget Sound Health Care System", Geriatrics Research, Education and Clinical Center, Ann Arbor, MI, April 29, 1997.


Jan 1994  Invited Speaker, University of Washington Endocrine Days, "Is There a Role for Treatment of Elderly with Anabolic Hormones", Seattle, WA, January 28, 1994


June 1993  Invited Speaker, Contraceptive Research and Development (CONRAD) Program Male Systemic Methods of Contraception Meeting, "Levonorgestrel-Testosterone Combinations in Male Contraception", Alexandria, VA, June 16, 1993

May 1993  Invited Speaker, Vth International Congress of Andrology, Symposium on
Male Sexual Behavior, "Behavioral Effects of High Dose Androgens", Tokyo, Japan, May 6, 1993

June 1992 Invited Speaker, Endocrine Society Symposium on Hormonal Control of Spermatogenesis, "Hormonal Regulation of Spermatogenesis in Humans", San Antonio, TX, June 25, 1992

Mar 1992 Invited Speaker, Wyeth-Ayerst Research, "The Use of Progestin-Androgen Combinations in Male Contraception", Radnor, PA, March 26, 1992

Nov 1990 Invited Speaker, NICHHD Conference on Reproductive Issues and the Aging Male "Aging and Human Male Reproductive Function," NIH, Bethesda, MD, November 26, 1990

Feb 1990 Invited Speaker, International Conference on Perspectives in Primate Reproductive Biology, "The Hormonal Regulation of Spermatogenesis in Man," Indian Institute of Science, Bangalore, India, February 6, 1990


May 1986 Invited Speaker, Recent Advances in Neuroendocrinology Symposium, "Clinical Studies Using LHRH", University of British Columbia, Vancouver, B.C., Canada, May 4, 1986


May 1984 Invited Speaker, Basic Science Foundations in Endocrinology Lecture Series, "Gonadotropin control of spermatogenesis in man," Harbor-UCLA Medical Center, Los Angeles, CA, May 4, 1984


69
17. MILITARY
   1979-80 United States Public Health Service, Commissioned Officer, Inactive Reserve
   1976-79 United States Public Health Service, Commissioned Officer, Active Grade 0-4 (Lieutenant Commander)
Testosterone Testing
Teresa L. Rogstad, MPH,
Project Leader, Hayes, Inc.
March 20, 2015

Presentation overview

- Policy Context and Clinical Background
- Scope, Methods, and Search Results
- Inferences Based on Indirect Evidence
- Summary: Indirect Evidence, Practice Guidelines, and Payer Policies
- Final Comments
Policy Context and Clinical Background

- Controversy
  - Diagnostic criteria for hypogonadism
  - Benefits and harms of treatment
  - New, easier-to-use formulations; direct-to-consumer advertising

- Analysis of claims data, 2000–2010 (Layton et al., 2014)
  - ↑ new testing (from 39.6 – 170.0/10,000 person–years)
    - But constant prevalence
  - Diagnosis prior to testing
    - Erectile dysfunction (10.4%); diabetes (15.1%)
    - Hypertension (28.7%); fatigue (19.8%)
  - Substantially different patterns in UK

- National policies
  - No CMS policy or USPSTF recommendation
  - FDA approval of T products: primary/secondary "organic" hypogonadism
Rationale for this report

- Nonspecific indicators for testing
- Threats to analytic validity
- Clinical validity: link with some medical conditions
  - But no definitive cutoff values for predicting risk based on T levels
- Uncertain benefits, long-term safety of T therapy
- Evidence needed
  - Clinical utility studies

Low testosterone/hypogonadism

- Prevalence, low testosterone (T) levels, American men
  - Age 45–54 years, 9.0%; 55–64 years, 16.5%; 65–74 years, 18.3%
- Hypogonadism
  - Primary (abnormalities at testicular level)
  - Secondary (defects in testes and pituitary)
  - Age-related hypogonadism (androgen deficiency)
    - Low serum T levels + characteristic symptoms
    - “Male menopause”, “andropause”, “late-onset hypogonadism (LOH)”, “androgen decline in the aging male (ADAM)”
    - Prevalence, age > 40 years: 2%–6%
- How low is low?
  - Reference ranges for healthy young men
  - Typical cutoff values: **280–300 ng/dL (9.7–10.4 nmol/L)**
Characteristic signs/symptoms (The Endocrine Society)

More specific (classic)
- Incomplete or delayed sexual development
- Reduced libido
- Decreased spontaneous erections
- Breast discomfort/enlargement
- Loss of body hair
- Very small/shrinking testes
- Inability to father children
- Low or zero sperm count
- Osteoporosis
- Hot flushes, sweats

Less specific
- Decreased energy, motivation, initiative, and self-confidence
- Depressed mood
- Poor concentration/memory
- Sleep problems
- Mild anemia
- Reduced muscle bulk and strength
- Increased body fat or body mass index
- Diminished physical or work performance

Low T levels and patient complaints

Background evidence (observational studies)
- Symptoms of sexual dysfunction
  - Association (2 studies)
  - OR of 3 simultaneous symptoms (low vs high T level): 1.64–2.24
- Health status, physical performance, psychological symptoms
  - Inclusive evidence (4 studies)

Endocrine Society recommendations (2010)
- Test in patients with more–specific symptoms
- Consider testing, patients with less–specific symptoms
  Weak recommendations, very–low–quality evidence
### Low T levels and poor health

<table>
<thead>
<tr>
<th>Background evidence (observational data)</th>
<th>Endocrine Society: consider testing if</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Prevalence data</td>
<td>- No symptoms but</td>
</tr>
<tr>
<td>◦ Chronic kidney disease, COPD, HIV</td>
<td>◦ Pathology/radiation, sellar region</td>
</tr>
<tr>
<td>- Meta-analyses (risk estimates)</td>
<td>◦ Medications (glucorticoids, anabolic steroids, opioids)</td>
</tr>
<tr>
<td>◦ Osteoporosis, metabolic syndrome (MetS), type 2 DM, cardiovascular disease (CVD) and mortality, all-cause mortality</td>
<td>◦ HIV-related weight loss</td>
</tr>
<tr>
<td>◦ Osteoporosis</td>
<td>◦ Osteoporosis</td>
</tr>
<tr>
<td>- Individual studies (risk estimates)</td>
<td>◦ Symptoms and</td>
</tr>
<tr>
<td>◦ Obesity, poorer lifestyle or life situation</td>
<td>◦ Type 2 DM</td>
</tr>
<tr>
<td>◦ Direction of causality uncertain</td>
<td>◦ End-stage renal disease (ESRD)</td>
</tr>
</tbody>
</table>

*Weak recommendations, very-low-quality evidence*

### Medical treatment

- Address reversible conditions first
- Indications used in practice*
  - Improve sexual function
  - Promote well-being
  - Correct effects of HIV treatment, glucocorticoids, opioids
- Positive evidence of efficacy (meta-analyses)
  - Sexual dysfunction, especially in hypogonadism
  - Diabetes-related outcomes, depending on outcome measure
- Safety in older men
  - Erythrocytosis
  - Prostate events?
  - Conflicting evidence: obstructive sleep apnea, cardiovascular events, mortality
  - FDA is reassessing

*All supported by *strong* Endocrine Society recommendations; *low* quality evidence.
Testing T levels: technical issues

- Total, free, bioavailable testosterone
- Threats to analytic validity
  - Diurnal/day-to-day/age-related variation
  - Variation across labs (different populations)
  - Variation across commercial assays
  - Precision poor at lower limit of reference ranges
- Best practice
  - Measure total testosterone (TT) 8:00–10:00 a.m.
  - Measure ≥ 2 times, different days
  - TT near lower limit of normal range → measure free/bioavailable T levels
- Voluntary quality control programs

Testing T levels: other considerations

- Clinical validity
  - Decline starts approximately at age 30
  - To evaluate symptomatic men, regardless of age
    - Compare levels with normal range for young men
  - No cutoff for assessing health risk
- Monitoring
  - No definitive schedule
  - During therapy, assess need for adjustments
Scope, Methods, and Search Results

PICO

- **Population**: Adult men
- **Interventions**: Measurement of circulating total, free, or bioavailable testosterone as an initial assessment of possible hypogonadism
- **Comparisons**: Investigation and clinical management of symptoms or health problems without the use of testosterone testing
- **Outcomes**: Outcomes such as symptom improvement; general health outcomes (e.g., osteoporosis, chronic disease, mortality); clinical management decisions; potential harms; potential harms resulting from testosterone treatment decisions; cost and cost-effectiveness
**Key Questions**

1. Is there evidence that testosterone testing improves outcomes?
   
   1a. Does the impact on outcomes vary according to age, race/ethnicity, baseline testosterone levels, treatment status, or clinical history?

   1b. What is the minimum interval required to assess a change in testosterone status in untreated and treated individuals?

2. What are the potential harms of testosterone testing, including potential subsequent harms resulting from treatment decisions?

3. What are the costs and cost-effectiveness of testosterone testing?

**Methods for selecting key question (KQ) evidence**

- Searched for direct evidence
  - Consistent with PICO
    - KQ #1, #1a, #2 (effectiveness and safety of testing)
      - Any study comparing groups tested and not tested
      - Published 1990 or later
    - KQ #1b (monitoring intervals)
      - Longitudinal studies
      - Published 1990 or later
    - KQ #3 (cost implications)
      - Published 2003 or later
  - **No eligible studies identified**
Post hoc analysis: indirect evidence

- 2 subpopulations selected based on systematic reviews (SRs) and large population studies
  - Type 2 DM or metabolic syndrome (MetS)
    - 3 SRs: association with low T levels
    - 1 SR: efficacy of T therapy*
  - Sexual dysfunction
    - 2 large population studies: association with low T levels
    - 1 SR: efficacy of T therapy

*A second review published after Draft Report cast doubt on conclusions regarding treatment efficacy.

Post hoc analysis: indirect evidence (cont.)

- Systematic search for new publications published since recent SRs and population studies

<table>
<thead>
<tr>
<th>Topic</th>
<th>Studies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Association with MetS or type 2 DM</td>
<td>15</td>
</tr>
<tr>
<td>Efficacy of T therapy, men with type 2 DM</td>
<td>5</td>
</tr>
<tr>
<td>Low T levels and sexual symptoms</td>
<td>4</td>
</tr>
<tr>
<td>Efficacy of T therapy, men with sexual dysfunction</td>
<td>No studies</td>
</tr>
</tbody>
</table>

*Studies potentially matching inclusion criteria of systematic reviews.

Post hoc search did not suggest change in conclusions
Indirect evidence, KQs #1, #1a: Effectiveness of testing in men with type 2 DM

<table>
<thead>
<tr>
<th>Indirect Evidence</th>
<th>Findings from Indirect Evidence</th>
<th>Inferences re: KQs</th>
</tr>
</thead>
</table>
| 2 fair or good MAs (≥32 studies) | MetS vs TT level:  
  - RR, 0.38; CI, 0.25–0.50  
  - Significant differences | Unclear implications for effectiveness of testing |
| 1 fair MA (33 studies) | Type 2 DM vs TT level:  
  - Significant differences  
  - Especially in younger men or higher BMI | |
| 2 fair or good MAs (9 RCTs) | Effect of T therapy on diabetes–related outcomes  
  - Varies by outcome measure and study selection  
  - Baseline T levels low/low-normal in most participants  
  - Confounding by medications changes? | |
### Detail: T therapy in men with type 2 DM (Cai et al., 2014)

<table>
<thead>
<tr>
<th>MA Description</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>5 RCTs</td>
<td>Mean difference, control minus T therapy: FPG (nmol/L): -1.10 (CI, -1.88 to -0.31) (5 RCTs)</td>
</tr>
<tr>
<td>351 men w/ LOH and type 2 DM</td>
<td>FSI (mIU): -2.73 (CI, -3.62 to -1.84) (4 RCTs)</td>
</tr>
<tr>
<td>Mean age, 44–64 yrs</td>
<td>HbA1c (%): -0.87 (CI, -1.32 to -0.42) (3 RCTs)</td>
</tr>
<tr>
<td>F/u, 3–12 mos</td>
<td>Triglycerides (mmol/L): -0.35 (CI, -0.62 to -0.07) (4 RCTs)</td>
</tr>
<tr>
<td>2 RCTs compared w/ no treatment rather than placebo</td>
<td>Generally low heterogeneity.</td>
</tr>
<tr>
<td>Fair quality</td>
<td>SR-assigned study quality, 5–7 on a 0–8 scale.</td>
</tr>
<tr>
<td></td>
<td>Some inconsistency in study results, FSI and HbA1c.</td>
</tr>
<tr>
<td></td>
<td>No effect, body fat or blood pressure (3 RCTs each).</td>
</tr>
</tbody>
</table>

### Detail: T therapy in men with MetS/type 2 DM (Grossman et al., 2014)

<table>
<thead>
<tr>
<th>MA Description</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>7 RCTs (double-blind, placebo-controlled)</td>
<td>Mean difference, control minus T therapy: HOMA-IR: -0.26 (CI, -1.09 to 0.57) (7 RCTs [3 included by Cai et al.])</td>
</tr>
<tr>
<td>833 men w/ MetS (1 RCT) or type 2 DM (6 RCTs)</td>
<td>Trials using more conventional, less rigorous technique: SMD–0.34 (CI, -0.51 to –0.16)</td>
</tr>
<tr>
<td>Mean age, 44–64 yrs</td>
<td>HbA1c (%): -0.15 (CI, -0.39 to 0.10) (6 RCTs [3 included by Cai et al.])</td>
</tr>
<tr>
<td>Mean TT, 8.6–10.1 nmol/L</td>
<td>Larger trials: no difference</td>
</tr>
<tr>
<td>F/u, 3–12 mos</td>
<td>High heterogeneity; SR-assigned study quality 14–24 on 0–25 scale.</td>
</tr>
<tr>
<td>Good quality</td>
<td>Modest effect, lipids; no effect, triglycerides and blood pressure.</td>
</tr>
</tbody>
</table>

*HOMA-IR=Homeostasis Model Assessment for Insulin Resistance*
Indirect evidence, KQs #1, #1a: Effectiveness of testing in men with sexual dysfunction

<table>
<thead>
<tr>
<th>Indirect Evidence</th>
<th>Findings</th>
<th>Inferences re: KQs</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 population studies</td>
<td>Low T levels associated w/ ED (1 small study)</td>
<td>Positive but weak inference of clinical utility of testing</td>
</tr>
<tr>
<td>414 men (fair); 3369 men (good)</td>
<td>Low T levels vs simultaneous multiple symptoms (1 large study): ORs, 1.64–2.24</td>
<td></td>
</tr>
<tr>
<td>1 MA (17–24 RCTs per symptom)</td>
<td>T therapy improves sexual symptoms • Significant standardized mean differences (SMDs): 0.68–0.82 • More so in men with low T levels (SMDs 1.00–1.23) • More so in men with type 2 DM • No evidence of superiority to conventional medication or effectiveness as add-on</td>
<td></td>
</tr>
<tr>
<td>Men with erectile dysfunction (ED)</td>
<td>Fair quality</td>
<td></td>
</tr>
</tbody>
</table>

KQ #1b: Minimum interval to assess change in T status

<table>
<thead>
<tr>
<th>Evidence</th>
<th>Potentially Policy-Relevant Information</th>
<th>Inferences re: KQ</th>
</tr>
</thead>
<tbody>
<tr>
<td>No direct evidence</td>
<td>• 1 study (282 men, age 60–82 yrs after 5 yrs f/u) • TT and bioavailable T had declined • 9 of 10 symptoms remained constant • Check T levels at 3–6 mos following initiation of therapy • Weak recommendation, very-low-quality evidence (Endocrine Society)</td>
<td>• Frequent testing in untreated men may not be necessary • Since no evidence of benefit of T therapy at above-normal levels • Monitoring men receiving T therapy might avoid adverse treatment effects</td>
</tr>
</tbody>
</table>
**KQ #2: Harms of testing and consequent treatment**

**No significant procedure harms**

**Safety of T therapy (typical follow-up 2–3 years)**

<table>
<thead>
<tr>
<th>Category</th>
<th>Effect Size</th>
<th>CI</th>
<th>Low Heterogeneity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Composite prostate outcome</td>
<td>RR, 1.41</td>
<td>0.93–2.14;</td>
<td>Low</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1 MA (15 studies)</td>
<td></td>
</tr>
<tr>
<td>Erythrocytosis</td>
<td>RR, 3.15</td>
<td>1.56–6.35;</td>
<td>Low</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1 MA (11 studies)</td>
<td></td>
</tr>
<tr>
<td>Obstructive sleep apnea</td>
<td>Inconsistent findings</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Small case series</td>
<td></td>
</tr>
<tr>
<td>Cardiovascular events</td>
<td>No clear overall effect</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>Conflicting evidence for subpopulations</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>2 population studies</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>1 MA (31 studies)</td>
<td></td>
</tr>
<tr>
<td>All-cause mortality</td>
<td>Hazard ratio (HR), 0.61</td>
<td>0.42–0.88;</td>
<td>Protective</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1 observational study (follow-up, 41 mos)</td>
<td></td>
</tr>
</tbody>
</table>

**Inference, KQ: Testing → unknown risk from long-term T therapy**

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**KQ #2: RCT evidence of no overall cardiovascular risk (Corona et al., 2014)**

- **MA**
  - 5464 men; mean age 60 years
  - Mean duration of treatment 34 weeks
- **OR (T therapy vs placebo)**
  - Any cardiovascular event: 1.07 (CI, 0.69–1.65) (31 studies)
  - MACE, overall: 1.01 (CI, 0.57–1.77) (26 studies)
  - **Considerable inconsistency**, direction of results
- **Metaregression**: no differential risk of MACE established for
  - Age/frailty
  - TT < 12 nmol/L
  - Diabetes
### KQ #2: Cardiovascular risk, Xu vs Corona MA

<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Any CV event: OR, 1.54 (CI, 1.09–2.18) (27 RCTs)</td>
<td>Any CV event: OR, 1.07 (CI, 0.69–1.65) (31 RCTs)</td>
</tr>
<tr>
<td>Pharma funding: OR, 0.89 (CI, 0.5–1.6)</td>
<td></td>
</tr>
<tr>
<td>No pharma funding: OR, 2.06 (CI, 1.34–3.1)</td>
<td></td>
</tr>
<tr>
<td>No calculation of MACE</td>
<td>MACE: OR, 1.01 (CI, 0.57–1.77) (26 studies)</td>
</tr>
<tr>
<td>PubMed and WHO trial registry</td>
<td>MEDLINE, Embase, Cochrane, ClinicalTrials.gov</td>
</tr>
<tr>
<td>End of 2012</td>
<td>January 2014</td>
</tr>
<tr>
<td>2 RCTs not in Corona review</td>
<td>5 RCTs not in Xu review</td>
</tr>
<tr>
<td>1 RCT, significant elevated risk (Baseria et al., 2010)</td>
<td>1 RCT, significant elevated risk (Baseria et al., 2010)</td>
</tr>
</tbody>
</table>

### KQ #2: Observational studies, T therapy and cardiovascular risk, FDA concern

<table>
<thead>
<tr>
<th>Vigen et al. (2013)</th>
<th>Finkle et al. (2014)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Retrospective cohort</td>
<td>Retrospective cohort</td>
</tr>
<tr>
<td>8709 men, prior coronary angiography, low T levels Follow-up, 2 yrs</td>
<td>55,593 men Follow-up, 90 days</td>
</tr>
<tr>
<td>Cumulative incidence, death/MI/stroke (T therapy vs no T therapy)</td>
<td>RR of MI in 90 days after initial T prescription vs 1 yr prior to prescription</td>
</tr>
<tr>
<td>25.7% vs 19.9% Risk difference 5.8% (CI, –1.4% to 13.1%)</td>
<td>Age ≥65 yrs 2.19 (CI, 1.27–3.77) Age &lt;65 yrs and prior history of heart disease 2.90 (CI, 1.49–5.62) Age &lt;65 yrs and no history of heart disease No effect</td>
</tr>
<tr>
<td>HR adjusted for CAD: 1.29 (CI, 1.04–1.58) No treatment–CAD interaction</td>
<td></td>
</tr>
</tbody>
</table>

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KQ #2: Recent observational study, T therapy and reduced mortality (Shores et al., 2012)

- Retrospective cohort study
  - 1031 men
  - Age >40 years; mean, 63 treated, 61 untreated
  - TT <250 ng/dL (8.7 nmol/L)
  - No history of prostate cancer
  - Mean follow-up 41 months
- Mortality (treated vs untreated)
  - 10.3% vs 20.7% ($P<0.0001$)
- Cumulative mortality (treated vs untreated)
  - 3.4 vs 5.7 deaths/100 person–years
- Adjusted HR, 0.61 (CI, 0.42–0.88)

KQ #3: Costs, cost-effectiveness

- No direct or indirect evidence
Summary of Indirect Evidence, Practice Guidelines, and Payer Policies

Organizations with no relevant policy

- CMS
- USPSTF
- GroupHealth
- OR Health Evidence Review Commission (HERC)
- Regence
## Primary hypogonadism

<table>
<thead>
<tr>
<th>Guideline Indications</th>
<th>Relevant Policies</th>
<th>Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>FDA-approved indications for T therapy</td>
<td>Aetna covers anabolic steroids for constitutional delay in growth, delayed male puberty, Klinefelter’s syndrome w/ hypogonadism, microphallus</td>
<td>---</td>
</tr>
</tbody>
</table>

Examples: chromosomal or genetic disorders, toxin exposure or chemotherapy, orchitis due to mumps or an autoimmune disorder, trauma, hemochromatosis, medications that inhibit androgen biosynthesis, damage due to varicocele

## Secondary hypogonadism: conditions that might prompt testing

<table>
<thead>
<tr>
<th>Guideline Indications</th>
<th>Relevant Policies</th>
<th>Evidence Cited in Background Section (SRs cited where possible)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Endocrine Society • Pathology, sellar regions • Medications • HIV, weight loss • Osteoporosis (T therapy also recommended)</td>
<td>FDA-approved general indication Aetna covers anabolic steroids for AIDS wasting syndrome</td>
<td><strong>Opioid dose vs TT</strong>: Inverse association in 3 of 4 studies (1 SR) <strong>HIV</strong> • High prevalence of low T level • T therapy: Small positive effect only when T levels are normal (1 good SR) <strong>Osteoporosis</strong> • High vs low T level: OR, 1.76–2.77) (1 large observational study) • T therapy: Possible benefit; no evidence regarding fracture (2 good SRs)</td>
</tr>
</tbody>
</table>
Secondary hypogonadism: conditions in which characteristic signs/symptoms might prompt testing

<table>
<thead>
<tr>
<th>Guideline Indications</th>
<th>Relevant Policies</th>
<th>Evidence Cited in Background Section (SRs cited where possible)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Endocrine Society</td>
<td></td>
<td>*MetS/Type 2 DM</td>
</tr>
<tr>
<td>• Type 2 DM</td>
<td>FDA-approved</td>
<td><strong>MetS vs TT:</strong> RR, 0.38 (CI, 0.25–0.50) (1 good SR)</td>
</tr>
<tr>
<td>• ESRD</td>
<td>general</td>
<td><strong>Type 2 DM vs TT:</strong> Sig differences (1 fair SR)</td>
</tr>
<tr>
<td>• COPD</td>
<td>indication</td>
<td><strong>Type 2 DM outcomes, T therapy:</strong></td>
</tr>
<tr>
<td>American Urological</td>
<td></td>
<td>• Some positive effects, 1 fair SR (3 RCTs)</td>
</tr>
<tr>
<td>Association (AUA)</td>
<td></td>
<td>• No sig overall effects, 1 good SR (7 RCTs)</td>
</tr>
<tr>
<td>• Infertility</td>
<td></td>
<td><strong>Chronic kidney disease:</strong> Some evidence of association</td>
</tr>
</tbody>
</table>

**Infertility:** None cited in sources used

*Evidence subjected to post hoc analysis.

Symptoms of sexual dysfunction are relatively specific symptoms that might prompt testing

<table>
<thead>
<tr>
<th>Guideline Indications</th>
<th>Relevant Policies</th>
<th>Evidence Cited in Background Section (SRs cited where possible)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Endocrine Society</td>
<td></td>
<td>Symptoms vs low T levels:</td>
</tr>
<tr>
<td>• Consider testing</td>
<td></td>
<td>• OR 2.24 (n=3369)</td>
</tr>
<tr>
<td>• T therapy an option for low libido or ED, after established therapies tried</td>
<td></td>
<td>3 simultaneous symptoms</td>
</tr>
<tr>
<td>AUA</td>
<td></td>
<td>• Both TT and free T considered</td>
</tr>
<tr>
<td>• Impaired sexual function</td>
<td></td>
<td>• Otherwise, smaller or nonsignificant ORs</td>
</tr>
<tr>
<td>• Clinical findings (not specified)</td>
<td></td>
<td>• ED but not sex drive (n=414)</td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>T therapy:</strong></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Positive effect in men with ED</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Especially if hypogonadal or type 2 DM at baseline</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• 1 fair SR</td>
</tr>
<tr>
<td></td>
<td></td>
<td>NOTE: Evidence subjected to post hoc analysis.</td>
</tr>
</tbody>
</table>

*Evidence subjected to post hoc analysis.
### Other possible indications for T testing

<table>
<thead>
<tr>
<th>Guideline Indications</th>
<th>Relevant Policies</th>
<th>Evidence Cited in Background Section (SRs cited where possible)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Endocrine Society: TEST</td>
<td>Aetna covers anabolic steroids</td>
<td><strong>Classic symptoms</strong>: See previous</td>
</tr>
<tr>
<td>• Classic symptoms* of androgen deficiency</td>
<td>• Symptomatic androgen deficiency</td>
<td><strong>Less specific symptoms</strong>:</td>
</tr>
<tr>
<td>CONSIDER testing</td>
<td>• Weight loss from cancer</td>
<td>Physical symptoms:</td>
</tr>
<tr>
<td>• Less specific symptoms</td>
<td></td>
<td>• Associated with low T levels, but no OR or RR (2 observational studies)</td>
</tr>
<tr>
<td>DO NOT test</td>
<td></td>
<td>• No T therapy evidence</td>
</tr>
<tr>
<td>• On basis of age alone</td>
<td>Psychological symptoms:</td>
<td></td>
</tr>
<tr>
<td>• During acute or subacute illness</td>
<td>• Mixed findings of association (2 large observational studies)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• T therapy: positive effect on depression, regardless of hypogonadal status (1 good SR)</td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>Age alone</strong>: None</td>
<td></td>
</tr>
</tbody>
</table>

*E.g., sexual symptoms, loss of body hair, osteoporosis, hot flashes.*
General observations

- No direct empirical evidence that testing for low testosterone in any subpopulation leads to better health outcomes

- Endocrine Society guidelines
  - Evidence for testing and treatment recommendations is “low” or “very low”

- Concerns regarding analytic validity

General conclusions (cont.)

- Subpopulations most likely to benefit
  - Type 2 DM and symptomatic hypogonadism
  - Sexual dysfunction and low T levels

- Caveats
  - Latest systematic review of T therapy for improvement of type 2 DM showed uncertain benefit
  - T testing in men with diabetes:
    - Intended to address symptomatic hypogonadism, not diabetes (Endocrine Society)
  - Clinical relevance of gains in sexual function uncertain
  - Insufficient evidence
    - T therapy instead of/in addition to ED medication
Evidence gaps

- Cutoff points associated with health risk
- Clinical trials designed to compare health outcomes, testing versus no testing
- Large, long-term studies of T therapy
  - Durability of benefits
  - Risks
- Cost and cost-effectiveness of testing in specific subpopulations

Limitations of this report

- Post hoc process for identification of subpopulations with best indirect evidence
- Unknown efficacy of T treatment in subpopulations for which no systematic reviews have been published
- No detailed review or critical appraisal of studies published more recently than systematic reviews
To find best outcomes and value for the state and the patient, the HTA program focuses on three questions:

1. Is it safe?
2. Is it effective?
3. Does it provide value (improve health outcome)?

The principles HTCC uses to review evidence and make determinations are:

### Principle One: Determinations are evidence-based

HTCC requires scientific evidence that a health technology is safe, effective and cost-effective\(^1\) as expressed by the following standards\(^2\):

- Persons will experience better health outcomes than if the health technology was not covered and that the benefits outweigh the harms.
- The HTCC emphasizes evidence that directly links the technology with health outcomes. Indirect evidence may be sufficient if it supports the principal links in the analytic framework.
- Although the HTCC acknowledges that subjective judgments do enter into the evaluation of evidence and the weighing of benefits and harms, its recommendations are not based largely on opinion.
- The HTCC is explicit about the scientific evidence relied upon for its determinations.

### Principle Two: Determinations result in health benefit

The outcomes critical to HTCC in making coverage and reimbursement determinations are health benefits and harms\(^3\):

- In considering potential benefits, the HTCC focuses on absolute reductions in the risk of outcomes that people can feel or care about.
- In considering potential harms, the HTCC examines harms of all types, including physical, psychological, and non-medical harms that may occur sooner or later as a result of the use of the technology.
- Where possible, the HTCC considers the feasibility of future widespread implementation of the technology in making recommendations.
- The HTCC generally takes a population perspective in weighing the magnitude of benefits against the magnitude of harms. In some situations, it may make a determination for a technology with a large potential benefit for a small proportion of the population.
- In assessing net benefits, the HTCC subjectively estimates the indicated population's value for each benefit and harm. When the HTCC judges that the balance of benefits and harms is likely to vary substantially within the population, coverage or reimbursement determinations may be more selective based on the variation.
- The HTCC considers the economic costs of the health technology in making determinations, but costs are the lowest priority.

\(^1\) Based on Legislative mandate: See RCW 70.14.100(2).

\(^2\) The principles and standards are based on USPSTF Principles at: http://www.ahrq.gov/clinic/ajpmsuppl/harris3.htm

\(^3\) The principles and standards are based on USPSTF Principles at: http://www.ahrq.gov/clinic/ajpmsuppl/harris3.htm
Using evidence as the basis for a coverage decision

Arrive at the coverage decision by identifying for Safety, Effectiveness, and Cost whether (1) evidence is available, (2) the confidence in the evidence, and (3) applicability to decision.

1. **Availability of Evidence:**
   Committee members identify the factors, often referred to as outcomes of interest, that are at issue around safety, effectiveness, and cost. Those deemed key factors are ones that impact the question of whether the particular technology improves health outcomes. Committee members then identify whether and what evidence is available related to each of the key factors.

2. **Sufficiency of the Evidence:**
   Committee members discuss and assess the evidence available and its relevance to the key factors by discussion of the type, quality, and relevance of the evidence\(^4\) using characteristics such as:
   - Type of evidence as reported in the technology assessment or other evidence presented to committee (randomized trials, observational studies, case series, expert opinion);
   - The amount of evidence (sparse to many number of evidence or events or individuals studied);
   - Consistency of evidence (results vary or largely similar);
   - Recency (timeliness of information);
   - Directness of evidence (link between technology and outcome);
   - Relevance of evidence (applicability to agency program and clients);
   - Bias (likelihood of conflict of interest or lack of safeguards).

Sufficiency or insufficiency of the evidence is a judgment of each clinical committee member and correlates closely to the GRADE confidence decision.

<table>
<thead>
<tr>
<th>Not Confident</th>
<th>Confident</th>
</tr>
</thead>
<tbody>
<tr>
<td>Appreciable uncertainty exists. Further information is needed or further information is likely to change confidence.</td>
<td>Very certain of evidentiary support. Further information is unlikely to change confidence</td>
</tr>
</tbody>
</table>

3. **Factors for Consideration - Importance**
   At the end of discussion a vote is taken on whether sufficient evidence exists regarding the technology’s safety, effectiveness, and cost. The committee must weigh the degree of importance that each particular key factor and the evidence that supports it has to the policy and coverage decision. Valuing the level of importance is factor or outcome specific but most often include, for areas of safety, effectiveness, and cost:
   - Risk of event occurring;
   - The degree of harm associated with risk;
   - The number of risks; the burden of the condition;
   - Burden untreated or treated with alternatives;

\(^4\) Based on GRADE recommendation: [http://www.gradeworkinggroup.org/FAQ/index.htm](http://www.gradeworkinggroup.org/FAQ/index.htm)
- The importance of the outcome (e.g. treatment prevents death vs. relief of symptom);
- The degree of effect (e.g. relief of all, none, or some symptom, duration, etc.);
- Value variation based on patient preference.

**HEALTH TECHNOLOGY EVIDENCE IDENTIFICATION**

**Discussion Document:**
What are the key factors and health outcomes and what evidence is there?

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Safety</strong></td>
<td><strong>Safety</strong></td>
</tr>
<tr>
<td>Overtreatment</td>
<td></td>
</tr>
<tr>
<td>Treatment related harms</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Efficacy – Effectiveness</strong></th>
<th><strong>Efficacy / Effectiveness</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Test characteristics</td>
<td></td>
</tr>
<tr>
<td>Improved health outcomes</td>
<td></td>
</tr>
<tr>
<td>Clinical management</td>
<td></td>
</tr>
<tr>
<td>Symptom improvement</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Special Population / Considerations</strong></th>
<th><strong>Special Populations/ Considerations</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td></td>
</tr>
<tr>
<td>Race/ethnicity</td>
<td></td>
</tr>
<tr>
<td>Baseline testosterone levels</td>
<td></td>
</tr>
<tr>
<td>Treatment status</td>
<td></td>
</tr>
<tr>
<td>Clinical history</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Cost</strong></th>
<th><strong>Cost</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Cost</td>
<td></td>
</tr>
<tr>
<td>Cost-effectiveness</td>
<td></td>
</tr>
<tr>
<td>Cost-utility</td>
<td></td>
</tr>
</tbody>
</table>
Medicare Coverage and Guidelines

[From Page 28 of evidence report]

CMS: No CMS National Coverage Determination (NCD) was identified for testosterone testing.
<table>
<thead>
<tr>
<th>Sponsor, Title</th>
<th>Screening/Testing</th>
<th>Diagnosis</th>
<th>Testosterone Therapy</th>
<th>Monitoring T Levels During Treatment</th>
<th>Quality*/Main Limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>American College of Physicians (ACP) (Qaseem et al., 2009)</strong></td>
<td>No recommendation for or against routine hormonal blood tests (testosterone or prolactin) for management of ED. Insufficient evidence.</td>
<td>---</td>
<td>No recommendation for or against hormonal treatment for management of ED. Insufficient evidence.</td>
<td>---</td>
<td>6 – Good</td>
</tr>
<tr>
<td><strong>American Diabetes Association (ADA) (2014)</strong></td>
<td>No specific recommendation, but document states that “obesity is a major confounder” (p. S49) and cites Endocrine Society guidelines and their recommendations to test only in the presence of symptoms.</td>
<td>---</td>
<td>No specific recommendation, but document states that “evidence for effects of testosterone replacement on outcomes is mixed” (p. S49) and cites Endocrine Society guidelines regarding treatment.</td>
<td>---</td>
<td></td>
</tr>
<tr>
<td><strong>American Urological Association (AUA) (2010b)</strong></td>
<td>Endocrine evaluation if (1) abnormal semen analysis, (2) impaired sexual function, or (3) other clinical findings (not specified) suggestive of a specific endocrinopathy. Minimum initial hormonal evaluation should include T and FSH. All recommendations based on expert opinion due to insufficient evidence.</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>6 – Good</td>
</tr>
<tr>
<td><strong>American Urological Association (AUA) (2010a)</strong></td>
<td>Minimum initial hormonal evaluation should include T and FSH. All recommendations based on expert opinion due to</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>6 – Good</td>
</tr>
<tr>
<td><strong>NOTE:</strong> A best practice statement based on expert opinion was issued because the literature search did not identify sufficient evidence.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sponsor, Title</td>
<td>Relevant Recommendations (Strength of Recommendation; Quality of Evidence According to Authors)</td>
<td>Quality*/Main Limitations</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>---------------</td>
<td>-----------------------------------------------------------------------------------------------</td>
<td>--------------------------</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Practice Statement</strong></td>
<td>insufficient evidence.</td>
<td>issued because the literature search did not identify sufficient evidence.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>The Endocrine Society</strong> (Bhasin et al., 2010) <em>Testosterone Therapy in Adult Men with Androgen Deficiency Syndromes</em></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Screening/Testing</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Diagnosis</strong></td>
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<td></td>
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</tr>
<tr>
<td><strong>Testosterone Therapy</strong></td>
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<td></td>
<td></td>
</tr>
<tr>
<td><strong>Monitoring T Levels During Treatment</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Screening</strong></td>
<td>Do not screen in general population. Strong; very low. Consider case detection by total T measurement in conditions in which there is a high prevalence of low T levels. Weak; very low.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Testing to diagnose</strong></td>
<td>Test patients with more specific signs and symptoms suggestive of AD.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Consider testing patients with less specific signs and symptoms.</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Diagnose AD only with consistent symptoms and signs and unequivocally low serum T levels. Strong; very low. Do not diagnose AD during acute or subacute illness. Weak; low.</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Recommended for Symptomatic men with classical AD syndromes</strong> for purposes of including and maintaining secondary sex characteristics and improving sexual function, sense of well-being, and BMD. Strong; low. Suggested as an option for Low T levels and low libido. Weak; very low. Low T levels and ED after evaluation of underlying causes of ED and consideration of established causes.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>3-6 mos after initiation of T therapy to assess whether T levels have reached the normal range. Weak recommendation; very low.</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>5 (fair) (search details and study selection criteria not provided).</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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5 According to Table 3 in the guidelines: Conditions in which T measurement should be based on characteristic symptoms include type 2 diabetes, end-stage renal disease, and moderate to severe COPD; symptoms such as sexual dysfunction, unexplained weight loss, weakness, or mobility limitation may indicate the need for testing. These symptoms were identified on the basis of panelists’ experience rather than population surveys. Conditions in which measurement of T levels may be indicated regardless of symptoms include mass in, radiation of, or disease of sellar region (a depression in the upper surface of the sphenoid bone in which the pituitary gland sits); medications that affect T production or metabolism (e.g., glucocorticoids and opioids); HIV-associated weight loss; or osteoporosis or low-trauma fracture (especially in a young man).

6 According to Table 1 in the guidelines: A. **More specific signs and symptoms** (incomplete or delayed sexual development; eunuchoidism; reduced sexual desire (libido) and activity; decreased spontaneous erections; breast discomfort, gynecomastia; loss of body [axillary and pubic] hair, reduced shaving; very small [especially <5 mL] or shrinking testes; inability to father children, low or zero sperm count; height loss, low-trauma fracture, low BMD; hot flushes, sweats.

7 According to Table 1 in the guidelines: B. **Other less specific signs and symptoms** (decreased energy, motivation, initiative, and self-confidence; feeling sad or blue, depressed mood, dysthymia; poor concentration and memory; sleep disturbance, increased sleepiness; mild anemia (normochromic, normocytic, in the female range); reduced muscle bulk and strength; increased body fat, BMI; diminished physical or work performance).
<table>
<thead>
<tr>
<th>Sponsor, Title</th>
<th>Relevant Recommendations (Strength of Recommendation; Quality of Evidence According to Authors)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td><strong>Screening/Testing</strong></td>
</tr>
<tr>
<td></td>
<td>Test morning total T. All testing recommendations: Weak; very low. Exclude reversible illness, drugs that can deplete T levels, nutritional deficiency (not rated) Confirmatory testing to establish androgen deficiency Repeat measurement of total T. <strong>Strong; low quality.</strong> Measure free or bioavailable serum T in some men w/ total serum T near lower limit of normal and in whom alterations of SHBG are suspected. Weak; low. Additional testing to establish etiology LH+FSH</td>
</tr>
</tbody>
</table>

8 See More specific signs and symptoms in Footnote 2.
<table>
<thead>
<tr>
<th>Sponsor, Title</th>
<th>Relevant Recommendations (Strength of Recommendation; Quality of Evidence According to Authors)</th>
<th>Screening/Testing</th>
<th>Diagnosis</th>
<th>Testosterone Therapy</th>
<th>Monitoring T Levels During Treatment</th>
<th>Quality*/Main Limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>The Endocrine Society (Watts et al., 2012)</td>
<td><strong>Osteoporosis in Men</strong></td>
<td>Test for TT in men being evaluated for OP or considered for pharmacological treatment w/ bone-active agents. Weak; low. In men w/ a history or physical examination suggesting a specific cause of OP, conduct further testing, e.g., calculated FT or BT. Weak; low.</td>
<td></td>
<td>Offer in lieu of “bone drug” for men at borderline high risk for fracture who have serum T levels &lt;200 ng/dL (6.9 nmol/L) on &gt;1 determination, if accompanied by signs or symptoms of AD or “organic” hypogonadism (e.g., due to hypothalamic, pituitary, or specific testicular disorder). Weak; low. Consider for men at high risk for fracture w/ T levels &lt;200 ng/dL (6.9 nmol/L) who lack standard indications for T therapy but who have contraindications to approved pharmacological agents for OP. Weak; low.</td>
<td></td>
<td>5 (fair) (search details and study selection criteria not provided).</td>
</tr>
</tbody>
</table>
Clinical Committee Findings and Decisions

Efficacy Considerations

- What is the evidence that use of the technology results in more beneficial, important health outcomes? Consider:
  - Direct outcome or surrogate measure
  - Short term or long term effect
  - Magnitude of effect
  - Impact on pain, functional restoration, quality of life
  - Disease management
- What is the evidence confirming that use of the technology results in a more beneficial outcome, compared to no treatment or placebo treatment?
- What is the evidence confirming that use of the technology results in a more beneficial outcome, compared to alternative treatment?
- What is the evidence of the magnitude of the benefit or the incremental value?
- Does the scientific evidence confirm that use of the technology can effectively replace other technologies or is this additive?
- For diagnostic tests, what is the evidence of a diagnostic tests’ accuracy?
  - Does the use of the technology more accurately identify both those with the condition being evaluated and those without the condition being evaluated?
- Does the use of the technology result in better sensitivity and better specificity?
- Is there a tradeoff in sensitivity and specificity that on balance the diagnostic technology is thought to be more accurate than current diagnostic testing?
- Does use of the test change treatment choices?

Safety

- What is the evidence of the effect of using the technology on significant morbidity?
  - Frequent adverse effect on health, but unlikely to result in lasting harm or be life-threatening, or;
  - Adverse effect on health that can result in lasting harm or can be life-threatening?
- Other morbidity concerns?
- Short term or direct complication versus long term complications?
- What is the evidence of using the technology on mortality – does it result in fewer adverse non-fatal outcomes?

Cost Impact

- Do the cost analyses show that use of the new technology will result in costs that are greater, equivalent or lower than management without use of the technology?

Overall

- What is the evidence about alternatives and comparisons to the alternatives?
- Does scientific evidence confirm that use of the technology results in better health outcomes than management without use of the technology?
Next Step: Cover or No Cover
If not covered, or covered unconditionally, the Chair will instruct staff to write a proposed findings and decision document for review and final adoption at the following meeting.

Next Step: Cover with Conditions
If covered with conditions, the Committee will continue discussion.

1) Does the committee have enough information to identify conditions or criteria?
   - Refer to evidence identification document and discussion.
   - Chair will facilitate discussion, and if enough members agree, conditions and/or criteria will be identified and listed.
   - Chair will instruct staff to write a proposed findings and decision document for review and final adoption at next meeting.

2) If not enough or appropriate information, then Chair will facilitate a discussion on the following:
   - What are the known conditions/criteria and evidence state
   - What issues need to be addressed and evidence state

The chair will delegate investigation and return to group based on information and issues identified. Information known but not available or assembled can be gathered by staff; additional clinical questions may need further research by evidence center or may need ad hoc advisory group; information on agency utilization, similar coverage decisions may need agency or other health plan input; information on current practice in community or beneficiary preference may need further public input. Delegation should include specific instructions on the task, assignment or issue; include a time frame; provide direction on membership or input if a group is to be convened.

Clinical Committee Evidence Votes

First Voting Question
The HTCC has reviewed and considered the technology assessment and information provided by the administrator, reports and/or testimony from an advisory group, and submissions or comments from the public. The committee has given greatest weight to the evidence it determined, based on objective factors, to be the most valid and reliable.

Is there sufficient evidence under some or all situations that the technology is:

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Discussion
Based on the evidence vote, the committee may be ready to take a vote on coverage or further discussion may be warranted to understand the differences of opinions or to discuss the implications of the vote on a final coverage decision.

- Evidence is insufficient to make a conclusion about whether the health technology is safe, efficacious, and cost-effective;
- Evidence is sufficient to conclude that the health technology is unsafe, inefffectual, or not cost-effective
- Evidence is sufficient to conclude that the health technology is safe, efficacious, and cost-effective for all indicated conditions;
- Evidence is sufficient to conclude that the health technology is safe, efficacious, and cost-effective for some conditions or in some situations

A straw vote may be taken to determine whether, and in what area, further discussion is necessary.

Second Vote
Based on the evidence about the technologies’ safety, efficacy, and cost-effectiveness, it is

- _____ Not Covered
- _____ Covered Unconditionally
- _____ Covered Under Certain Conditions

Discussion Item
Is the determination consistent with identified Medicare decisions and expert guidelines, and if not, what evidence is relied upon.

Next Step: Proposed Findings and Decision and Public Comment
At the next public meeting the committee will review the proposed findings and decision and consider any public comments as appropriate prior to a vote for final adoption of the determination.

1) Based on public comment was evidence overlooked in the process that should be considered?

2) Does the proposed findings and decision document clearly convey the intended coverage determination based on review and consideration of the evidence?

Next Step: Final Determination
Following review of the proposed findings and decision document and public comments:

Final Vote
Does the committee approve the Findings and Decisions document with any changes noted in discussion?

If yes, the process is concluded.

If no, or an unclear (i.e., tie) outcome Chair will lead discussion to determine next steps.