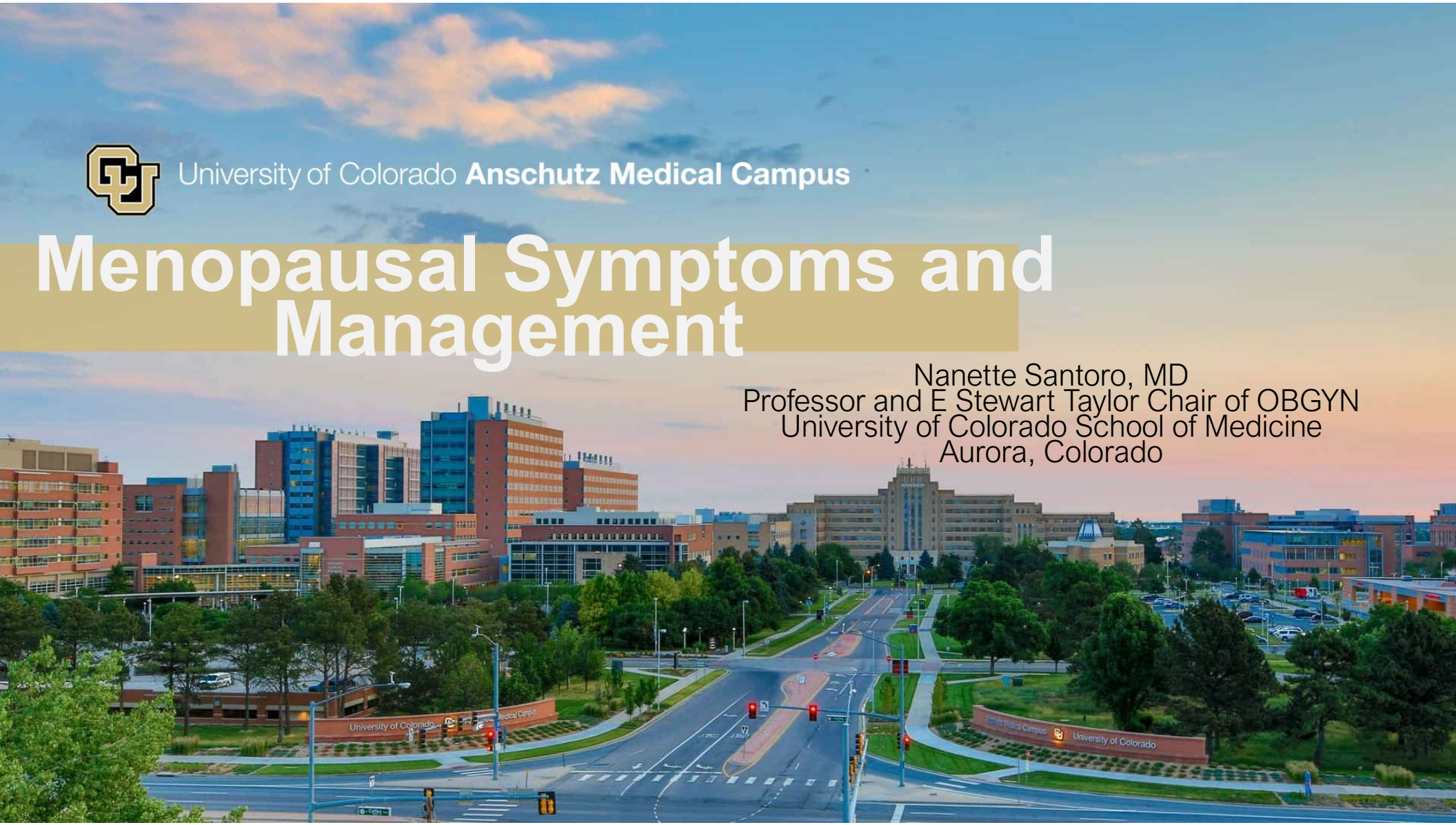


Menopausal Symptoms and Management

Nanette Santoro, MD
Professor and E Stewart Taylor Chair of OBGYN
University of Colorado School of Medicine
Aurora, Colorado

Learning Objectives

At the end of this lecture, the listener is expected to:

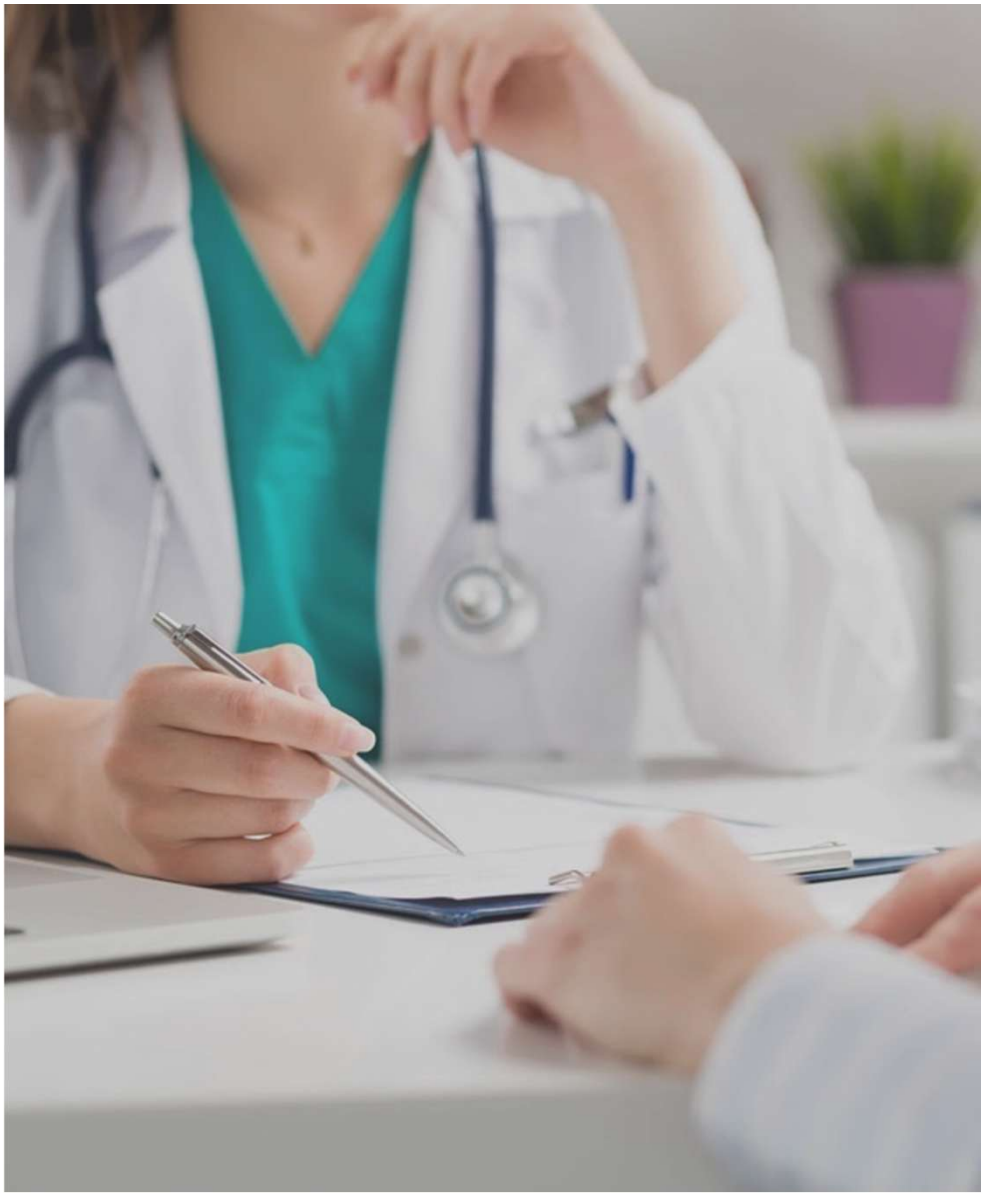
Determine the reasons for hormone therapy for menopause

Understand what hormones can and cannot do

Look past the hype to detect misinformation

Describe risks and benefits of hormone therapy

University of Colorado
Anschutz Medical Campus



Financial Disclosure for Nanette Santoro

I have the following financial relationships with ACCME defined ineligible companies to report over the past 24 months:

- Menogenix: scientific advisory board
- ASTELLAS: scientific advisory board
- Ansh Laboratories: consultant
- Amazon Ember: Scientific Advisory Board
- Novo Nordisk: Consultant

Unlabeled/Investigational Uses

I will be discussing unlabeled or investigational uses of the following pharmaceutical products:

- Off label use of non hormonal medications for hot flashes
- Off label use of testosterone for hypoactive sexual desire disorder

Menopause Is Having “A Moment”

NEWS

Firing of Canadian news anchor, reportedly due to gray hair, sparks controversy

Lisa LaFlamme said she was “blindsided” and is “still shocked and saddened” by CTV News’ decision to le go.

GLOBAL HR

UK Officials Address Menopause in the Workplace

By Dinah Wisenberg Brin
April 18, 2022

LIKE SAVE PRINT EMAIL REUSE PERMISSIONS

Officials in the U.K. are exploring ways to support menopausal employees in the workplace, taking a global lead on the issue.

University of Anschutz M

THE SATURDAY ESSAY

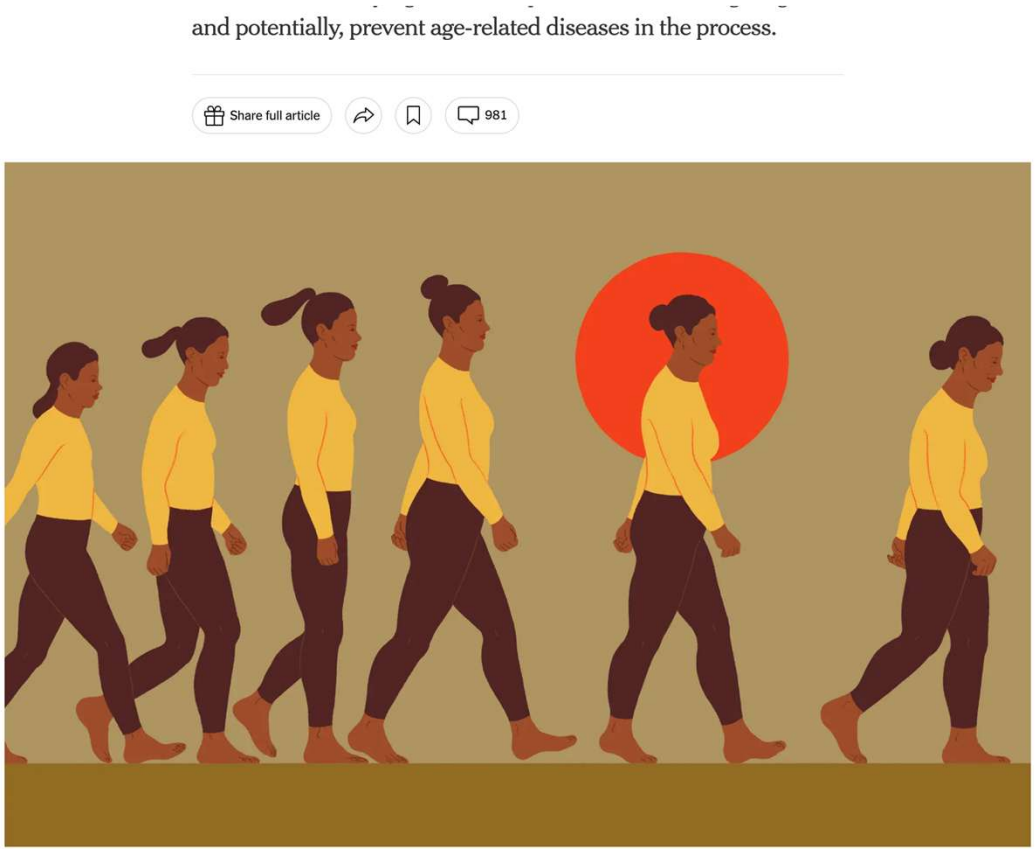
What if We Could Get Rid of Menopause?

New efforts to boost women’s health and extend fertility depend on developing tools to slow the aging of ovaries

Is Delaying Menopause the Key to Longevity?

NYT June 24, 2024

Hmm. Let's take a closer look at the assumptions that underly such bold statements…



Oh, I'm So Glad I Can Continue Having Menstrual Periods and Need Contraception Until the End of My Life*…

*…said no one, ever

Logical Flaws in the Quest for Eternal Ovarian Function

- We have already tried giving menopausal women essential ovarian hormones to reduce heart disease…and it didn't work
- This model assumes that women evolved to have regular menstrual cycles throughout their reproductive lifespan…but this is not the case
- Prolonged exposure to reproductive hormones carries some cancer risks (breast, ovary and endometrium)

Let's Do Some Ovary Math

Most of human evolution

- Women had menses begin around age 15-16
- They were either
  - Pregnant
  - Breastfeeding and not having periods
  - Too thin or stressed (or both) to have periods
- Fewer women made it to menopause

The past few centuries

- Women had menses around age 12 or older
- They had regular menstrual cycles if they lived where food was adequate
- They had limited ability to space their pregnancies
- More women made it to menopause

More Ovary Math

Prehistoric Woman

- Ages 16-46: reproductive life span
- 15 pregnancies: 11 years with no periods
- 20 years of lactation with no/few periods
- **4 possible years of cycling** or stress/weight related amenorrhea

Modern Woman

- Ages 12-51: reproductive life span
- 1.6 average completed pregnancies: 1.2 years with no periods
- Average breastfeeding duration of 7 months: less than 1 year
- **Almost 38 years of menstrual cycles!**

Are There Downsides to Endless Monthly Cycles?

- Endometriosis: painful menses, infertility (10%)
- Adenomyosis: painful menses, heavy bleeding, anemia (20-40%)
- Fibroids: painful menses, heavy bleeding, anemia (70-80%)
- PMDD (20-40%)
- Dysmenorrhea (45-93%)

How do we achieve a balance between symptom treatment and 'pathologizing' menopause?

- There is a false syllogism that feeds a powerful narrative:
  - Menopause=end of estrogen
  - Menopause=aging
  - End of estrogen=aging
- Ergo if we can continue estrogen exposure we will eliminate aging!
- Disentangling reproductive and somatic aging facilitates patient awareness and opens up more treatment options

Hickey M, Hunter MS, Santoro N. Normalising menopause BMJ 2022; 377:e069369)

What Are the Indications for Hormone Therapy in 2025?

- ❑Hot Flashes
- ❑Night Sweats
- ❑Genitourinary Syndrome of Menopause (GSM)
- ❑Poor Sleep
- ❑Adverse Mood
- ❑Prevention of postmenopausal bone loss
- ❑Premature hypogonadism

University of Colorado
Anschutz Medical Campus

NIH Consens State Sci Statements. 2005 Mar 21-23;22(1):1-38. PMID: 17308548; Faubion, S S, et al The 2022 hormone therapy position statement of The North American Menopause Society. Menopause 29(7):p 767-794, July 2022.

What Are NOT Indications for Hormone Therapy in 2025?

- ❑Prevention of heart disease
- ❑Prevention of Alzheimer Disease or other dementia

University of Colorado
Anschutz Medical Campus

NIH Consens State Sci Statements. 2005 Mar 21-23;22(1):1-38. PMID: 17308548; Faubion, S S, et al The 2022 hormone therapy position statement of The North American Menopause Society. Menopause 29(7):p 767-794, July 2022.

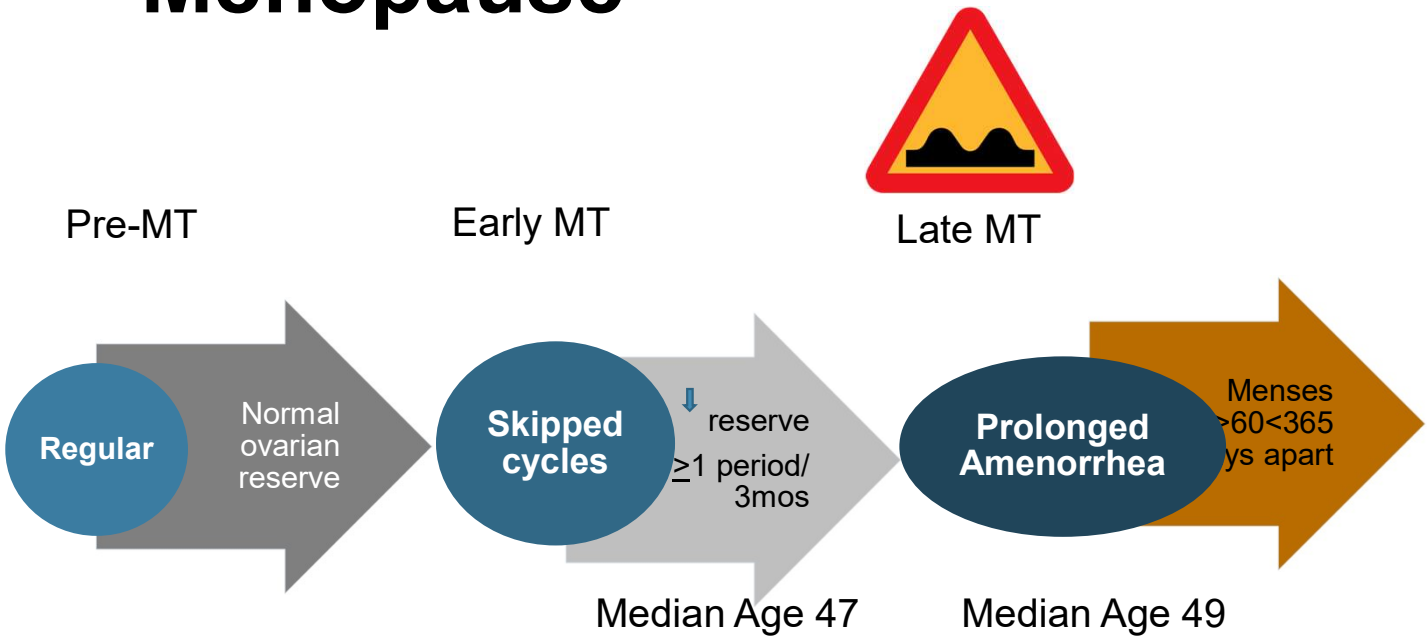
The Big Picture

- 60-85% of women will report hot flashes at some point during their menopausal transition
- Various estimates of workplace losses 2/2 menopause (hot flash) related disabilities, up to $7,000 per year in one study(Utian)
- For 85% of women, hot flashes eventually go away

When Do They Start?

- 22-68% of premenopausal, regularly cycling women report hot flashes (Gold, Reed)
- Prevalence varies several-fold by ethnicity
- Prevalence increases as women enter and traverse the menopause transition
- They are at their worst the year before and after the final menstrual period

The Road to Menopause

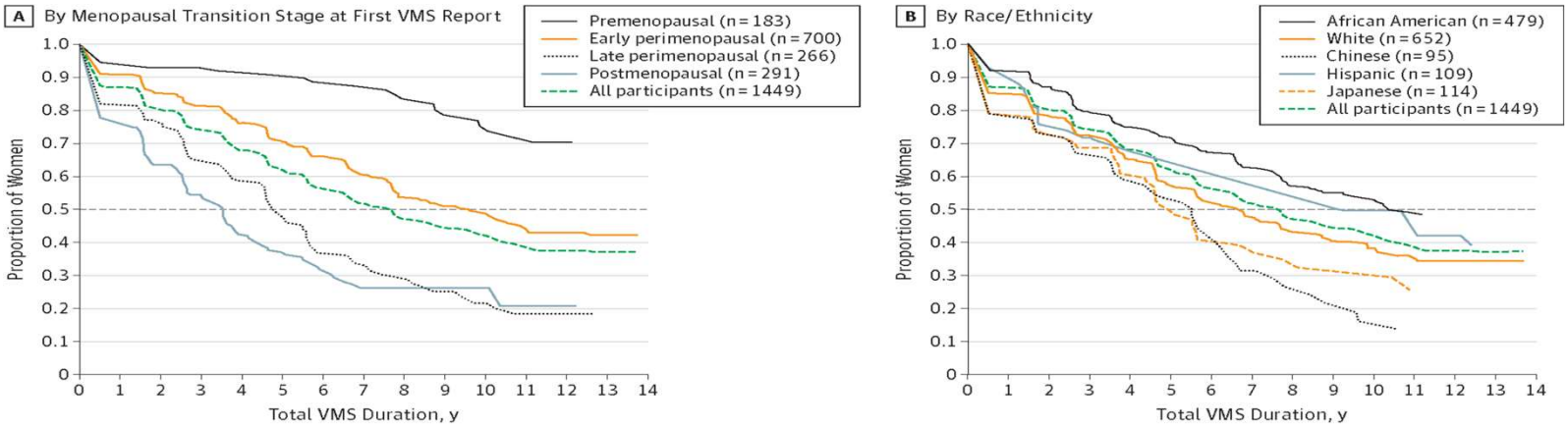


University of Colorado
Anschutz Medical Campus

Santoro, J Womens Health 2016; 25: 332-339

The JAMA Network

Duration of Menopausal Vasomotor Symptoms Over the Menopause Transition



Avis, JAMA Intern Med 2015; 175: 531-9

Date of download: 2/28/2015

Copyright © 2015 American Medical Association. All rights reserved.

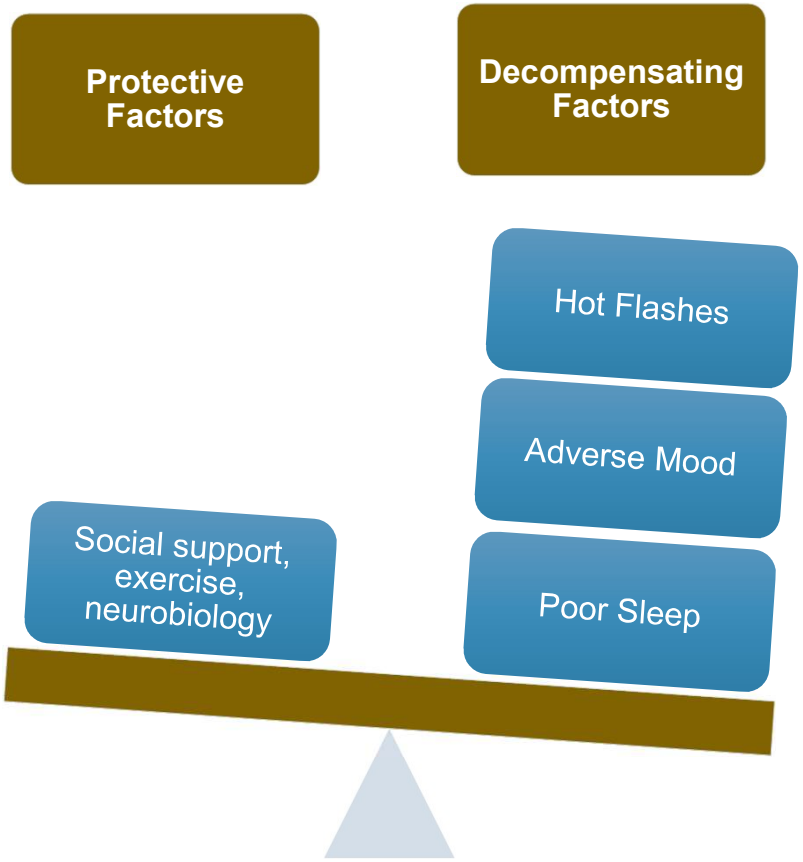
University of Colorado
Anschutz Medical Campus

How Many Women Seek Treatment for Symptoms?

- Population based survey of women aged 40-65 (N=3135)
- 60% sought care for symptoms
- Most common symptom: hot flashes
  - 34% used hormone therapy
  - 12% used CAM
  - 16% used both
  - ***That leaves 38% of women untreated***

Williams R Maturitas 2007; 58: 348

How Hot Flashes Erode Well Being



Early Menopause, POI, and Hormone 'Replacement'

- Menopause is early when it occurs < age 45 (5% prevalence)
- POI (primary ovarian insufficiency) is when menopause occurs < age 40 (1.1% prevalence)
  - More years of life with minimal exposure to estradiol
  - Greater lifetime risks of heart disease and osteoporosis
- Worse health outcomes for both oophorectomy and idiopathic POI
- In these cases HT is considered H**R**T or true replacement
- Based on limited data, it seems reasonable to replace women with E and/or P up to the age at natural menopause (app 51 yrs) when it is reasonable to do so

Luborsky JL, et al. Premature menopause in a multi-ethnic population study of the menopause transition. Hum Reprod. 2003 Jan;18(1):199-206.

Symptoms and Premenopausal Oophorectomy

- Believed to be more severe
  - Sleep
  - Mood (not all studies support risk; see Gibson vs Schuster
  - Hot flashed
  - Vaginal Dryness
- Independent risk factor for failure to ever wean off of hormones (Grady)

Gibson, Ob/Gyn 2012; 119: 935; Schuster, Menopause Int 2008; 14:111; Grady, Ob/Gyn 2003; 102:1233

Premenopausal Oophorectomy

Olmstead County Study:

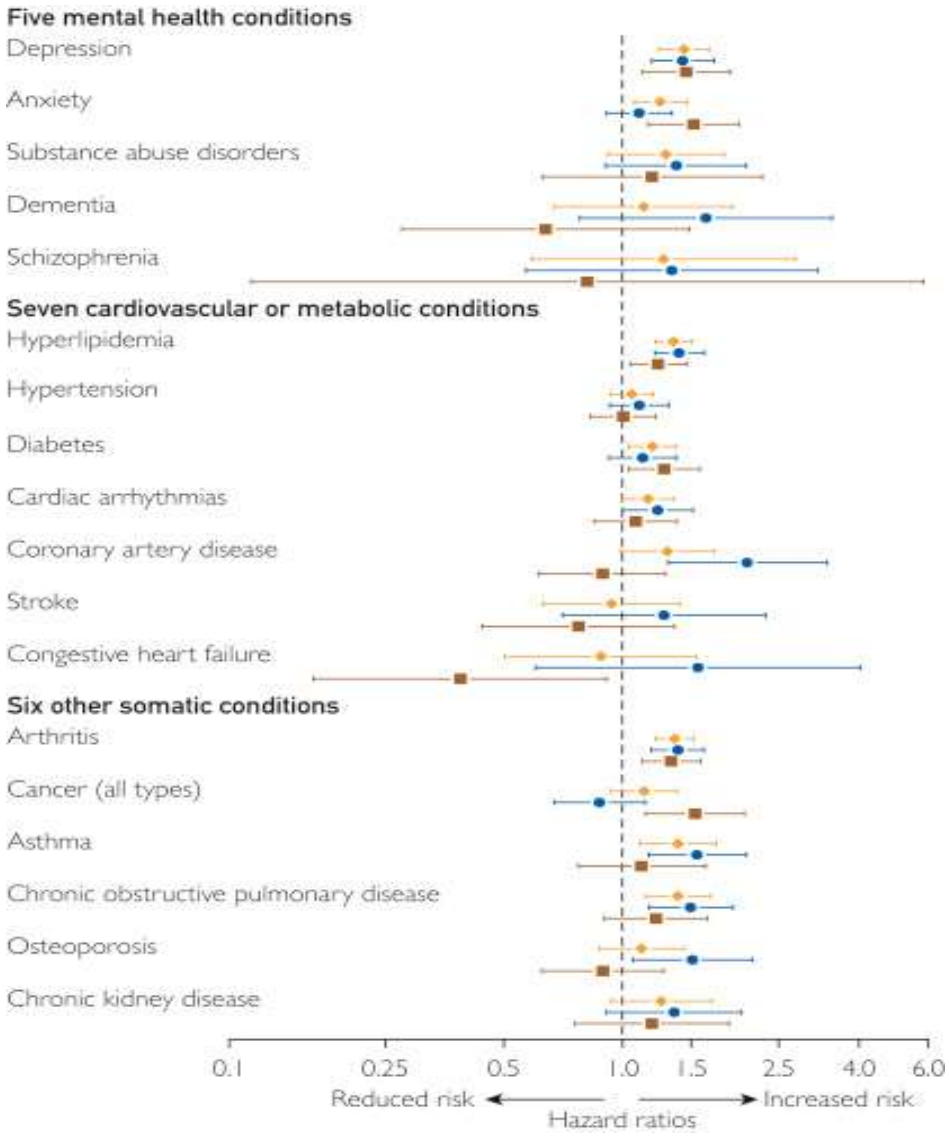
- 1,274 women with unilateral oophorectomy
- 1,091 women with bilateral oophorectomy
- 2,383 referent women age matched
- All surgeries performed 1950-1987

Premenopausal Oophorectomy

- Many years of life without hormones
- Worse menopausal symptoms
- Likely long-term consequence: bone resorption
- Possible long-term consequences:
  - Mortality (RR=1.5 [.97,2.34]), cancer (RR=2.34 [1.52, 4.98]; Cooper)
  - Adverse mood (Rocca)
  - Dementia (Rocca)
  - Cardiovascular disease (RR=1.17 [1.02, 1.35]; Parker)

Cooper, Am J Epi 1998; 8:229; Rocca, Mol Cell Endo 2014; Rocca, Neurodeg Dis 2012; 10:175; Parker WH, Ob/Gyn 2009; 113:1027

Multimorbidity Increased for Many Diseases After Premenopausal Oophorectomy …But Not By Much



Terms and Conditions

Mayo Clinic Proceedings 2016 911577-1589DOI: (10.1016/j.mayocp.2016.08.002

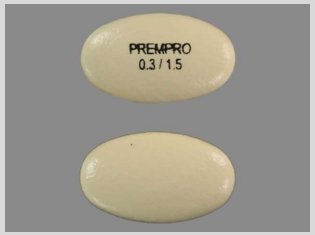
University of Colorado
Anschutz Medical Campus

Clinical Guidelines

- The Endocrine Society (2015), AACE (Cobin, 2017) and the North American Menopause Society (2022) recommendations favor:
  - Use of ‘natural’ E and P
  - Use of non-oral E
  - Consideration for extended use in women without a uterus (E alone) who remain symptomatic
  - Periodic re-evaluation of risks, benefits and alternatives

Stuenkel CA, J Clin Endocrinol Metab 2015; 100: 3975-4011; Cobin RH, Endocrine Pract 2017; 23: 869-881; The 2022 hormone therapy position statement of the North American Menopause Society Advisory Panel. Menopause 2022; 29: 767-794

MANY WAYS TO GIVE HORMONES



University of Colorado
Anschutz Medical Campus

Hormones or No Hormones?

Systemic Options

- Transdermal (non oral) estradiol[1]
- Oral estradiol
- Oral conjugated equine estrogens
- Progestin
  - Oral micronized progesterone
  - LNG IUD
  - Medroxyprogesterone acetate
- No progestin needed
  - Conjugated equine estrogen + bazedoxifene

Non hormonal options[2]

- Fezolinetant[3]
- SSRI
  - Paroxetine mesylate[3]
  - Venlafaxine
  - Citalopram/escitalopram
- Gabapentin
- Oxybutinin
- Clonidine

University of Colorado
Anschutz Medical Campus

[1] Preferred; [2] Practice Bulletin #141: Management of Menopausal Symptoms. Obstet Gynecol 2016; 127: 166; [3] FDA approved

Clinical Pearls on HT or HRT Use

- Women with early menopause or POI frequently need higher doses of estrogen to control their symptoms
- If one is taking on the risks and benefits of HT or HRT, symptoms should be well controlled ('lowest dose for shortest time' does not mean undertreatment!)
- Women with atypical but bothersome symptoms may benefit from a 3 month trial of HT to assess improvements
  - It is not necessary to go steady with hormones immediately, it's OK to date!
  - Approach allows a deferral of detailed risk/benefit discussions until the benefit can be established

Absolute Risks and Benefits of MHT
WHI Cases /10,000 Women-Years

EVENT	E+P	E-Alone
CHD	+ 6	- 3
Stroke	+ 7	+12
VTE	+18	+ 8
Breast Ca	+ 8	- 6
Hip Fracture	- 5	- 6
Colon Ca	- 6	+ 1
Ovarian Ca	+1.5	--
Lung Ca	+2.5	+2.0

Statistically significant

WHI Publications, various.

How to Understand Risks

Disease	Background risk/10K woman-yrs	Attributable Risk From HT	Cases/yr with HT/10K woman-yrs
VTE	12	8-18	20-30
CHD	26	-3 to +6	23-29
Stroke	23	7-12	29-41
Breast Cancer (E+P)	600	8	608
Breast Cancer (E Alone)	600	-6	594
Colon Cancer	8	-6 to +1	2-9

References: VTE: https://academic.oup.com/humupd/article/19/5/471/614569; CHD: https://www.ahajournals.org/doi/10.1161/01.CIR.99.9.1165; breast cancer: https://www.cancer.gov/types/breast/risk-fact-sheet and https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/breast-cancer/incidence-invasive#heading-One; stroke: https://www.ahajournals.org/doi/10.1161/STROKEAHA.120.028910; Hip fracture: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2766835/; colon cancer: https://www.cancer.org/content/dam/cancer-org/research/cancer-facts-and-statistics/colorectal-cancer-facts-and-figures/colorectal-cancer-facts-and-figures-2020-2022.pdf

Was the WHI Right About Everything?

It remains the largest and most comprehensive RCT of HT ever performed, but consider:

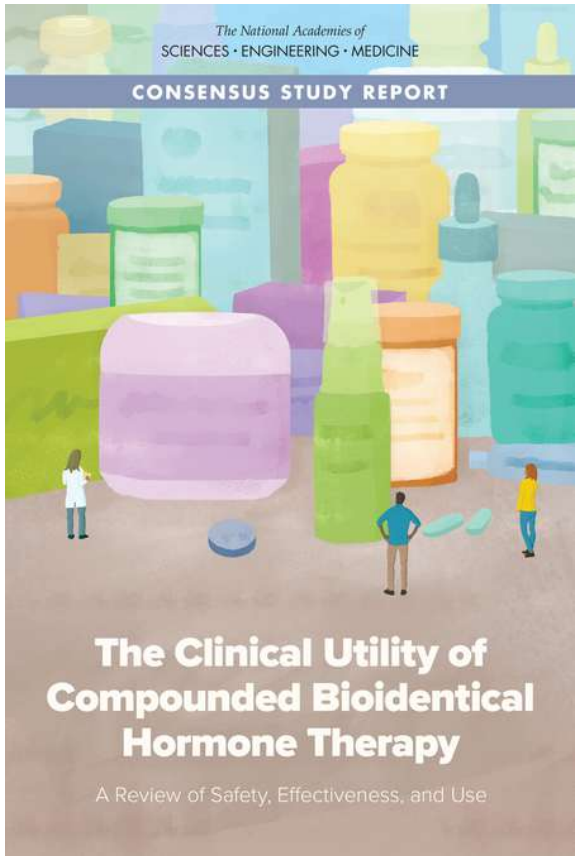
- **It was not designed to demonstrate the usefulness of hormone therapy for menopausal symptoms**
- 1/3 of enrolled participants were in the 50-59 age range at study start
- Women with the worst symptoms were likely excluded (3 month hormone washout required)
- Hormones used are no longer first line for HT (CEE and MPA) and may have different tissue specific effects than currently used preparations

Beware the Pellet, 'Compounded Bioidentical Hormones', and Other Products of the Disinformation highway

- Compounded hormones are not subject to FDA regulation; they are classified as dietary supplements
- No need to support a proof of claim
- Pellet hormone therapy increases patient and healthcare system costs, results in more visits for bleeding, and supraphysiologic hormone levels*

University of Colorado
Anschutz Medical Campus

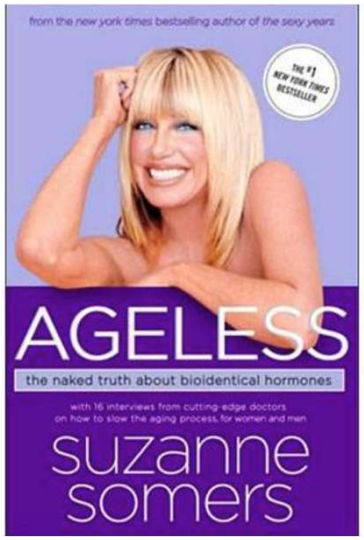
*Jiang X, et al Safety assessment of compounded non-FDA-approved hormonal therapy versus FDA-approved hormonal therapy in treating postmenopausal women. Menopause. 2021 May 10;28(8):867-874.



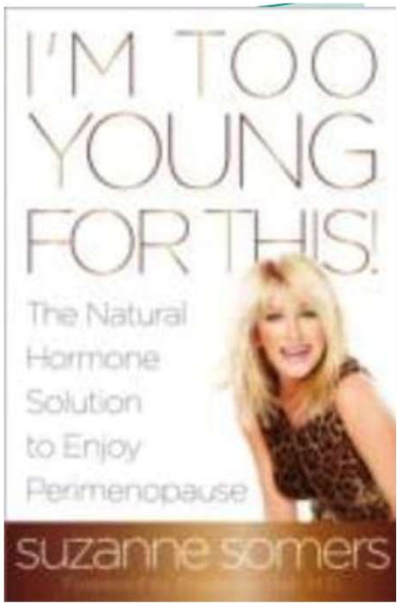
National Academy of Medicine

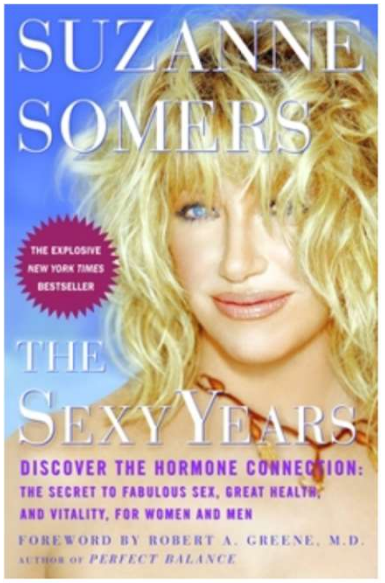
- Recommends against use
- Calls for oversight of COIs, increased surveillance and expansion of medical evidence
- Consider select agents ‘difficult to compound’

Spokesmodel for ‘Compounded Bioidentical Hormones’



Breast cancer
from CBHT!

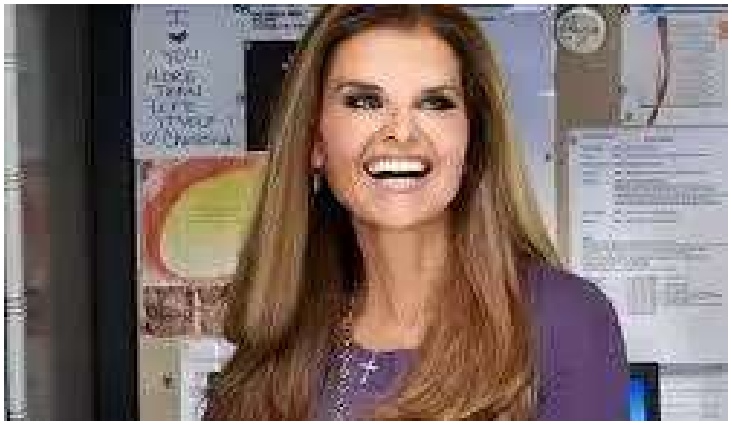




Endometrial cancer
from CBHT!

University of Colorado
Anschutz Medical Campus

Our 2025 Spokesmodels



University of Colorado
Anschutz Medical Campus

Doc, I Need You to Check My Hormone Levels

- When using FDA approved medications with known PK there is ***no reason*** to check hormone levels
- Doses are titrated to symptom control, therefore aiming for a target hormone level is not logical
- There is also no menopause test
  - FSH, when very high is a reasonable predictor of imminent menopause (within one year)
  - So is antimullerian hormone (AMH)
  - Both are age dependent in predictive value
  - Can be helpful in women who do not have menses

Finkelstein JS, et al. Antimullerian Hormone and Impending Menopause in Late Reproductive Age: The Study of Women's Health Across the Nation. J Clin Endocrinol Metab. 2020 Apr 1;105(4):e1862–71.

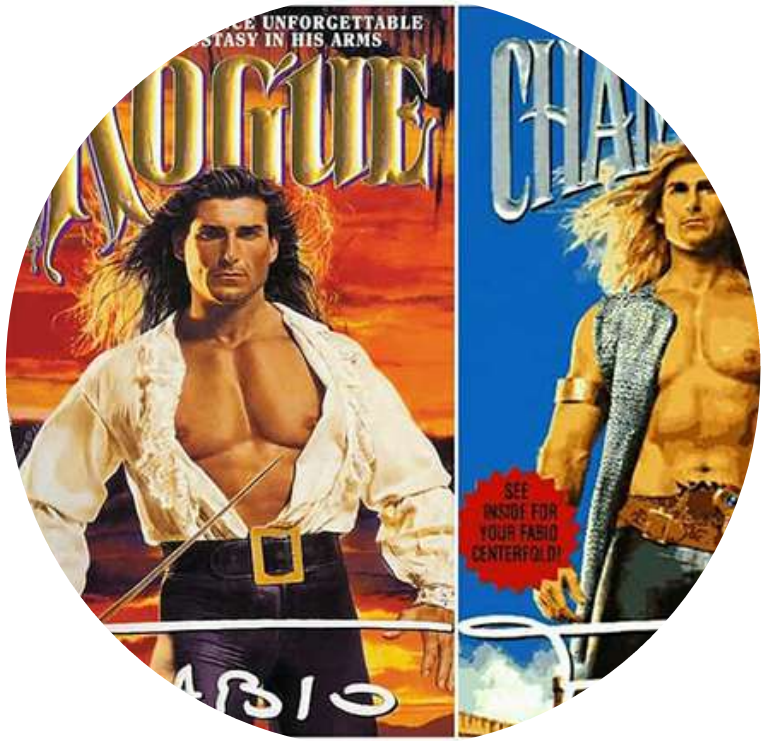
Is There a Role for Testosterone?

- There is no FDA approved testosterone preparation for women
- Off label use for **hypoactive sexual desire disorder only**
- Testosterone does NOT decrease with menopause
- Aim for ULN of normal female range, recheck at 3 months and if no improvement>>>STOP
- T is similar to CBT (and other meds) in efficacy for HSDD
- The online hype is far beyond its actual effectiveness

Davis SR, et al. Testosterone for low libido in postmenopausal women not taking estrogen. N Engl J Med. 2008 Nov 6;359(19):2005-17; Pyke RE, Clayton AH. Effect Size in Efficacy Trials of Women With Decreased Sexual Desire. Sex Med Rev. 2018 Jul;6(3):358-366.

Reasons for Skepticism

- There is no defined testosterone deficiency syndrome in women
- There is no measurable level of testosterone below which women become ill
- There is no sudden drop in testosterone at menopause in women—circulating levels do not change and bioavailable T may even increase!
- There is a wildly lucrative business selling the Mystique of Testosterone to women
- There is no increase in sexual dysfunction concentrated around menopause



Summary

- Hormone therapy is a generally overall benign treatment for symptomatic menopausal women without contraindications
- Women with early or premature menopause should receive replacement gonadal hormones at least until the median age at natural menopause and then be re evaluated
- Compounded hormones should be avoided and used only for the usual reasons (intolerance of all FDA approved meds or no FDA preparation available


University of Colorado Anschutz Medical Campus
THANK YOU