Managing complications of cancer therapy in the female veteran/patient

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VA HEALTH CARE Defining EXCELLENCE in the 21st Century

Disclosure

- I have no actual or potential conflicts of interest in regards to this presentation
- The planners, editors, and reviewers of this activity have no relevant financial relationships to disclose

Objectives

- Review 2018 ASCO guidelines on fertility preservation
- Identify patients at risk for osteopenia and osteoporosis secondary to cancer therapy
- Discuss treatment options for vasomotor symptoms of menopause

Fertility Preservation

Question # 1

Which of the following is not considered to be a reasonable approach for fertility preservation for a female patient with melanoma according to guidelines from the American Society of Clinical Oncology and the National Comprehensive Cancer Network?

A. Embryo cryopreservation
B. Oocyte cryopreservation
C. Ovarian tissue cryopreservation
D. Goserelin 3.6mg SubQ injection every 28 days until conclusion of chemotherapy

Background

- Nearly 70,000 individuals between the ages of 15-39 years are diagnosed with cancer each year in the United States
- According to one estimate, 42% of female cancer patients of reproductive age may develop premature ovarian failure as a result of their chemotherapy
- As an increasing number of women choose to delay childbirth until later in life, the concept of fertility preservation has become more important because these women are getting diagnosed before having children

"Adolcescents and Young Adults with Cancer." Cancer.gov. National Cancer Institute. 31 January 2018. Web. 30 July 2018
Larsen EC, et al. J Clin Endocrinol Met 2003;88:5307–5314.
Levine J, et al. J Clin Oncol. 2010; 28: 4831-4841

Risk of Amenorrhea Associated with Various Treatment Agents

Risk Category	Treatment Agents and Modalities
High Risk (>80% of women develop amenorrhea post-treatment)	• Any alkylating agent + total brain or pelvic radiation • Alkylating chemotherapy (e.g. cyclophosphamide, busulfan, melphalan) when used in conditioning for bone marrow transplant • CMF, CEF, CAF 6 cycles in women age 40 and older*
Medium Risk (30-70%)	• CMF, CEF, CAF 6 cycles in women age 30-39* • Doxorubicin/cyclophosphamide x 4 cycles in women > 40 years
Low Risk (<20%)	• CMF, CEF, CAF 6 cycles in women under 30 years of age*
Unknown Risk (examples)	• Tyrosine kinase inhibitors • Monoclonal antibodies

*Breast cancer treatment regimens with combinations of cyclophosphamide, methotrexate, fluorouracil, doxorubicin, and epirubicin

Lee AJ, et al. J Clin Oncol. 2006; 24 (18): 2917-2932); Meirow D, et al. Clin Obstet Gynecol. 2010; 53: 727-739; Liedtke C, et al. Geb Fra. 2012; 72(9): 809–818

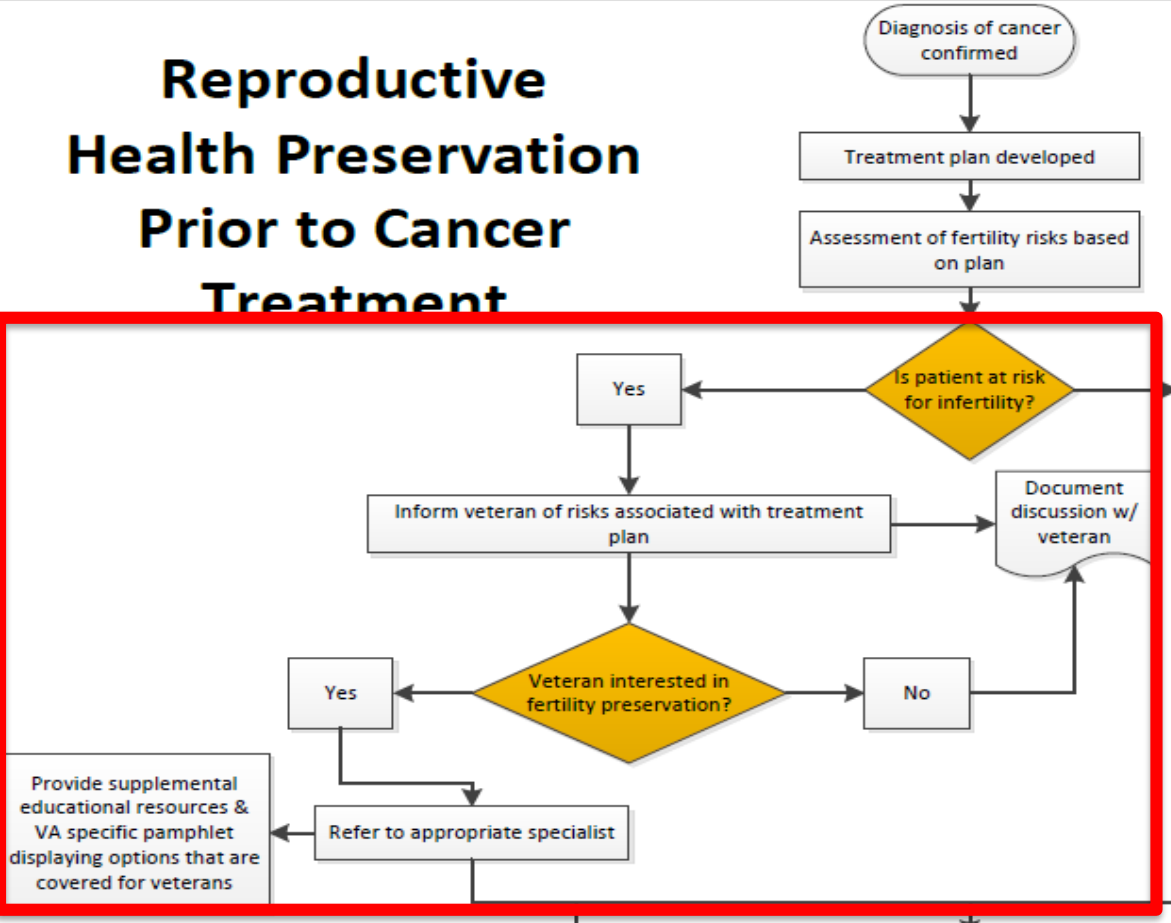
General Recommendations on Fertility Preservation in Females

ASCO	NCCN
• Healthcare providers should address infertility before treatment starts • Interested patients should be referred to reproductive specialists • Refer patients to psychosocial providers when they are distressed about potential infertility	• Options for fertility preservation should be discussed prior to starting treatment • A referral should be placed within 24 hours for patient interested in fertility preservation • Refer to a mental health professional to assist with complex decision making

Oktay K, et al. J Clin Oncol. 2018; 1994-96
Cocca PF, et al. J Natl Canc Netw. 2017; 10-14

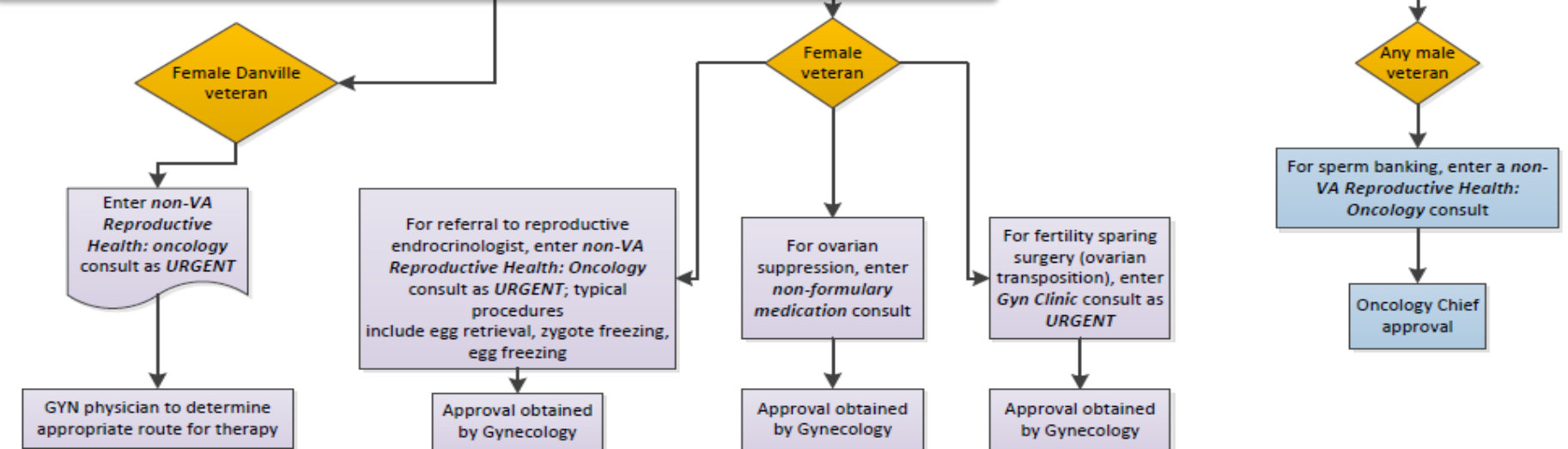
ASCO: American Society of Clinical Oncology
NCCN: National Comprehensive Cancer Network

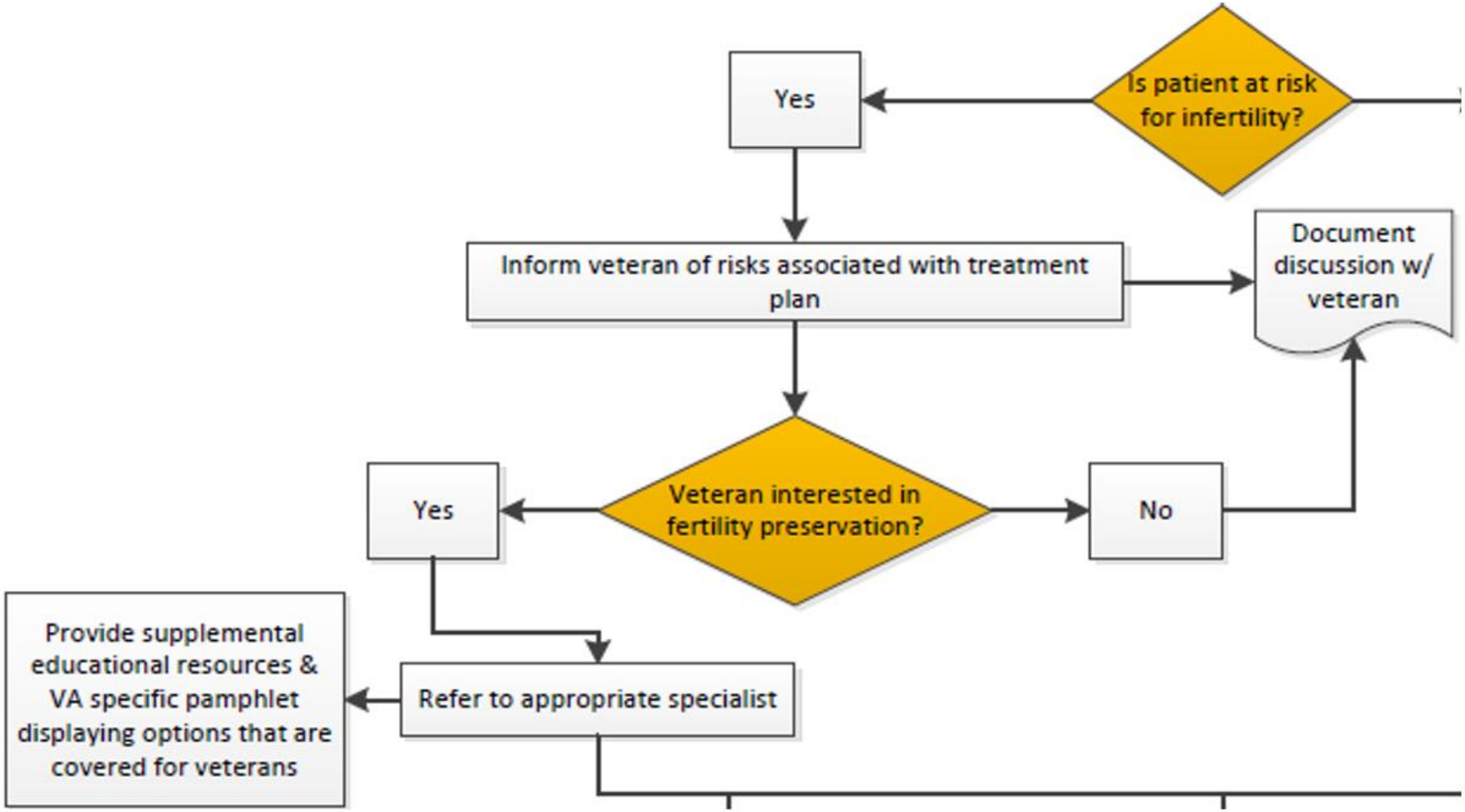
Reproductive Health Preservation Prior to Cancer Treatment



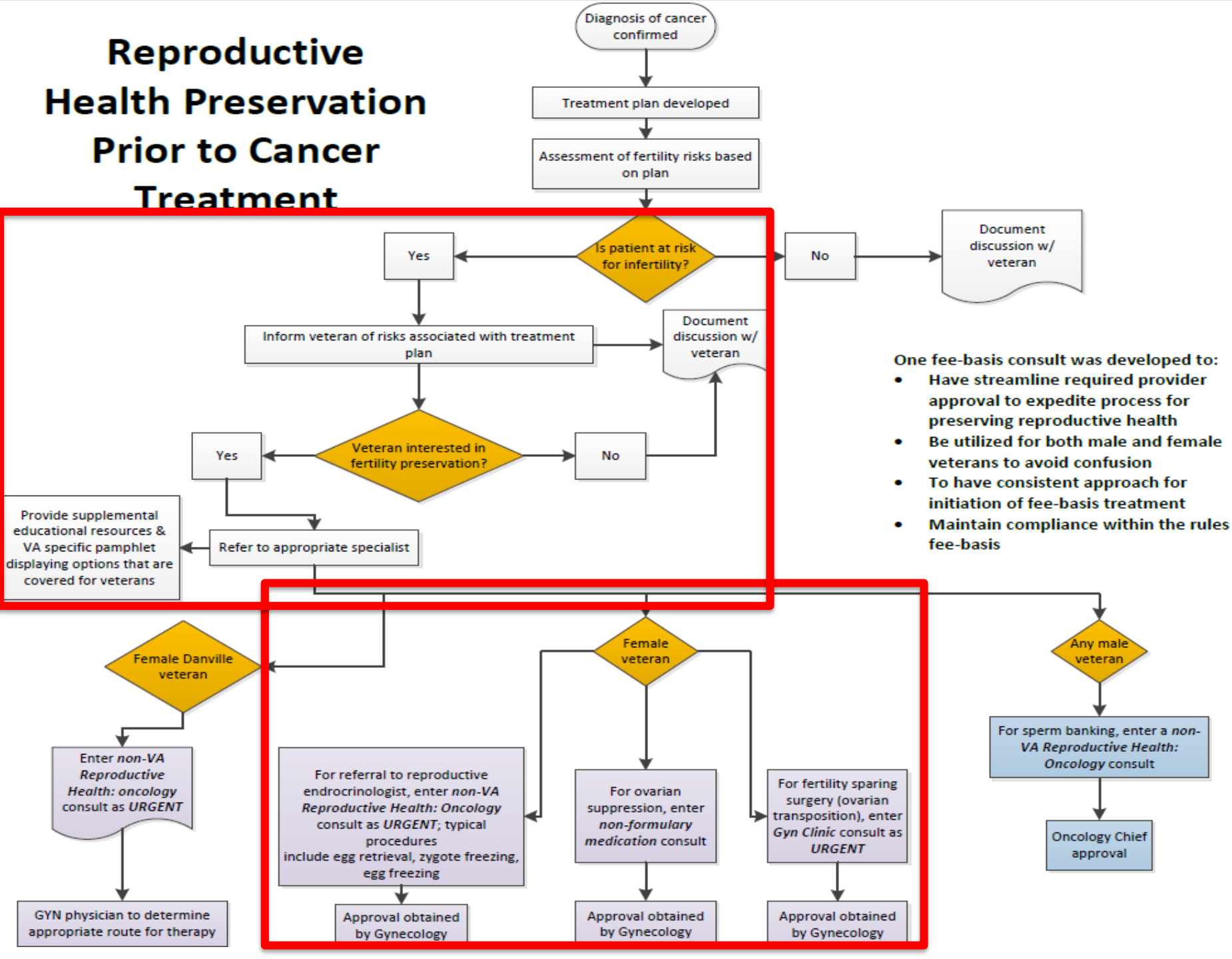
One fee-basis consult was developed to:

- **Have streamline required provider approval to expedite process for preserving reproductive health**
- **Be utilized for both male and female veterans to avoid confusion**
- **To have consistent approach for initiation of fee-basis treatment**
- **Maintain compliance within the rules for fee-basis**




Is patient at risk for infertility?
Yes
Inform veteran of risks associated with treatment plan
Document discussion w/ veteran
Veteran interested in fertility preservation?
Yes
No
Refer to appropriate specialist
Provide supplemental educational resources & VA specific pamphlet displaying options that are covered for veterans

Reproductive Health Preservation Prior to Cancer Treatment



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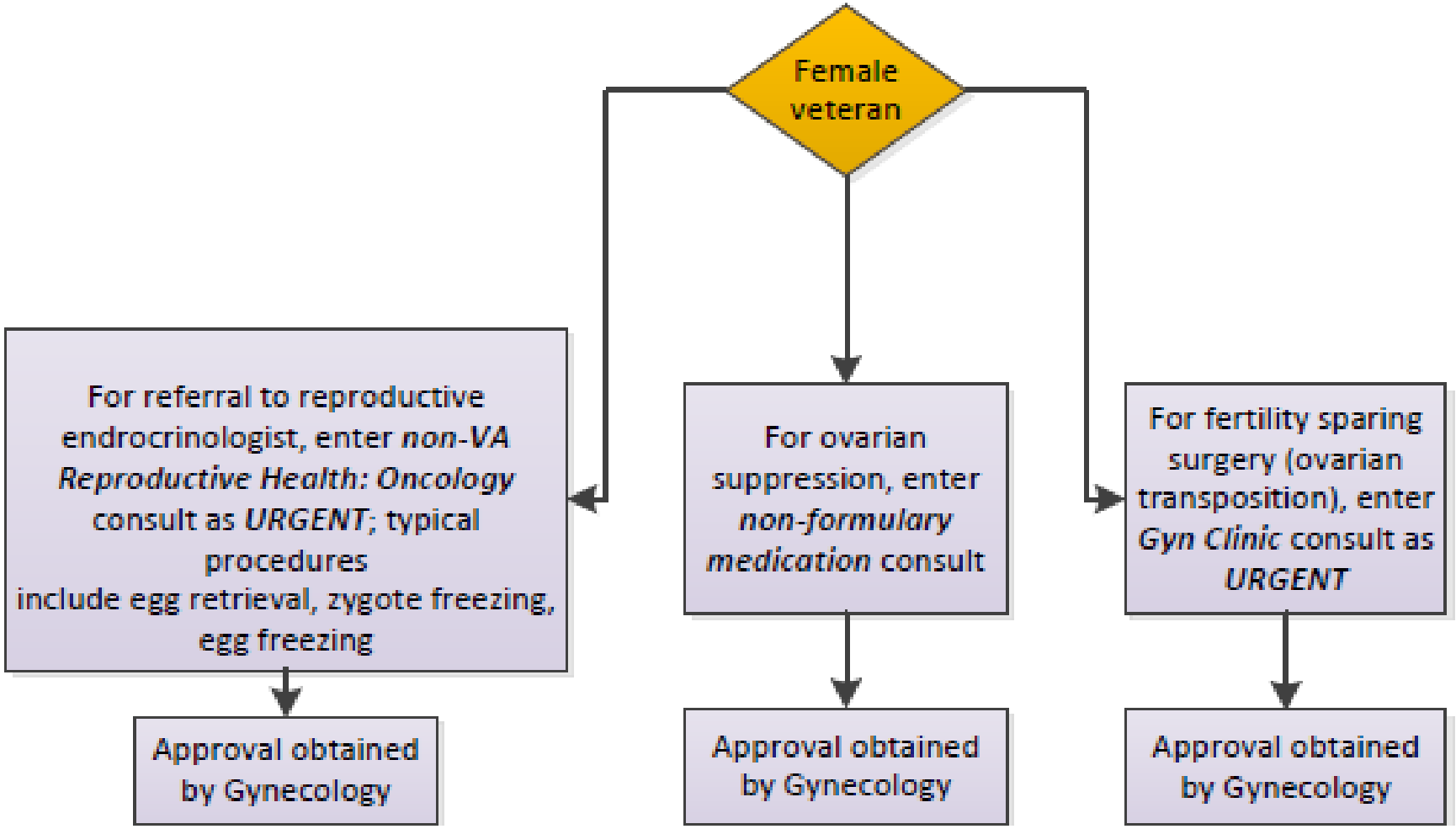
Female veteran
For referral to reproductive endrocrinologist, enter *non-VA Reproductive Health: Oncology* consult as *URGENT*; typical procedures include egg retrieval, zygote freezing, egg freezing
Approval obtained by Gynecology
For ovarian suppression, enter *non-formulary medication* consult
Approval obtained by Gynecology
For fertility sparing surgery (ovarian transposition), enter *Gyn Clinic* consult as *URGENT*
Approval obtained by Gynecology

Recommendations on Fertility Preservation Procedures

ASCO	NCCN
• Ovarian transposition can be offered when pelvic radiation is performed • Embryo cryopreservation is an established fertility method • Cryopreservation of oocytes is an additional option *New Update* • Ovarian tissue cryopreservation is still an experimental procedure in this country	• Ovarian transposition should be considered for all female patients who will be receiving radiation treatment • Embryo and oocyte cryopreservation are options and should be discussed • Ovarian tissue cryopreservation may also be considered if available

Oktay K, et al. J Clin Oncol. 2018; 1994-96
Cocca PF, et al. J Natl Canc Netw. 2017; 10-14

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Methods of Fertility Preservation

Ovarian Transposition

- Surgical repositioning of ovaries away from radiation field
- Does not protect from chemotherapy

Oocyte Cryopreservation and Embryo Cryopreservation

- Gold standards of fertility preservation
- ~2 weeks for oocyte retrieval
- Cycle-day independent schedule

Ovarian Tissue Cryopreservation

- Does not require ovarian stimulation
- Less evidence regarding utility
- Concern for cancer recurrence

GnRH Agonists

- Mechanism of Action
  - Causes a sustained suppression in luteinizing hormone (LH) and follicle stimulating hormone (FSH) with chronic administration that results in a state of hypogonadal anovulation
- Adverse Effects (Females >30%)
  - headache, emotional lability, hot flashes, decreased libido
- Agents Investigated in Fertility Preservation
  - goserelin, triptorelin, buserelin

Recommendations Regarding GnRH Agonists

ASCO	NCCN
New Update • When other fertility preservation methods are not viable, and in the setting of young women with breast cancer, GnRH agonists may be offered • Due to conflicting evidence, GnRH agonists should not be used in place of proven fertility preservation methods	• GnRH agonists are currently not recommended as an option for fertility preservation due to insufficient evidence

Oktay K, et al. J Clin Oncol. 2018; 1994-96
Cocca PF, et al. J Natl Canc Netw. 2017; 10-14

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Resources

- The Oncofertility Consortium (Northwestern University)
  - Research group
  - Worldwide fertility clinic locator
  - Call center (FERTLINE) with patient navigators
- SaveMyFertility.org
  - Associated with Oncofertility Consortium
  - Pocket guides for patients and healthcare providers
- LIVESTRONG Foundation
  - Educational resources for healthcare providers
  - Financial assistance information for patients

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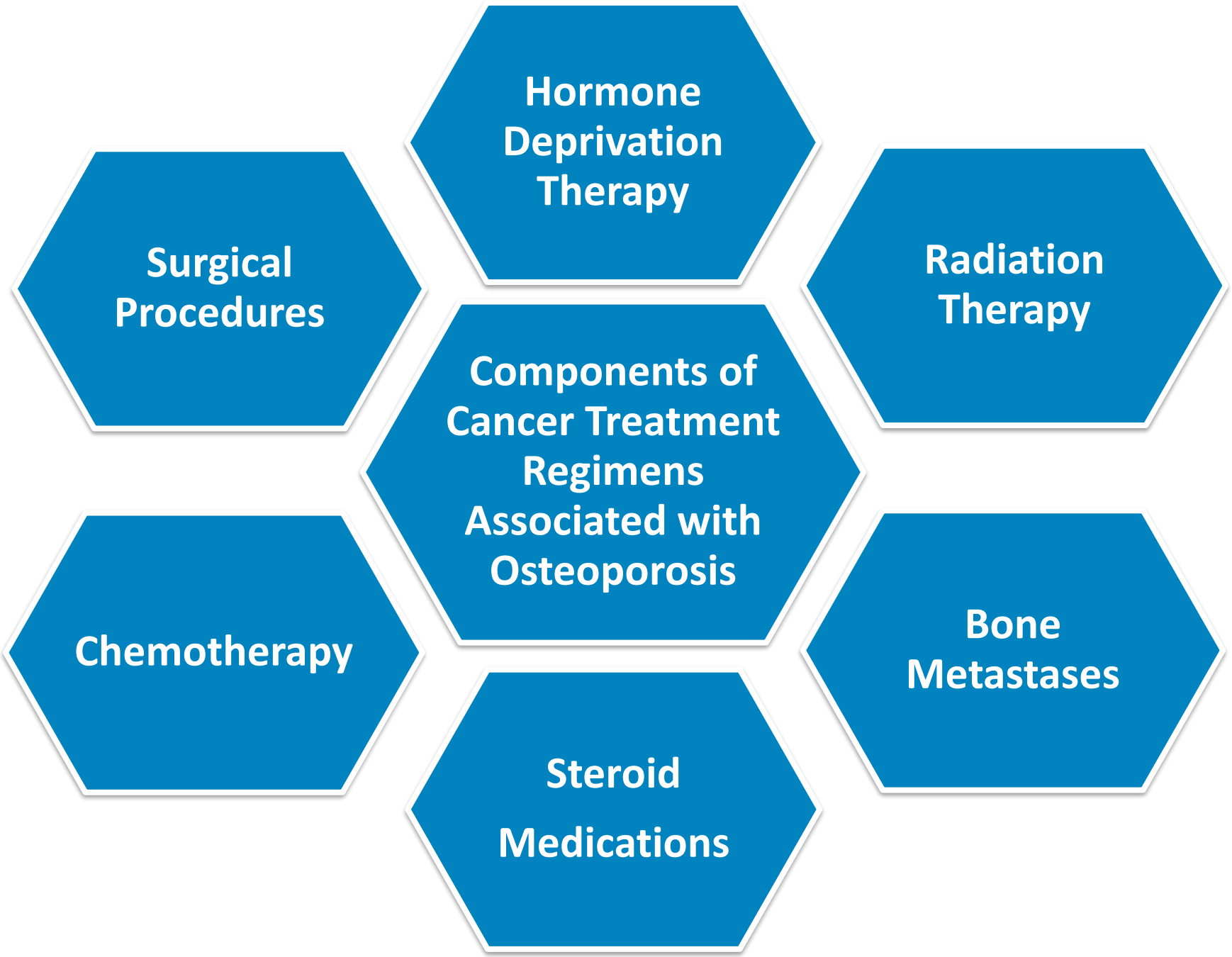
Osteopenia and Osteoporosis

Question # 2

According to recommendations from the American Society of Clinical Oncology, which of the following patients should have bone mineral density testing performed in order to evaluate bone strength:

A. A postmenopausal breast cancer survivor who has never had baseline testing done
B. An ovarian cancer survivor who has experienced chemotherapy induced premature menopause and has not had testing performed in 5 years
C. A premenopausal woman taking a GnRH agonist who has not had testing performed in the last 2 years
D. All of the above



Stava C, et al. J Can Surv. 2009; 3(2): 75-88

Assessment of Bone Health

- Risk factors for osteoporosis and fractures
  - Age, family history, smoking, alcohol intake, calcium/vitamin D deficiency, medication utilization
- Bone Mineral Density (BMD)
  - Dual X-ray absorptiometry (DXA) is the most common clinical tool to directly measure BMD and indirectly evaluate bone strength
- WHO fracture risk assessment tool (FRAX)
  - Algorithm for assessing 10-year risk of hip and major osteoporotic fracture in postmenopausal women
  - Not as commonly used as regular DXA procedure

Recommendations Regarding Screening for Osteoporosis in Women with a History of Cancer

ASCO	NCCN
• Postmenopausal cancer survivors should have baseline testing done to assess risk of osteoporosis • Repeat DXA scans should be obtained every 2 years for: - Women on aromatase inhibitors - Premenopausal women on GnRH agonists - Women who have treatment induced premature menopause	• All women who have received therapy for cancer that: - Induced early menopause - Reduced sex steroid levels or interfered with their function should undergo testing to assess risk of bone loss and osteoporosis

Gralow JR, et al. J Nat Comp Can Net. 2013; 11: 1-38
Runowicz RD, et al. J Clin Oncol. 2016; 34 (6): 611-635

Management of Bone Health in Cancer Survivors

Lifestyle Modifications

- Exercise
- Smoking cessation
- Avoidance of excessive alcohol consumption

Vitamin Supplementation

- Calcium
  - 1000 - 1200mg/day
- Vitamin D
  - 600 - 1000 IU/day

Gralow JR, et al. J Nat Comp Can Net. 2013; 11: 1-38

Management of Bone Health in Cancer Survivors

Bisphosphonates

- MOA: Act on osteoclasts to decrease bone resorption leading to an increase in bone mineral density
- Oral Agents: alendronate, risedronate, ibandronate
- IV Agents: pamidronate, zoledronic acid

RANK-L Inhibitor

- MOA: Binds to RANKL ligand to prevent binding with receptor, thereby preventing osteoclast formation and bone resorption
- IV Agent: denosumab

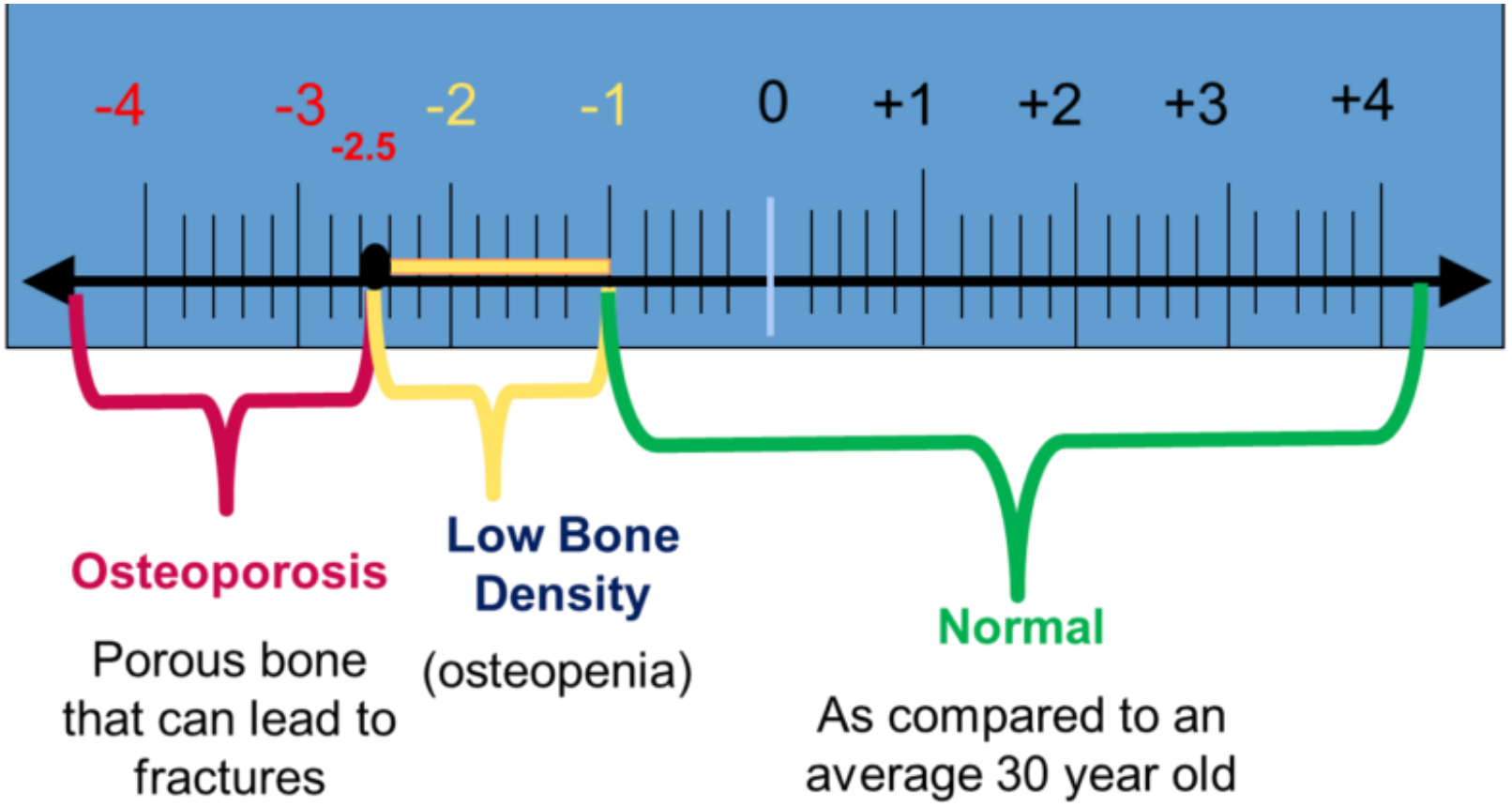
Recommendations Regarding Bone Modifying Agents in Cancer Patients and Survivors

National Comprehensive Cancer Network (NCCN)

- Pharmacologic therapy with bisphosphonates or denosumab should be initiated in patients with a DXA scan T score ≤ -2.0
- Therapy should also be considered for patients with a T score < -1.5 who have lost significant bone mineral density as a result of cancer therapy
- Optimal duration of therapy has not been established
- Factors to consider for duration of bone modifying agents include:
  - Bone mineral density
  - Response to therapy
  - Risk factors for continued bone loss or fracture

Gralow JR, et al. J Nat Comp Can Net. 2013; 11: 1-38

T-Score Relevance



"Understanding Bone Density Results." AmericanBoneHealth.org. n.d. Web. 31 Jul 2018

Adverse Effects of Bone Modifying Agents

- GI toxicity
  - Esophageal and gastric ulcers, esophagitis
- Flu-like symptoms
  - Myalgia, arthralgia, low-grade fever
- Renal dysfunction
  - Acute renal toxicity has occurred following infusion with IV agents
  - Denosumab may be a preferred agent for osteoporosis in patients with renal dysfunction

Guise TA. The Oncologist. 2006; 11:1121-1131
Camacho PM, et al. Endocr Pract. 2016; 22 (9): 1111-1118

Adverse Effects of Bone Modifying Agents

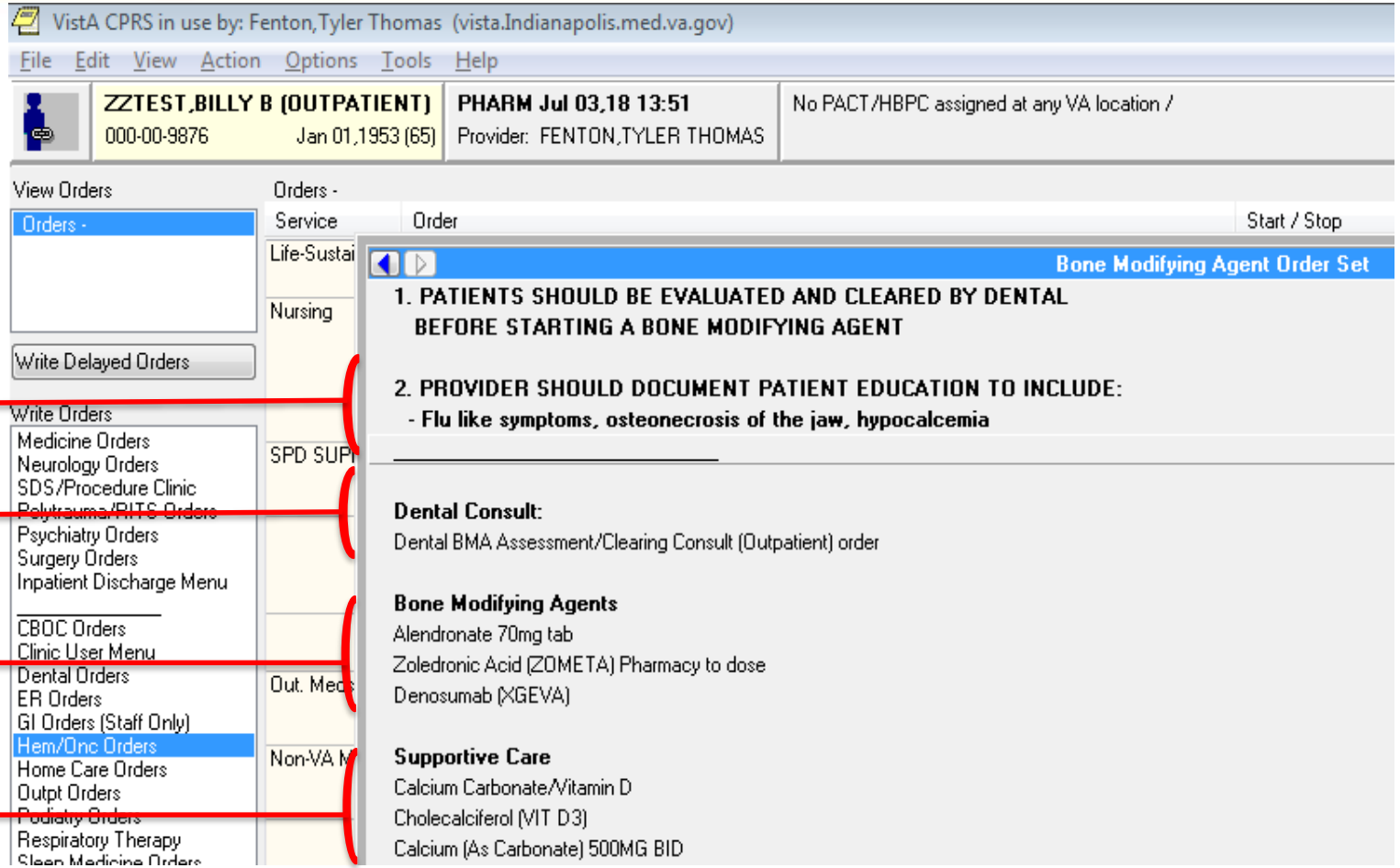
- Hypocalcemia
  - According to NCCN guidelines, all women taking bone modifying agents should also be taking supplemental calcium and vitamin D
- Osteonecrosis of the jaw (ONJ)
  - Risk factors include longer duration of treatment, dental extractions, periodontal disease, and older age
  - NCCN guidelines recommend a dental examination with any necessary preventive dentistry prior to initiation of therapy with bone modifying agents

Guise TA, et al. The Oncologist. 2006; 11:1121-1131
Badros A, et al. J Clin Oncol. 2006; 24: 945-952
Gradisher WJ, et al. NCCN Guidelines Breast Cancer. 2018; 1: 28

Handling Bone Modifying Agents at the Indianapolis VA Medical Center

- Creation of a bone modifying agent order set that includes the following information:
  - A dental consult order for patients before starting therapy
  - Selections for orderable bone modifying agents
  - Options for ordering calcium and vitamin D supplements
- Creation of a hormonal agents order set with the following information:
  - Recommendation for a DXA scan prior to starting therapy
  - Instructions on utilizing the bone modifying agent order set if hormonal agents are indicated

Handling Bone Modifying Agents at the Indianapolis VA Medical Center



Education

Dental Consult

Orderable BMAs

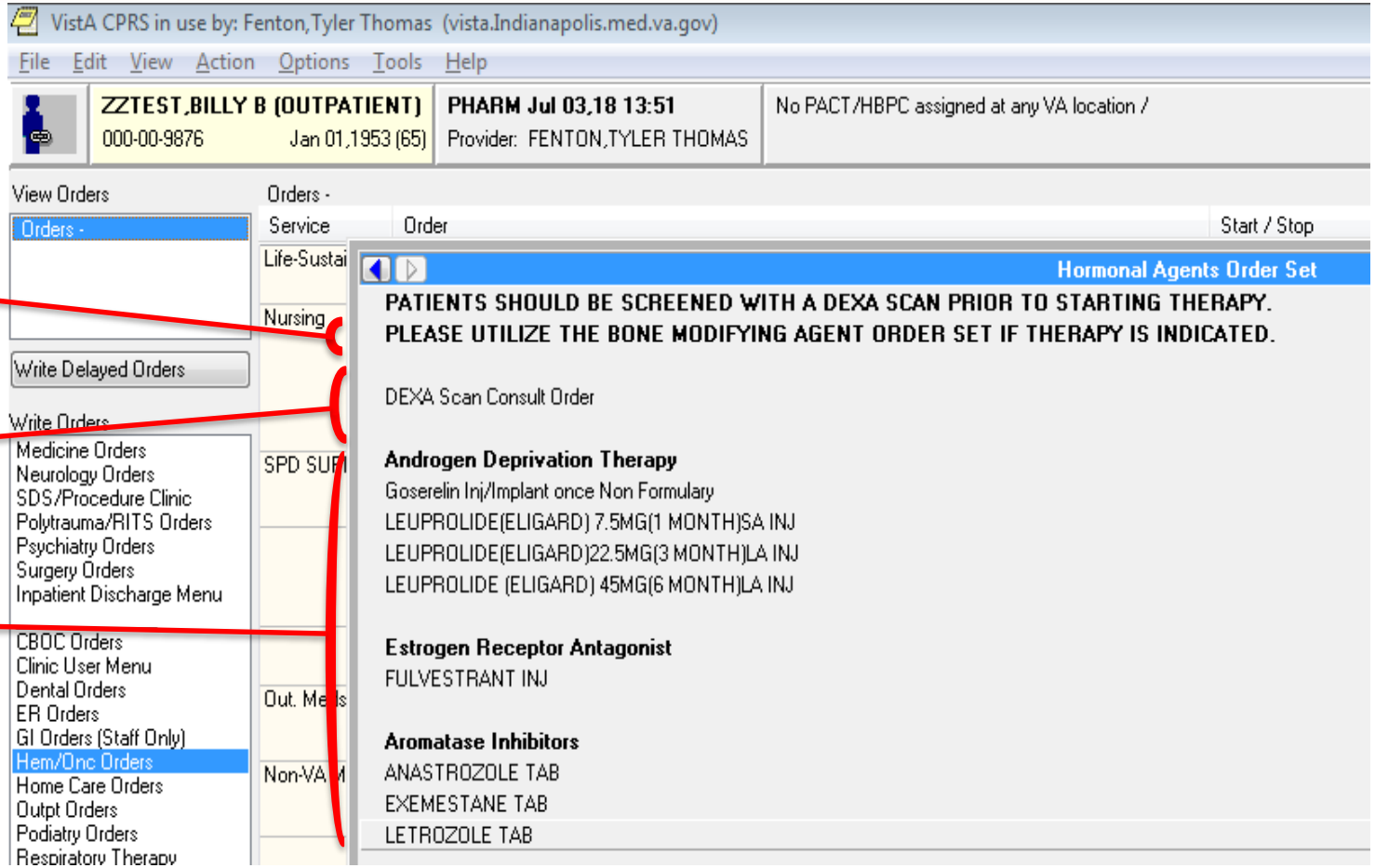
Supportive Care

Handling Bone Modifying Agents at the Indianapolis VA Medical Center

Utilize BMA Order Set

Baseline DXA Scan

Orderable Hormone Agents



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Vasomotor Symptoms

Question #3

Which of the following medications is FDA approved for the treatment of vasomotor symptoms associated with menopause:

A. Citalopram

B. Gabapentin

C. Pregabalin

D. Paroxetine

Background

- For the treatment of cancer in females, some approaches involving chemotherapy, radiation, and/or surgery carry a risk of ovarian failure and the accompanying symptoms of premature menopause
- Menopausal symptoms such as hot flashes are reported to occur in as many as 73% of breast cancer survivors
- Symptoms resulting from induced menopause are typically more severe in younger cancer survivors
- Proper treatment for these patients is important due, in part, to the total length of time that women can be suffering from hot flashes

Carmen MG, et al. Gynecol Oncol. 2017; 146: 427-435
Howard-Anderson J, et al. J Natl Cancer Inst. 2012; 104:386-405
Freeman EW, et al. Menopause. 2014; 21 (9): 924-932

Non-Pharmacologic Approaches

- Acupuncture
- Yoga
- Smoking Cessation
- Weight Loss
- Exercise

Hormonal Therapy for the Management of Hot Flashes

- Hormone therapy is the most effective treatment for the management of vasomotor symptoms
- Formulations of hormonal therapy products on the market include oral, transdermal, vaginal rings, and intrauterine devices
- Possible risks associated with MHT include stroke, venous thromboembolism, and an increased risk of first incidence or recurrence of certain cancers

Denlinger CS, et al. NCCN Guidelines Survivorship. 2018; 1: 32-36
Carmen MG, et al. Gynecol Oncol. 2017; 146: 427-435
Manson JE, et al. JAMA. 2013; 310: 1353-1368

Recommendations Regarding Menopausal Hormone Therapy (MHT)

NCCN

- Alternatives to MHT should typically be tried first and patients should be referred to an appropriate women's health specialist for management of MHT if it is warranted
- MHT is contraindicated in survivors with a history of hormonally mediated cancers
- When MHT is being used it should be the lowest dose possible to provide adequate control of symptoms

Denlinger CS, et al. NCCN Guidelines Survivorship. 2018; 1: 32-36

NCCN: National Comprehensive Cancer Network

Non-Hormonal Medication Options for Vasomotor Symptoms

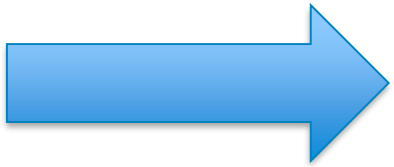
FDA Approved Treatment	
Medication	Dosing Instructions
Paroxetine (Brisdelle)	7.5mg once daily at bedtime
Non FDA Approved Treatment	
Medication	Dosing Instructions
Escitalopram	10mg once daily; may titrate every 4 weeks
Gabapentin	400mg once daily at bedtime; may titrate every 3-7 days
Pregabalin	50mg once daily at bedtime; may titrate every week
Venlafaxine ER	37.5mg once daily; may titrate every week

Complementary and Alternative Medicine

Vitamin E

Black Cohosh

Phytoestrogens



Mixed or limited data on effectiveness and safety

Denlinger CS, et al. NCCN Guidelines Survivorship. 2018; 1: 32-36
Jazieh, et al. J Altern Complement Med. 2004; 10 (3): 560-564

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Acknowledgements

- Brooke Crawford, PharmD, BCOP
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- Kellie Weddle-Jones, PharmD, BCOP, FCCP, FHOPA
  - Hematology/Oncology Pharmacist
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  - Women's Health Pharmacist
- Kristen Strachman, LCSW
  - Hematology/Oncology Social Worker

Questions

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