Oncology Clinical Pathways
Breast Cancer

March 2024 – V3.2024

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Breast Cancer – Presumptive Conditions

VA automatically presumes that certain disabilities were caused by military service. This is because of the unique circumstances of a specific Veteran's military service. If a presumed condition is diagnosed in a Veteran within a certain group, they can be awarded disability compensation.

Atomic Veterans Exposed to Ionizing Radiation

- Breast cancer

Gulf War and Post 9/11 Veterans

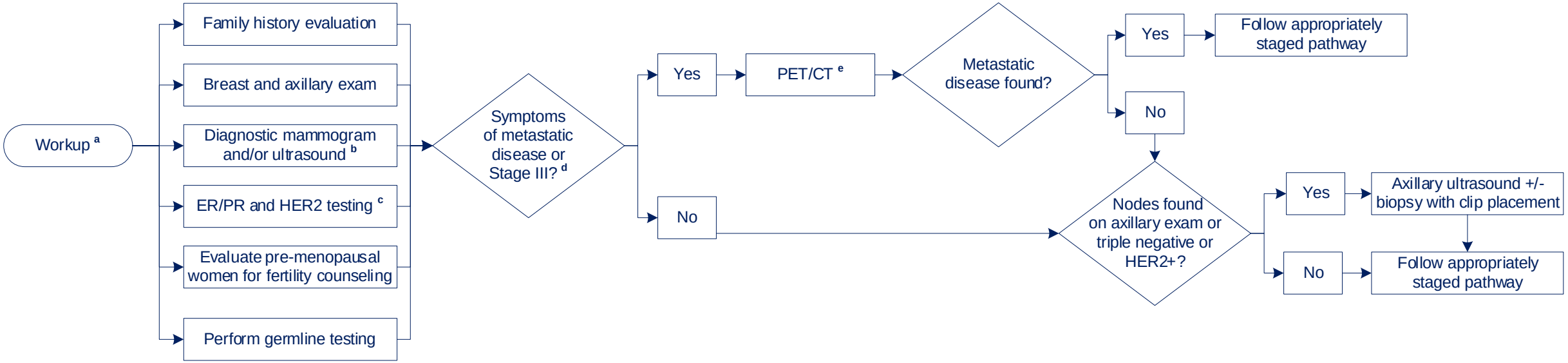
If the patient served on or after Sept. 11, 2001, in Afghanistan, Djibouti, Egypt, Jordan, Lebanon, Syria, Uzbekistan, or Yemen or if the patient served in the *Southwest Asia theater of operations, or Somalia, on or after Aug. 2, 1990, specific conditions include:

- Reproductive cancers of any type

* The Southwest Asia theater of operations refers to Iraq, Kuwait, Saudi Arabia, the neutral zone between Iraq and Saudi Arabia, Bahrain, Qatar, the United Arab Emirates, Oman, the Gulf of Aden, the Gulf of Oman, the Persian Gulf, the Arabian Sea, the Red Sea, and the airspace above these locations.

For more information, please visit U.S. Department of Veterans Affairs - Presumptive Disability Benefits (va.gov)

Breast Cancer – Workup



Clinical trial(s) always considered on pathway. For assistance finding a clinical trial, email CancerClinicalTrialsNavigation@va.gov.

[a] **Workup** after biopsy-proven invasive cancer

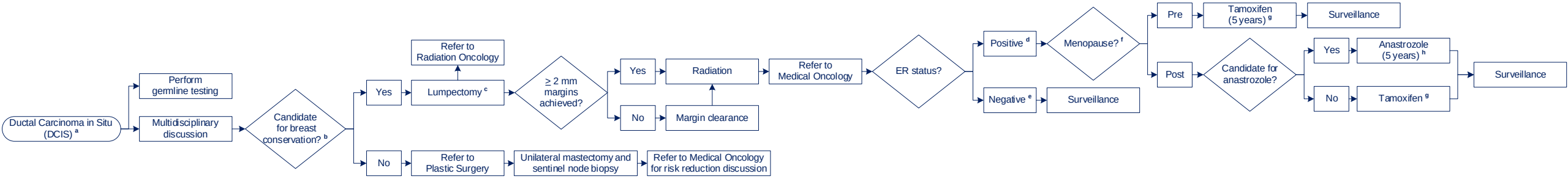
[b] **Diagnostic Imaging** if not previously performed; MRI not routinely recommended

[c] **ER/PR and HER2Testing** follow Pathology pathway for in-depth information

[d] **Metastatic Disease** confirmation by biopsy**;** symptoms include neurological symptoms, persistent cough, abnormal blood counts, abnormal LFTs, bone pain; if neurological symptoms, perform brain MRI with contrast

[e] **PET/CT** if unavailable, perform CT chest/abdomen/pelvis with bone scan

Breast Cancer – DCIS



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[a] **ER testing** is recommended; HER2 testing is not recommended

[b] **Breast Conservation** ineligibility includes inability to obtain clear margins without mastectomy or patient is not candidate for radiation

[c] **Lumpectomy** sentinel node biopsy may be recommended based on high grade, palpable tumor, anatomic location compromising future sentinel lymph node, or extensive volume

[d] **ER Positive** if staining ≥ 1% by IHC

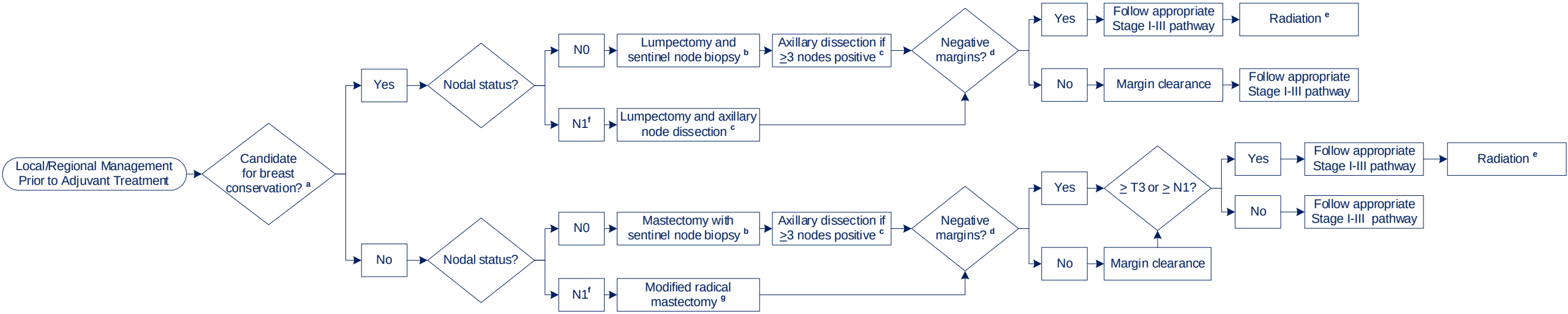
[e] **ER Negative** if staining < 1% by IHC

[f] **Menopausal** defined as patient that is ≥ 60 years of age; ≥ 1 year amenorrhea (not medically induced); history of Bilateral Salpingo-Oophorectomy (BSO); or confirmed with labs

[g] **Tamoxifen** avoid tamoxifen if prior history of DVT or known hypercoagulability

[h] **Anastrozole** evaluate baseline bone density; promote weight-bearing exercise, smoking cessation, reduced alcohol intake, and calcium/vitamin D supplementation

Breast Cancer – Local/Regional Management Prior to Adjuvant Treatment



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[a] **Breast Conservation** ineligibility includes inability to obtain clear margins without mastectomy, or patient is not candidate for radiation; if mastectomy early referral to Plastic Surgery is recommended; if lumpectomy early referral to Radiation Oncology is recommended; same treatment for male patients, however it is recognized that the majority of male patients will elect for mastectomy

[b] **Sentinel Node Biopsy** not routinely recommended if patient age > 69 and T1 ER+/HER2- tumors

[c] **Axillary Dissection** includes complete level I/II clearance

[d] **Negative Margins** defined as no tumor on ink

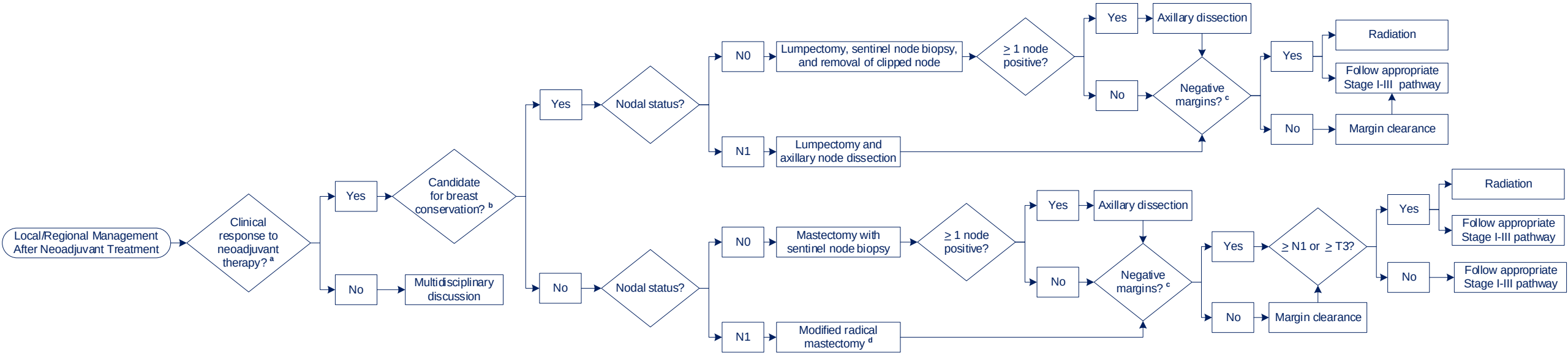
[e] **Radiation** if patient ≤T2 and ≤2 positive nodes patient can opt for nodal radiation in lieu of axillary dissection; in patients where (only) whole breast RT is planned, hypofractionated treatment is preferred over conventional fractionation; in select cases Accelerated Partial Breast Irradiation (APBI) is an acceptable treatment option

[f] **N1 Disease** recommend neoadjuvant chemotherapy include HER2+ and TNBC patients

[g] **MRM** includes axillary dissection

MRM Modified Radical Mastectomy
TNBC Triple Negative Breast Cancer

Breast Cancer – Local/Regional Management After Neoadjuvant Treatment



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[a] **Clinical Response** determined by exam and/or imaging

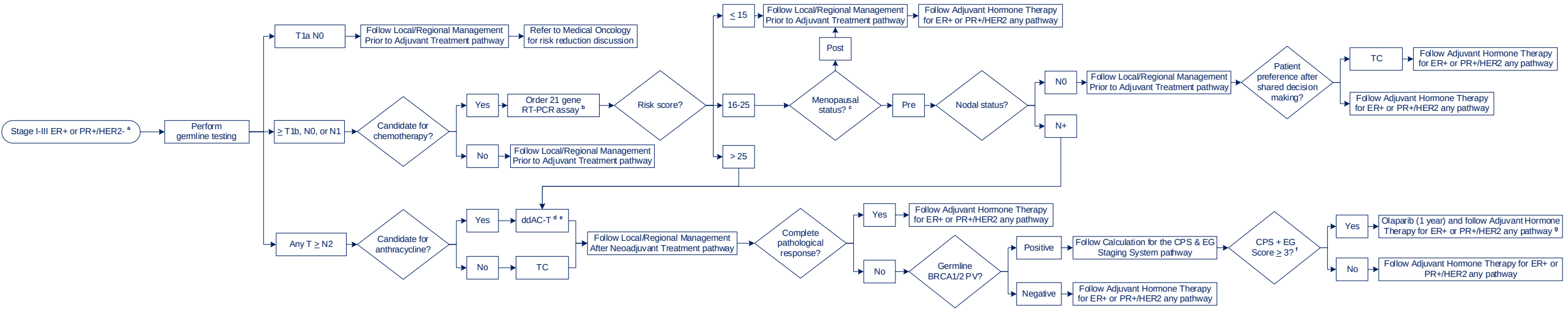
[b] **Breast Conservation** ineligibility includes inability to obtain clear margins without mastectomy or patient is not candidate for radiation; early referral to Plastic Surgery is recommended

[c] **Negative Margin**s defined as no tumor on ink

[d] **MRM** includes axillary dissection

MRM Modified Radical Mastectomy

Breast Cancer – Stage I-III ER+ or PR+/HER2-



Clinical trial(s) always considered on pathway. For assistance finding a clinical trial, email CancerClinicalTrialsNavigation@va.gov.

[a] **Invasive Carcinoma** to include ductal, lobular, metaplastic, and mammary; less aggressive breast carcinoma list includes tubular carcinoma, cribriform carcinoma, mucinous (colloid) carcinoma, mucinous cystadenocarcinoma, adenoid cystic carcinoma, secretory carcinoma, low-grade mucoepidermoid carcinoma, and tall cell carcinoma with reversed polarity

[b] **Blocks Preferred to Unstained Slides** if using unstained slides, one must submit 15 5-um-thick sections that are numbered to indicate their order; choose tissue from the block with the greatest contiguous area of the highest grade of invasive carcinoma; microinvasive carcinomas are not acceptable; biopsy, lumpectomy, and resection specimens can be used; tissue must have been fixed in formalin

[c] **Menopausal** defined as patient that is ≥ 60 years of age, ≥ 1 year amenorrhea (not medically induced), history of Bilateral Salpingo-Oophorectomy (BSO), or confirmed with labs

[d] **ddAC-T** followed by weekly paclitaxel (T)

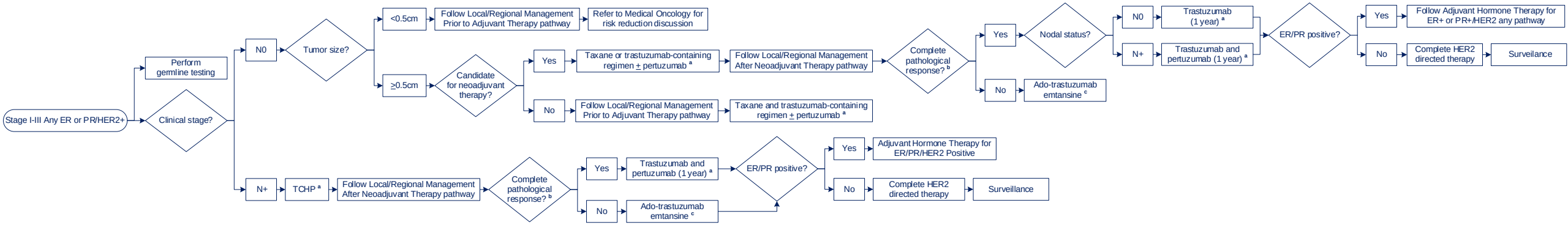
[e] **Evaluate Cardiovascular Risk** factors with baseline LVEF and CMP

[f] **CPS + EG Score** incorporates estrogen receptor (ER) status and tumor grade with pretreatment clinical stage (CS) and post-treatment pathologic stage (PS); Follow Calculation for CPS & EG Staging System pathway for further information

[g] **Olaparib** patients should not be on concomitant olaparib and abemaciclib therapy

CMP Comprehensive Metabolic Panel
ddAC-T Dose-dense AC-T (doxorubicin and cyclophosphamide)
LVEF Left Ventricular Ejection Fraction
PV Pathogenic Variant
TC docetaxel and cyclophosphamide

Breast Cancer – Stage I-III Any ER or PR/HER2+



Clinical trial(s) always considered on pathway. For assistance finding a clinical trial, email CancerClinicalTrialsNavigation@va.gov.

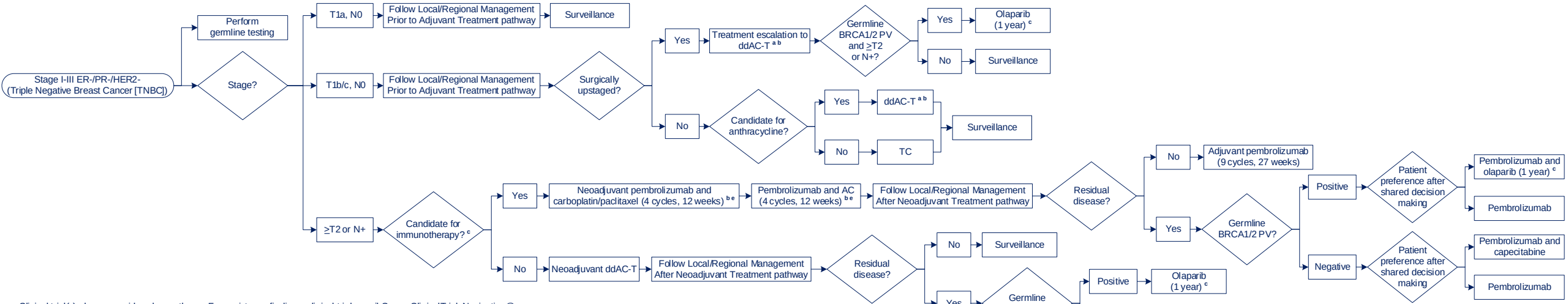
[a] **Evaluate Cardiovascular Risk Factors** with baseline LVEF (with ECHO or MUGA) and CMP; monitor LVEF every 3 months during therapy

[b] **Complete Pathological Response** absence of residual invasive carcinoma in both the breast and lymph nodes

[c] **Ado-trastuzumab Emtansine** radiation and hormone therapy can be given concomitantly with trastuzumab, pertuzumab, and ado-trastuzumab emtansine

TCHP docetaxel/carboplatin/trastuzumab/pertuzumab

Breast Cancer – Stage I-III ER-/PR-/HER2- (Triple Negative Breast Cancer [TNBC])



Clinical trial(s) always considered on pathway. For assistance finding a clinical trial, email CancerClinicalTrialsNavigation@va.gov.

[a] **ddAC-T** followed by weekly paclitaxel (T)

[b] **Evaluate Cardiovascular Risk Factors**, baseline LVEF (with ECHO or MUGA) and CMP

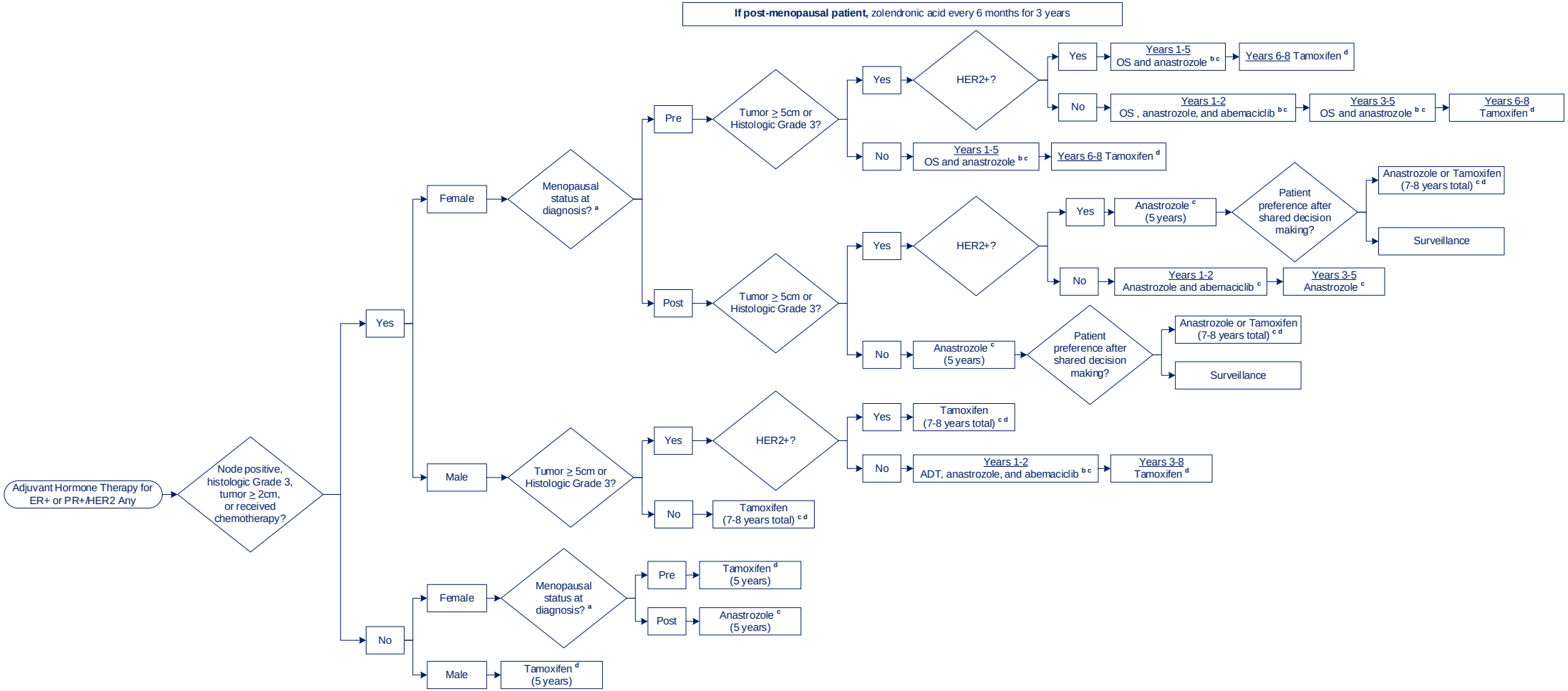
[c] **Olaparib** patients should not be on concomitant olaparib and abemaciclib therapy

[d] **Candidate for Immunotherapy** patient without active autoimmune disease, primary immune deficiency, concurrent immunosuppression (including pred. equiv. >10 mg/d), or prior HSCT/solid organ transplant

[e] **Effective Nonhormonal or Barrier Contraceptive Methods** should be used during treatment

ddAC-T dose-dense AC (doxorubicin and cyclophosphamide)
TC docetaxel and cyclophosphamide

Breast Cancer – Adjuvant Hormone Therapy for ER+ or PR+/HER2 Any



Clinical trial(s) always considered on pathway. For assistance finding a clinical trial, email CancerClinicalTrialsNavigation@va.gov.

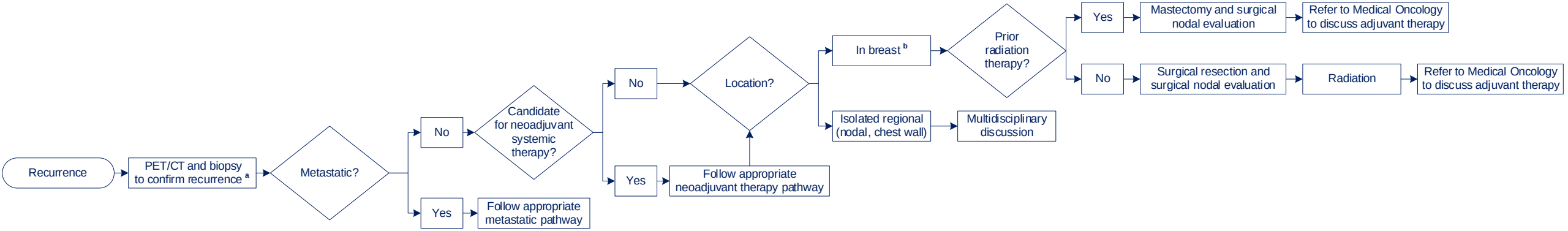
[a] **Menopausal** defined as patient that is ≥ 60 years of age; ≥ 1 year amenorrhea (not medically induced); history of Bilateral Salpingo-Oophorectomy (BSO); or confirmed with labs

[b] **Ovarian Suppression (OS)** includes surgical or medical suppression

[c] **Anastrozole** only for post menopausal women or women undergoing ovarian suppression; evaluate baseline bone density; promote weight-bearing exercise, smoking cessation, reduced alcohol intake, and calcium/vitamin D supplementation; if not a candidate for anastrozole, tamoxifen is an alternative; if patients do not tolerate one AI, any AI is a suitable alternative

[d] **Tamoxifen** avoid tamoxifen if prior history of DVT or known hypercoagulability; if contraindication to tamoxifen in men, prescribe AI with ADT; patients should use effective nonhormonal contraception or barrier contraceptive during tamoxifen therapy; continue for 2 months after last dose

Breast Cancer – Recurrence

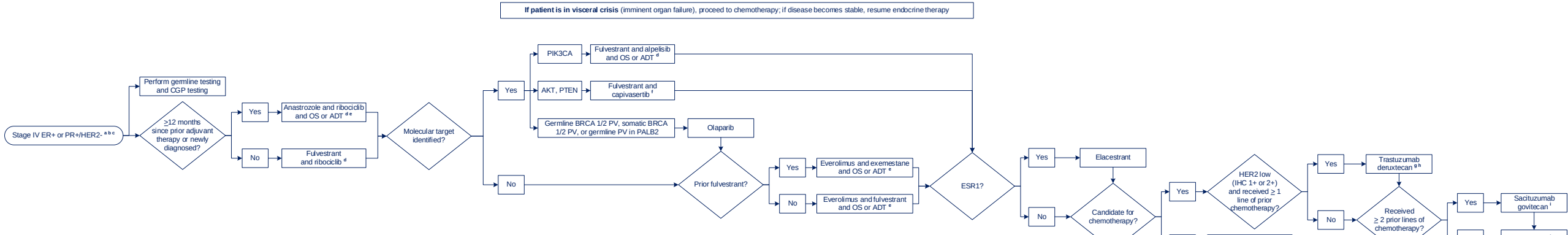


Clinical trial(s) always considered on pathway. For assistance finding a clinical trial, email CancerClinicalTrialsNavigation@va.gov.

[a] **PET/CT** if unavailable, perform CT chest/abdomen/pelvis with bone scan

[b] **Multidisciplinary Discussion** highly recommended for this patient presentation

Breast Cancer – Stage IV ER+ or PR+/HER2-



Clinical trial(s) always considered on pathway. For assistance finding a clinical trial, email CancerClinicalTrialsNavigation@va.gov.

[a] **If Bone Metastases** prescribe zoledronic acid; prescribe denosumab if contraindication; vitamin D and dental evaluation; if symptomatic, refer to Radiation Oncology

[b] **If Brain Metastases** referral to radiation oncology; refer to Neurosurgery

[c] **If MSI High or TMB ≥10** pembrolizumab is recommended to be given after endocrine therapy

[d] **Ribociclib** risk of QTc interval prolongation: evaluate ECG at baseline, regular intervals and as clinically indicated, ensure electrolyte abnormalities are corrected prior to start; monitor for neutropenia, hepatobiliary toxicity, cutaneous adverse reactions; reduce initial dose if renal and/or hepatic impairment

[e] **OS and/or ADT** ovarian Suppression (OS) must be added for women who are pre-menopausal or androgen deprivation therapy (ADT) for men

[f] **Capivasertib** evaluate fasting blood glucose and HbA1C prior to start and at regular intervals; closely monitor for diarrhea and cutaneous adverse reactions; note odd dosing: 4-days on then 3-days off

[g] **Evaluate Cardiovascular Risk Factors** with baseline LVEF (with ECHO or MUGA) and CMP; monitor LVEF every 3 months during therapy

[h] **Trastuzumab Deruxtecan** has proven overall survival advantage; one prior chemotherapy in the metastatic setting; monitor for interstitial lung disease

[i] **Sacituzumab Govitecan** has proven overall survival advantage; after two chemotherapies or one chemotherapy in the metastatic setting if adjuvant chemotherapy was given within the past 12 months; monitor for diarrhea and cytopenias

[j] **Paclitaxel** if not used in 1L setting; consider implications of hair loss

[k] **Capecitabine** if oral agent is preferred; less hair loss as compared to other agents

[l] **Carboplatin** if not used in 1L setting; preferred in women with BRCA pathogenic variants

[m] **Eribulin** monitor for neuropathy and cytopenias

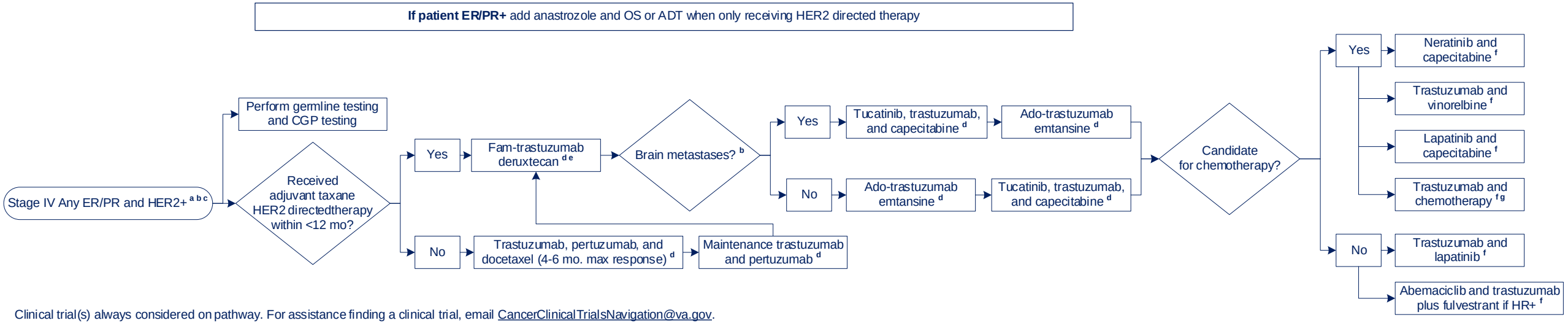
[n] **Liposomal Doxorubicin** baseline LVEF > 50% and/or no clinically significant cardiac disease

[o] **Vinorelbine** monitor for hepatic impairment, neurotoxicity, and cytopenias

[p] **Pembrolizumab** if MSI high or TMB ≥10

PV Pathogenic Variant

Breast Cancer – Stage IV Any ER/PR and HER2+



Clinical trial(s) always considered on pathway. For assistance finding a clinical trial, email CancerClinicalTrialsNavigation@va.gov.

[a] **If Bone Metastases** prescribe zoledronic acid; prescribe denosumab if contraindication; vitamin D and dental evaluation; if symptomatic, refer to Radiation Oncology

[b] **If Brain Metastases** referral to Radiation Oncology; fam-trastuzumab deruxtecan and tucatinib trastuzumab capecitabine are preferred in patients brain metastases

[c] **If MSI High or TMB ≥10** pembrolizumab is recommended to be given after endocrine therapy

[d] **Evaluate Cardiovascular Risk Factors** with baseline LVEF (with ECHO or MUGA) and CMP; monitor LVEF every 3 months during therapy

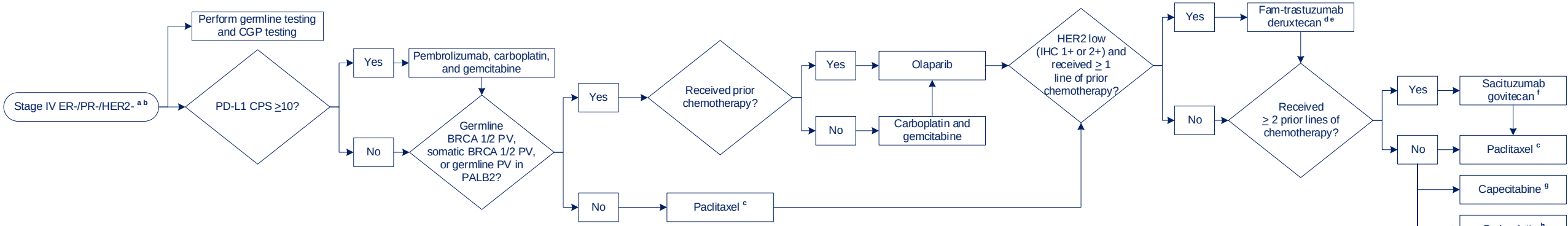
[e] **Fam-trastuzumab-Deruxtecan** avoid in pneumonitis, Interstitial Lung Disease (ILD)

[f] **Multiple Combinations of HER2 Directed Therapies** and chemotherapy are FDA approved but optimal sequencing unknown; consider performance status and toxicity profile

[g] **Chemotherapy** includes vinorelbine, docetaxel, carboplatin, eribulin, gemcitabine, capecitabine

PV Pathogenic Variant

Breast Cancer – Stage IV ER-/PR-/HER2-



Clinical trial(s) always considered on pathway. For assistance finding a clinical trial, email CancerClinicalTrialsNavigation@va.gov.

[a] **If Bone Metastases** prescribe zoledronic acid; prescribe denosumab if contraindication; vitamin D and dental evaluation; if symptomatic, refer to Radiation Oncology

[b] **If Brain Metastases** referral to Radiation Oncology and Neurosurgery

[c] **Paclitaxel** if not used in a prior line; consider implications of hair loss

[d] **Fam-tastuzumab Deruxtecan** has proven overall survival advantage after prior metastatic therapy or within 6 months of adjuvant therapy; monitor for interstitial lung disease

[e] **Evaluate Cardiovascular Risk Factors** with baseline LVEF (with ECHO or MUGA) and CMP; monitor LVEF every 3 months during therapy

[f] **Sacituzumab Govitecan** may be considered after ≥ 2 prior chemotherapies including neoadjuvant setting; monitor for diarrhea and cytopenias

[g] **Capecitabine** if oral agent is preferred; less hair loss as compared to other agents

[h] **Carboplatin** if not used in a prior line; preferred in women with BRCA pathogenic variants

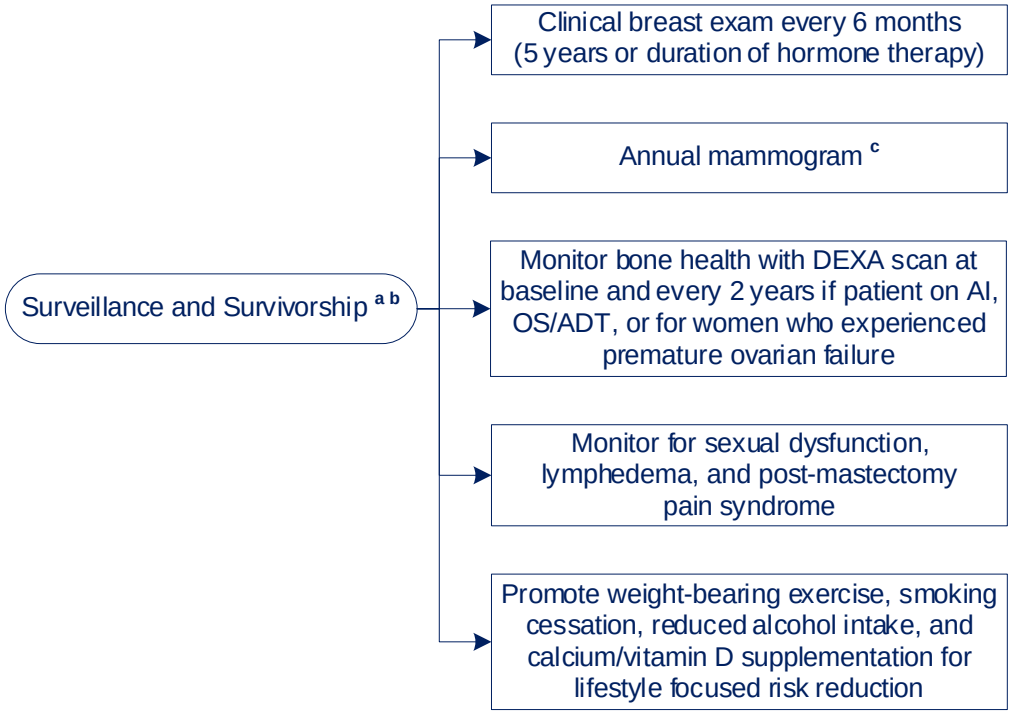
[i] **Eribulin** monitor for neuropathy and cytopenias

[j] **Liposomal Doxorubicin** baseline LVEF > 50% and/or no clinically significant cardiac disease

[k] **Vinorelbine** monitor for hepatic impairment, neurotoxicity, and cytopenias

[l] **Pembrolizumab** if MSI high or TMB ≥10

Breast Cancer – Surveillance and Survivorship



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[a] **Surveillance** labs, tumor marker, and systemic imaging not recommended for routine surveillance

[b] **Imaging Following Mastectomy** routine imaging of that breast is no longer recommended

[c] **Mammogram** routine mammograms are not recommended for men

Breast Cancer – Pathology

Pathology

All results reported in accordance with the CAP Breast Biomarker Reporting Protocol

Tissue Handling Requirements:
Specimen handling slice at 5-10 mm intervals prior to fixation
Cold ischemia time (tissue removal to initiation of fixation) <1 hour
Fixation time 6-72 hours in 10% neutral buffered formalin
Unstained slides used within 6 weeks for ER/PR/HER2 testing
Frozen Sections for sentinel lymph nodes, each gross slice should be no thicker than 2 mm and slices should be embedded in a consistent orientation such that consecutive sections represent tissue separated by no more than 2 mm in the direction of the long axis of the lymph node

Recommended Testing:
DCIS – ER testing only (IHC). Other biomarkers not recommended.
Primary invasive – ER (IHC), PR (IHC), and HER2 (IHC with reflex to FISH for equivocal IHC)
Recurrent/Metastatic – ER (IHC), PR (IHC), and HER2 (IHC with reflex to FISH for equivocal IHC)
Multiple invasive foci – test the largest and highest grade focus of each histologic type

HER2 Interpretation and Reflex:
Negative IHC (0 or 1+) – do **NOT** reflex
0 – no staining or membrane staining that is incomplete and is faint/barely perceptible and in ≤10% of tumor cells
1+ – incomplete membrane staining that is faint/barely perceptible and in >10% of tumor cells
Equivocal IHC (2+) – **REFLEX** to FISH
2+ – weak to moderate complete membrane staining in >10% of tumor cells or complete membrane staining that is intense but in ≤10% of tumor cells
Positive IHC (3+) – do **NOT** reflex
3+ – complete membrane staining that is intense and >10% of tumor cells
HER2 FISH – use dual probe strategy; reflex only if IHC is 2+/equivocal
Negative – an average < 4.0 *HER2* signals/cell
Positive – ≥ 6.0 *HER2* signals/cell, OR
– ≥ 4.0 *HER2* signals/cell AND *HER2*/CEP17 ratio ≥ 2.0

Breast Cancer – Calculation for the CPS and EG Staging System

Calculation for the CPS & EG Staging System		
Stage/Feature		**Points**
Clinical Stage (AJCC staging [1])	0-IIA	0
	IIB	1
	IIIA	1
	IIIB	2
	IIIC	2
Pathologic Stage (AJCC staging [1])	0-I	0
	IIA	1
	IIB	1
	IIIA	1
	IIIB	1
	IIIC	2
Receptor Status	ER negative [2]	1
Nuclear Grade [3]	Nuclear grade 3	1
Used to estimate disease specific survival in patients with breast cancer treated with neoadjuvant chemotherapy. To calculate a score: Add the points for clinical stage, pathologic stage, ER status and nuclear grade to derive a sum between 0 and 6.		

Breast Cancer – Molecular Testing Table

Eligibility	Test Category	Test Type	Recommended Vendors	NPOP Coverage	Specimen Type
All Breast Any Stage	IHC	ER, PR, HER2 (If 2+ reflect to FISH)	Local VA or locally contracted vendor	No	Tumor Tissue
	FISH	HER2 FISH (if HER2 IHC is 2+)	Local VA or locally contracted vendor	No	Tumor Tissue
	Germline NGS*	Germline breast cancer panel or VA common hereditary panel (**POC) or referral to CCGS	Fulgent Prevention Genetics	Yes Yes	Saliva, Blood
Stage I-III, ER+ or PR+/HER2-	IHC	ER, PR, HER2 (If 2+ reflect to FISH)	Local VA or locally contracted vendor	No	Tumor Tissue
	FISH	HER2 FISH (if HER2 IHC is 2+)	Local VA or locally contracted vendor	No	Tumor Tissue
	Gene Expression/Risk Score Test (21 gene RT-PCR Assay)	21 gene RT-PCR Assay (Oncotype DX 21-gene reoccurrence score) (MammaPrint)	Exact Sciences Biotheranostics	No No	Tumor Tissue
	Germline NGS*	Germline breast cancer panel or VA common hereditary panel (**POC) or referral to CCGS	Fulgent Prevention Genetics	Yes Yes	Saliva, Blood
All Metastatic	IHC	ER, PR, HER2 (If 2+ reflect to FISH) MMR	Local VA or locally contracted vendor Tempus (MMR)	No Yes (MMR when ordered with CGP)	Tumor Tissue
	FISH	HER2 FISH (if HER2 IHC is 2+)	Local VA or locally contracted vendor	No	Tumor Tissue
	Somatic NGS	Comprehensive genomic profiling (CGP)	Tempus Foundation Medicine	Yes Yes	Tumor Tissue***, Blood
	Germline NGS*	Germline breast cancer panel or VA common hereditary panel (**POC) or referral to CCGS	Fulgent Prevention Genetics	Yes Yes	Saliva, Blood
Stage IV ER+ or PR+, HER2-, Failed Endocrine Therapy, Evaluation for Elacestrant Therapy	Molecular Testing	ESR1 mutation testing	Single gene Mayo (tissue based)	No	Tumor Tissue
Triple Negative, Metastatic	IHC	ER, PR, HER2 (If 2+ reflect to FISH) PD-L1, 22C3 Clone with CPS Score (pembrolizumab) PD-L1, SP143 Clone (atezolizumab) MMR	Local VA or locally contracted vendor Tempus (PD-L1 & MMR) Foundation Medicine (PD-L1)	No Yes (when ordered with CGP) Yes (when ordered with CGP)	Tumor Tissue
	FISH	HER2 FISH (if HER2 IHC is 2+)	Local VA or locally contracted vendor	No	Tumor Tissue
	Somatic NGS	Comprehensive genomic profiling (CGP)	Tempus Foundation Medicine	Yes Yes	Tumor Tissue***, Blood
	Germline NGS*	Germline breast cancer panel or VA common hereditary panel (**POC) or referral to CCGS	Fulgent Prevention Genetics	Yes Yes	Saliva, Blood
Ductal Carcinoma In Situ	IHC	ER	Local VA or locally contracted vendor	No	Tumor Tissue
	Germline NGS*	Germline breast cancer panel or VA common hereditary panel (**POC) or referral to CCGS	Fulgent Prevention Genetics	Yes Yes	Saliva, Blood

* Germline NGS test should include at minimum ATM, BRCA1/2, CDH1, CHEK2, NBN, NF1, PALB2, PTEN, STK11, TP53

** For genetic online ordering, refer to CCGS page for further details

***Tissue preferred, but liquid acceptable if tissue insufficient