Oncology Clinical Pathways
Ampullary Cancer

April 2025 – V1.2025

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Ampullary 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 – Exposure to Ionizing Radiation

- Cancer of the small intestine, pancreas, and bile ducts

Gulf War and Post 9/11 Veterans

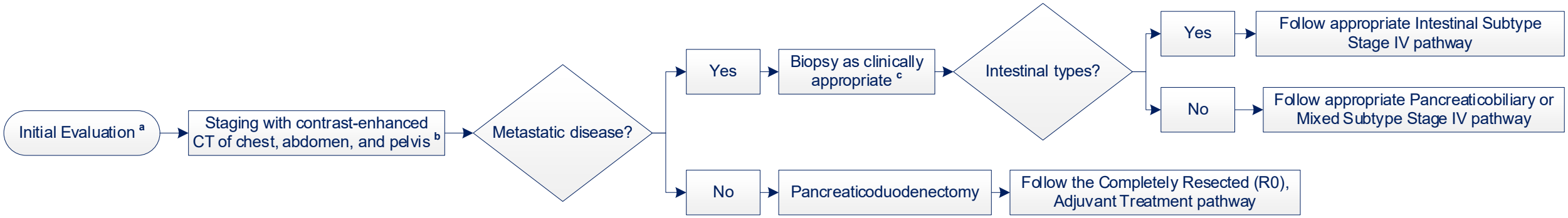
If the patient served on or after Sept. 11, 2001, in Afghanistan, Djibouti, Egypt, Jordan, Lebanon, Syria, Uzbekistan, or Yemen or if you served in the *Southwest Asia theater of operations, or Somalia, on or after Aug. 2, 1990, specific conditions include:

- Gastrointestinal cancer 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)

Ampullary Cancer – Initial Evaluation



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

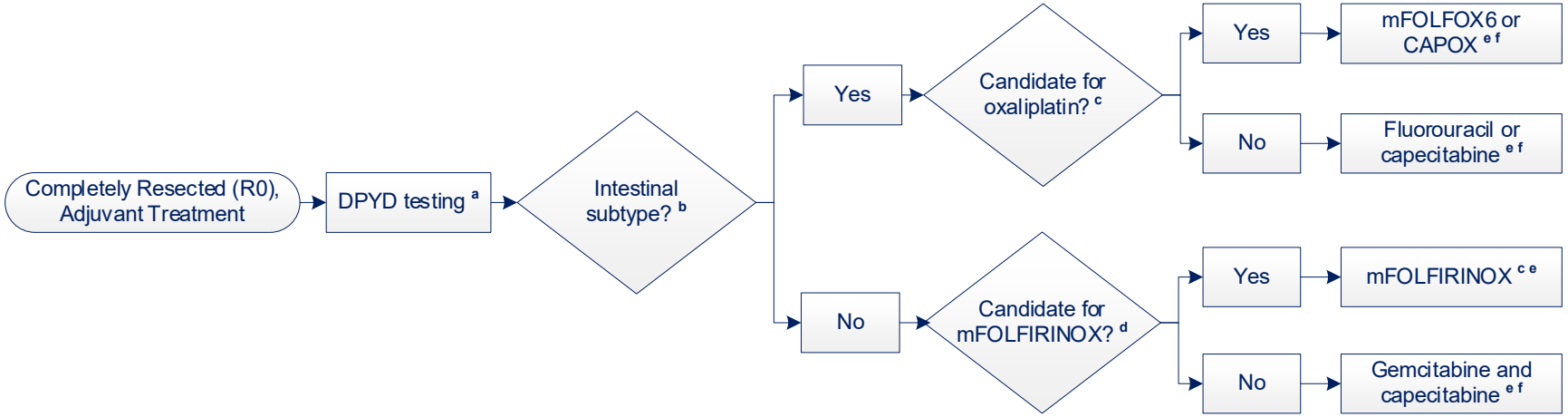
[a] **Initial evaluation** suspicious lesion or biopsy proven ampullary cancer; if suspicious lesion, the mass can be sampled using biopsy forceps, and if sample is not adequate or diagnostic, then EUS with fine needle aspiration or core biopsy can be done

[b] **Imaging** multiphase preferred; EUS staging can be considered on a case by case basis

[c] **Biopsy as clinically appropriate** at least two attempts to obtain core biopsy of the metastatic lesion is preferred, if feasible; if not feasible, the primary ampullary mass can be sampled using biopsy forceps; if sample is not adequate then EUS with fine needle aspiration or core biopsy can be done (include cell block for molecular testing purposes)

EUS endoscopic ultrasound

Ampullary Cancer – Completely Resected (R0), Adjuvant Treatment



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

[a] **Perform DPYD testing if not already performed** if DPYD PGx results return predicted phenotypes of either intermediate or poor metabolizer, please consult your local PGx pharmacist or submit an IFC Pharmacogenomics e-consult for assistance with therapeutic recommendation; a clinician may proceed without DPYD results if withholding chemotherapy for 2-3 weeks may gravely endanger patient's life; for example, if the disease burden is very high and it involves a large portion of vital organs such as liver, etc.

[b] **Intestinal subtype** subtyping is based on morphology; IHC can be used to confirm morphologic impression;
- **Intestinal:** cigar-shaped nuclei, pseudostratified columnar cells, complex or cribiform glandular structure, intraluminal necrosis; more likely to express CK20 and CDX2 and less likely to express MUC1 (EMA) and CK7
- **Pancreaticobiliary:** rounded/cuboidal nuclei, well-spaced simple glands, desmoplasia; more likely to express MUC1 (EMA) and CK7 and less likely to express CDX2 and CK20

[c] **Candidate for oxaliplatin** ECOG PS 0-1, lack of prohibitive neuropathy

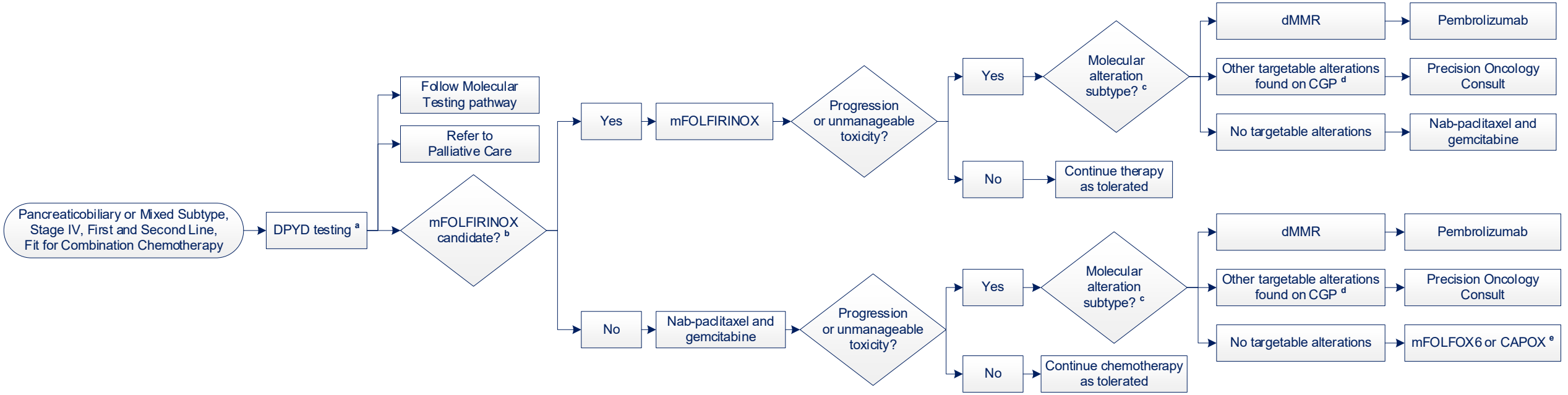
[d] **mFOLFIRINOX candidate** defined as patient with ECOG PS 0-1, absence of uncontrolled CAD, lack of prohibitive neuropathy, and patient commitment to lab draws, every 14-day clinic visits, and utilizing an ambulatory infusion pump

[e] **Duration of treatment** duration of therapy should be considered for 6 months

[f] **Capecitabine** avoid capecitabine if adherence issues, unable to self-report toxicity, or severe renal impairment (CrCl < 30ml/min)

DPYD dihydropyrimidine dehydrogenase
IHC immunohistochemistry

Ampullary Cancer – Pancreaticobiliary or Mixed Subtype, Stage IV, First and Second Line, Fit for Combination Chemotherapy



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[b] **mFOLFIRINOX candidate** defined as patient with ECOG PS 0-1, absence of uncontrolled CAD, lack of prohibitive neuropathy, and patient commitment to lab draws, every 14-day clinic visits, and utilizing an ambulatory infusion pump

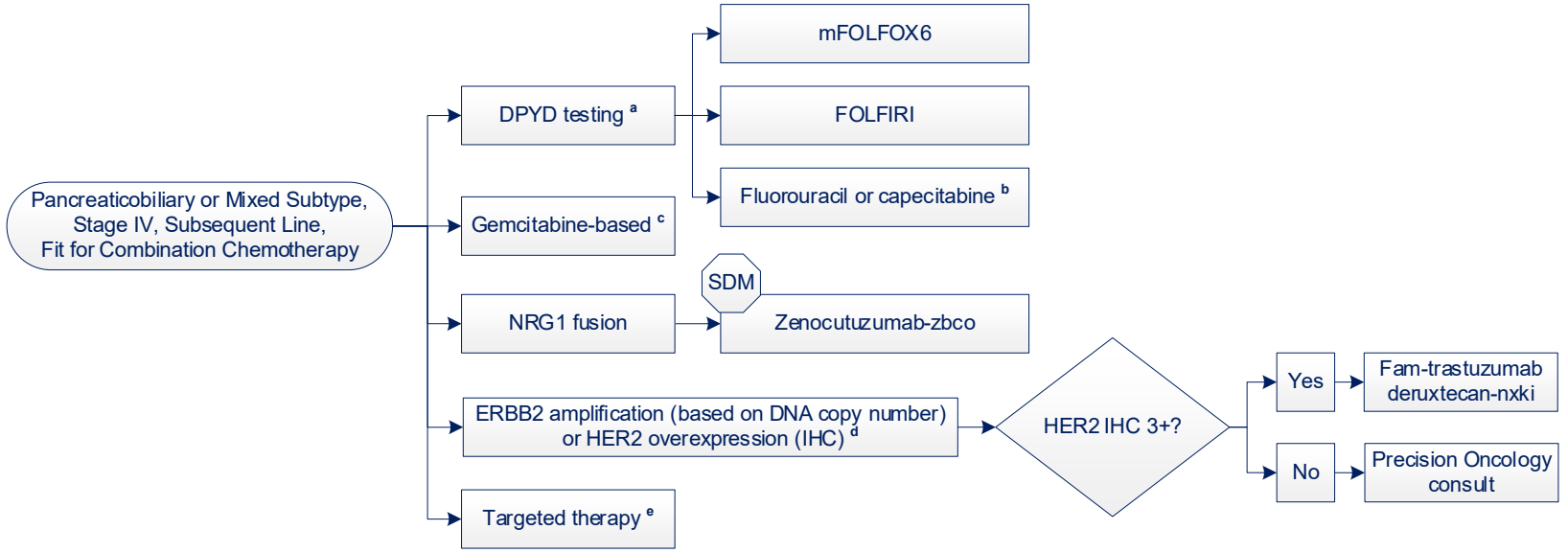
[c] **Molecular alteration subtype** based on CGP and/or germline testing

[d] **Other targetable alterations found on CGP** BRAF V600E, IDH mutation, FGFR2 fusion, NTRK fusion, and HER-2 overexpression

[e] **Capecitabine** avoid capecitabine if adherence issues, unable to self-report toxicity, or severe renal impairment (CrCl < 30ml/min)

CGP comprehensive genomic profiling
dMMR deficient mismatch repair

Ampullary Cancer – Pancreaticobiliary or Mixed Subtype, Stage IV, Subsequent Line, Fit for Combination Chemotherapy



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[b] **Capecitabine** avoid capecitabine if adherence issues, unable to self-report toxicity, or severe renal impairment (CrCl < 30ml/min)

[c] **Gemcitabine-based** options may include Gemcitabine single agent or combination with cisplatin (preferred) or carboplatin

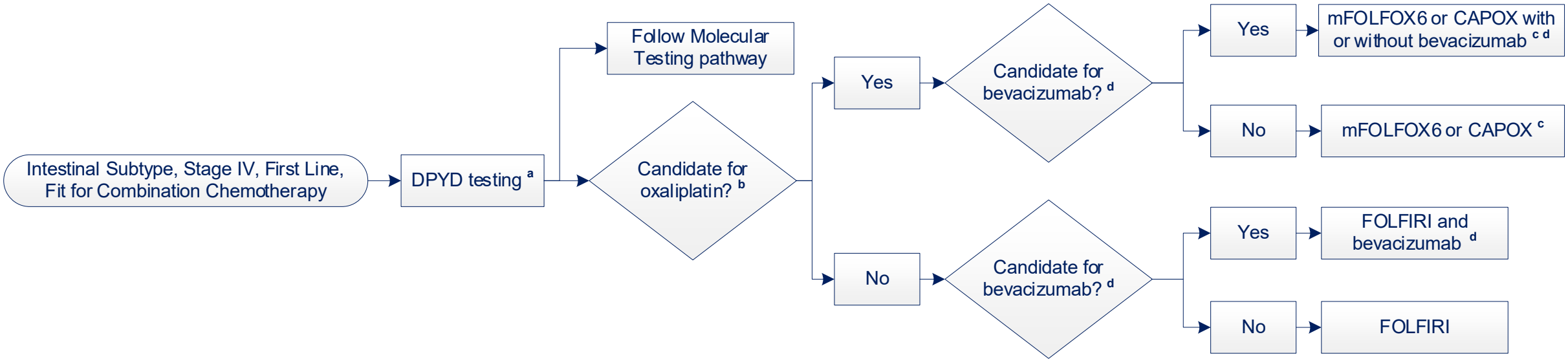
[d] **ERBB2 amplification** there is insufficient clinical trial evidence to use ERBB2 RNA overexpression in treatment decision making

[e] **Targeted therapy** strongly consider IFC consult to Precision Oncology if entertaining targeted therapy in later line therapies (especially if BRAF V600E and KRAS G12C)

SDM Zenocutuzumab-zbco shared decision making is recommended; FDA approval for the drug is based on response rate and PFS in a single-arm study, which did include patients with pancreatic and biliary but not necessarily ampullary cancer; do not use if the patient cannot take pre-medications

DPYD dihydropyrimidine dehydrogenase
SDM shared decision making

Ampullary Cancer – Intestinal Subtype, Stage IV, First Line, Fit for Combination Chemotherapy



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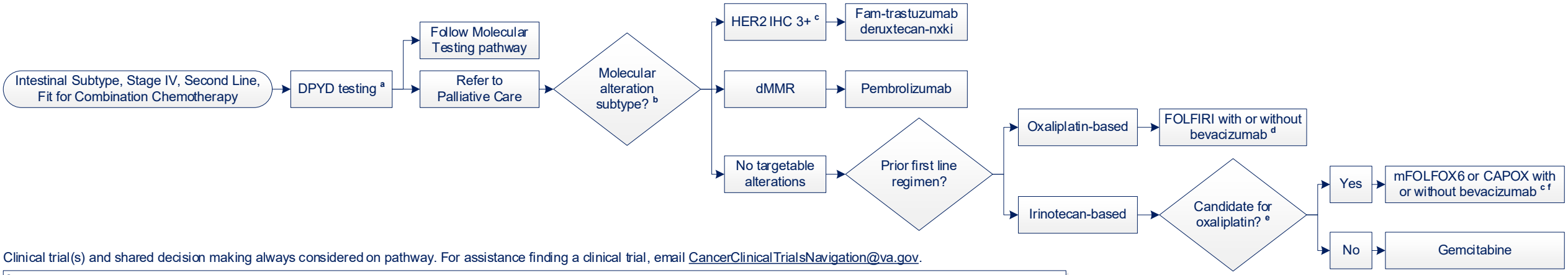
[b] **Candidate for oxaliplatin** contraindication if any adjuvant treatment in the past 12 months or preexisting neuropathy >1 grade neuropathy; patient preference to avoid neuropathy

[c] **Capecitabine** avoid capecitabine if adherence issues, unable to self-report toxicity, or severe renal impairment (CrCl <30 ml/min)

[d] **Candidate for bevacizumab** ECOG PS 0-2; ANC ≥ 1500/mm^3; due to anti-VEGF effects patients with the following should not receive bevacizumab: non-healing wound/fracture, major surgery in prior 4 weeks, bleeding disorder or coagulopathy, recent history of GI perforation, unstable cardiac condition (uncontrolled HTN, arterial thromboembolism, symptomatic CHF (NYHA II-IV) or arrhythmia), or active cocaine use

DPYD dihydropyrimidine dehydrogenase

Ampullary Cancer – Intestinal Subtype, Stage IV, Second Line, Fit for Combination Chemotherapy



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[b] **Molecular alteration subtype** based on CGP and/or germline testing

[c] **ERBB2 amplification** using NPOP approved vendors; if the amplification call is not from an NPOP-approved vendor, then HER2 IHC should be performed for confirmation

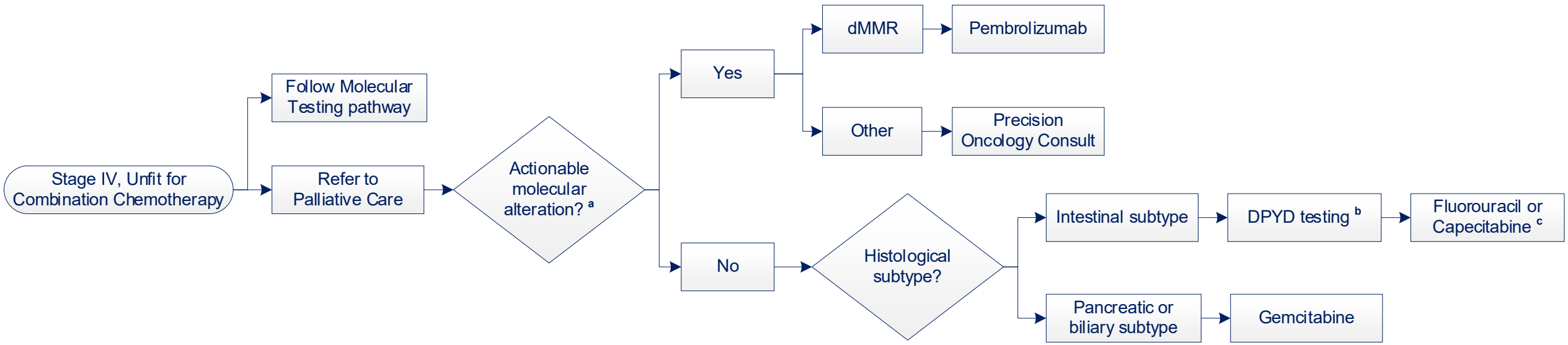
[d] **Candidate for bevacizumab** received fluoropyrimidine and platinum agent in the first-line setting; ECOG PS 0-2; ANC $\geq$ 1500/mm^3; due to anti-VEGF effects patients with the following should not receive bevacizumab: non-healing wound/fracture, major surgery in prior 4 weeks, bleeding disorder or coagulopathy, recent history of GI perforation, unstable cardiac condition (uncontrolled HTN, arterial thromboembolism, symptomatic CHF (NYHA II-IV) or arrhythmia), or active cocaine use

[e] **Candidate for oxaliplatin** contraindication if disease progression within 12 months of adjuvant treatment or preexisting neuropathy >1 grade neuropathy

[f] **Capecitabine** avoid capecitabine if adherence issues, unable to self-report toxicity, or severe renal impairment (CrCl <30 ml/min)

CGP comprehensive genomic profiling
dMMR deficient mismatch repair
DPYD dihydropyrimidine dehydrogenase

Ampullary Cancer – Stage IV, Unfit for Combination Chemotherapy



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

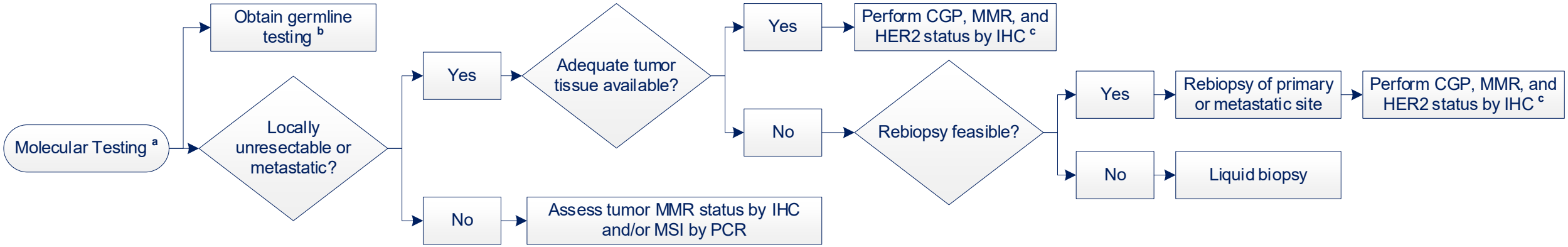
[a] **Molecular subtype** includes either somatic or germline

[b] **Perform DPYD testing if not already performed** if DPYD PGx results return predicted phenotypes of either intermediate or poor metabolizer, please consult your local PGx pharmacist or submit an IFC Pharmacogenomics e-consult for assistance with therapeutic recommendation; a clinician may proceed without DPYD results if withholding chemotherapy for 2-3 weeks may gravely endanger patient's life; for example, if the disease burden is very high and it involves a large portion of vital organs such as liver, etc.

[c] **Second line** if intolerant to or progressed on first line treatment

dMMR deficient mismatch repair
DPYD dihydropyrimidine dehydrogenase

Ampullary Cancer – Molecular Testing



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[a] **Molecular testing** perform for all pathologically confirmed ampullary cancer

[b] **Germline testing** for ampullary cancer should include at minimum the following genes: BRCA1, BRCA2, TP53, APC, ATM, MUTYH and the Lynch genes EPCAM2, MLH1, MSH2, MSH6, and PMS2

[c] **CGP** with platform that uses DNA and RNA based testing or DNA and RNA based CGP

CGP comprehensive genomic profiling
IHC immunohistochemistry
MMR mismatch repair
MSI microsatellite instability
PCR polymerase chain reaction

Ampullary Cancer – Molecular Testing Table

Eligibility	Test Category	Test Type	Recommended Vendors	NPOP Coverage	Specimen Type
Any Histology, Any Stage	PGx	DPYD testing*	Fulgent	Yes	Blood, Saliva
	Germline Testing	Germline NGS Panel**	Fulgent Prevention Genetics	Yes Yes	Blood, Saliva
Completely Resectable	IHC	MMR testing by IHC (to be performed with or without MSI by PCR)	Local VA or Locally Contracted Vendor	No	Tumor Tissue
	Molecular	MSI testing by PCR (to be performed with or without MMR by IHC)	GLA lab Local VA or Locally Contracted Vendor	Yes No	Tumor Tissue
Any Histology, Stage IV or Unresectable	Somatic NGS	Comprehensive genomic Profiling (CGP)	Foundation Tempus	Yes Yes	Tumor Tissue, Blood
	IHC	MMR testing by IHC	Foundation (if ordered with CGP) Tempus (if ordered with CGP) Local VA or Locally Contracted Vendor	Yes Yes No	Tumor Tissue
	IHC	HER2 (for trastuzumab deruxtecan)	Foundation (if ordered with CGP)	Yes	Tumor Tissue

* Perform DPYD Testing If Not Already Performed if DPYD PGx results return predicted phenotypes of either intermediate or poor metabolizer, please consult your local PGx pharmacist or submit an IFC Pharmacogenomics e-consult for assistance with therapeutic recommendation; a clinician may proceed without DPYD results if withholding chemotherapy for 2-3 weeks may gravely endanger patient's life; for example, if the disease burden is very high and it involves a large portion of vital organs such as liver, etc.

** VA Common Hereditary POC panel or Equivalent Germline Test; at minimum the Germline NGS Panel should include BRCA1, BRCA2, TP53, APC, ATM, and the Lynch genes EPCAM2, MLH1, MSH2, MSH6, and PMS2; For genetic online ordering, refer to CCGS page for further details