Oncology Clinical Pathways
Rectal Cancer

August 2024 – V4.2024

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Rectal 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.

Gulf War and Post 9/11 Veterans

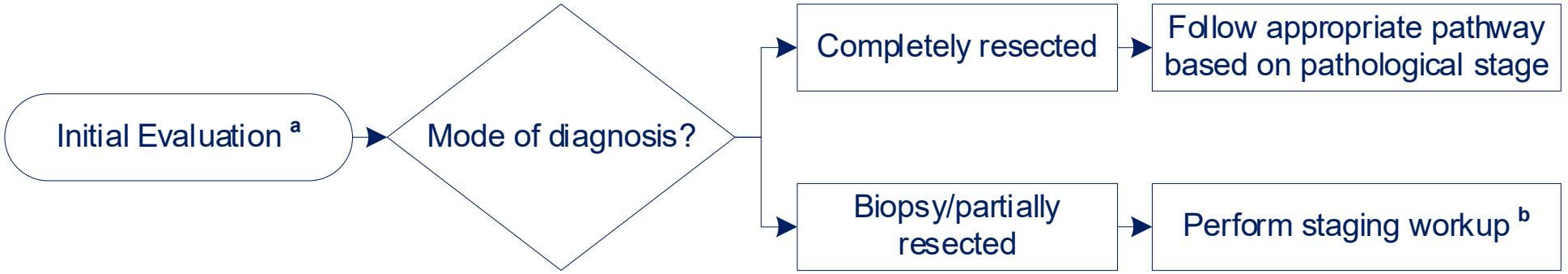
If the patient served on or after Sept. 11, 2001, in Afghanistan, Djibouti, Egypt, Jordan, Lebanon, Syria, Uzbekistan, or Yemen or if you served in the *Southwest Asia theater of operations, or Somalia, on or after Aug. 2, 1990, specific conditions include:

- 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)

Rectal Cancer – Initial Evaluation



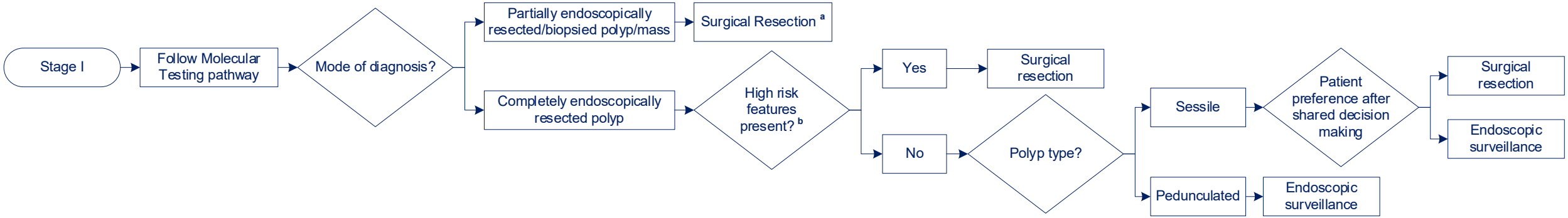
Clinical trial(s) always considered on pathway. For assistance finding a clinical trial, email CancerClinicalTrialsNavigation@va.gov.

[a] **Rectum** defined on rectal MRI as intestine that lies below a virtual line from the sacral promontory to the upper edge of the pubic symphysis and extending up to the anus

[b] **Staging Workup** for T and N stage is done with rectal protocol MRI (preferred) or EUS; M stage will be determined with CT of chest and abdomen as well as pelvis (if MRI pelvis is not performed)

EUS Endoscopic Ultrasound

Rectal Cancer – Stage I



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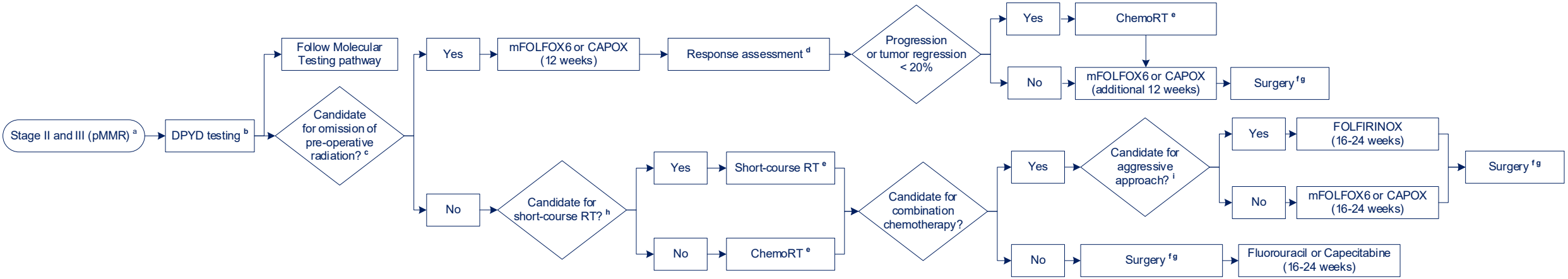
[a] **Surgical Resection** if not a complete resection, additional endoscopic resection may be considered if feasible

[b] **High Risk Features for Sessile Polyps** includes: poor tumor differentiation, lymphovascular invasion, submucosal invasion depth >1 mm, tumor involvement of the cautery margin, tumor budding; **High Risk Features for Pedunculated Polyps** includes: poor tumor differentiation, lymphovascular invasion, tumor within 1 mm of the resection margin

Rectal Cancer – Stage II and III (pMMR)



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[a] **Treatment for Stage II and III** dMMR rectal cancer is evolving; currently, the team does not have a separate pathway for dMMR stage II and III rectal cancer; but the pMMR stage II and III pathway as outlined above (on pathway) or an alternative off-pathway treatment (for example PD-1 blockade) can be utilized

[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] **Candidate for omission of pre-operative radiation** appropriate for those with cT1-3N1 or T3N0, no threatened CRM, tumor > 5cm from anal verge, sphincter preservation is not a concern, **AND** patient is a candidate for combination chemotherapy

[d] **Response Assessment** repeat pelvic imaging using same modality as in initial evaluation and consider flexible sigmoidoscopy

[e] **Candidate for Short-Course RT** patient is candidate for short-course RT if a surgery is planned and there are no features that in the opinion of the Radiation Oncologist would make them more suitable for (long-course) ChemoRT; short-course RT is delivered without chemotherapy; for ChemoRT infusional 5-fluorouracil or capecitabine chemotherapy with conventional fractionation radiation is preferred

[f] **Complete Response** restaging should be done with pelvic MRI and CT of chest and abdomen as well as pelvis (if pelvic MRI is not available and surgery is planned); defined as no evidence of residual tumor on digital rectal examination (DRE), rectal MRI, and direct endoscopic evaluation preferably 8 weeks following completion of radiation

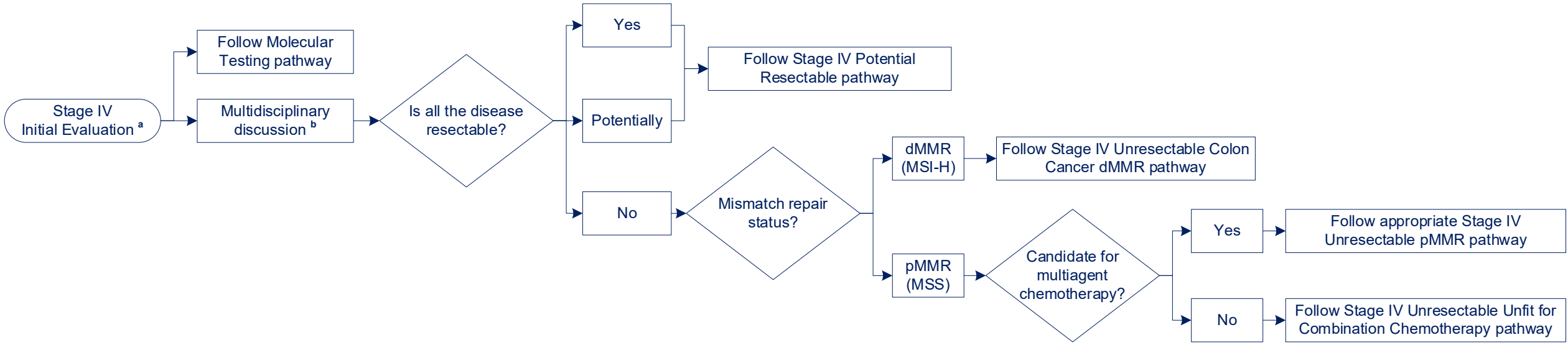
[g] **Surgery** is the most preferred approach; in select patients who have achieved clinical complete response [d] and considering wait and watch, the surveillance includes: sigmoidoscopy with DRE and CEA every 3-4 months for 2 years, then every 6 months for 3 years (years 3-5); rectal MRI every 6 months for 2 years, then annually for years 3-5; CT C/A/P annually for 5 years; colonoscopy years 1 and 4, then every 5 years

[h] **Operative Management** surgical resection is the most preferred approach; nonoperative management should only be considered in centers with experienced multidisciplinary teams and after careful discussion of risk tolerance with the patient

[i] **Aggressive Approach Indicated** may be considered in very fit patients with excellent performance status only after careful risk-benefit discussion with the patient and high risk disease defined as presence of one or more of the features: T4, N2, involved or threatened CRM (MRI), low-lying rectal cancer, or extramural venous invasion

DPYD Dihydropyrimidine Dehydrogenase

Rectal Cancer – Stage IV Initial Evaluation



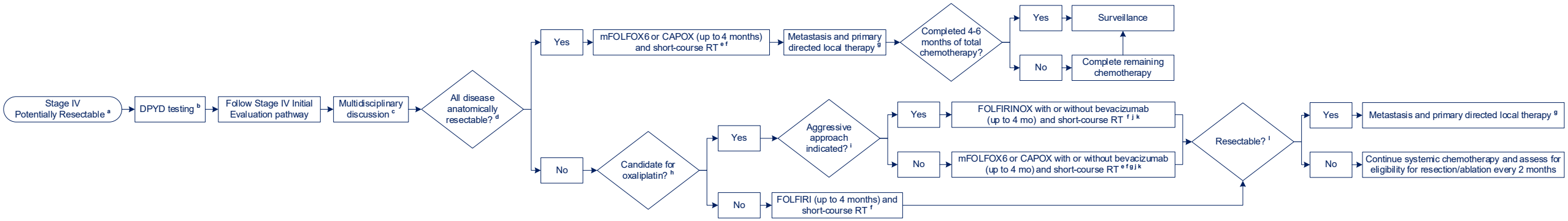
Clinical trial(s) always considered on pathway. For assistance finding a clinical trial, email CancerClinicalTrialsNavigation@va.gov.

[a] **Stage IV** determined by clinical evaluation and imaging and/or pathological confirmation post diagnosis; if primary is in place, perform pelvic MRI if disease is deemed resectable or potentially resectable

[b] **Multidisciplinary Discussion** includes but not limited to Medical Oncology, Radiation Oncology, Surgical Oncology, Thoracic Surgery, Interventional Radiology, Diagnostic Radiology, and/or Pathology

dMMR Mismatch Repair Deficient
MSI-H Microsatellite Instability High
MSS Microsatellite Stable
pMMR Proficient Mismatch Repair

Rectal Cancer – Stage IV Potentially Resectable



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

[a] **If neuropathy ≥ grade 2 develops** during neoadjuvant phase, complete treatment with fluorouracil and capecitabine

[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] **Multidisciplinary Discussion** includes but not limited to Medical Oncology, Radiation Oncology, Surgical Oncology, Thoracic Surgery, Interventional Radiology, Diagnostic Radiology, and/or Pathology

[d] **Anatomically Resectable** also includes ablative treatment

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

[f] **Short-Course RT** is delivered without chemotherapy; short-course RT can be sequenced before chemotherapy if the primary warrants immediate attention

[g] **Metastasis-Directed Local Therapy** options include surgery, radiation, and IR ablative techniques; surgery is preferred if feasible

[h] **Candidate for Oxaliplatin** contraindication if any adjuvant treatment in the past 12 months or preexisting neuropathy >1 grade neuropathy

[i] **Aggressive Approach Indicated** may be considered in very fit patients with excellent performance status

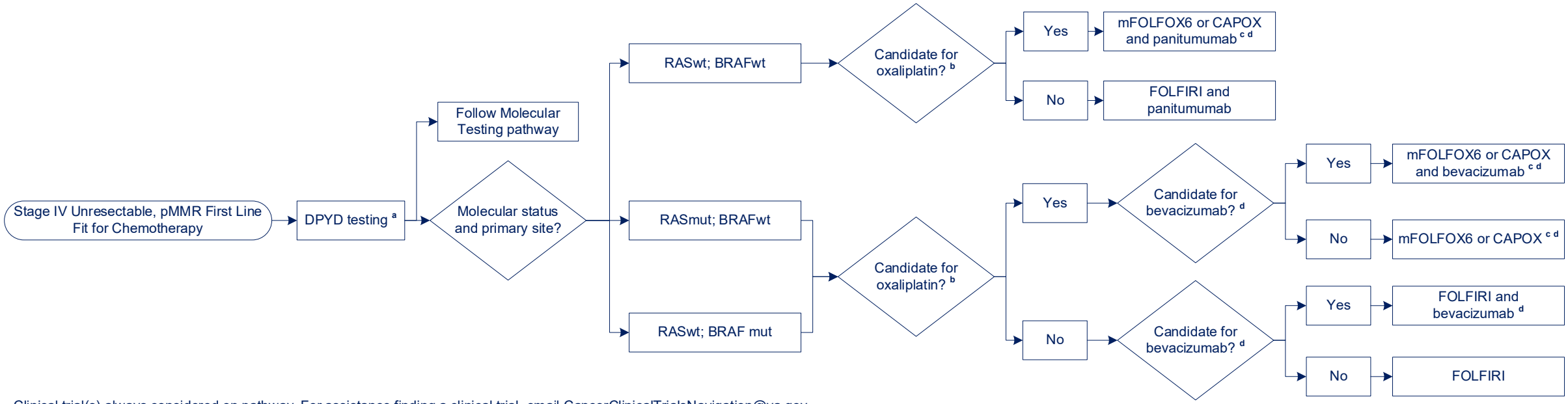
[j] **Candidate for Bevacizumab** received fluoropyrimidine and platinum agent in the first-line setting; ECOG PS 0-2; ANC ≥ 1500/mm^3; due to anti-VEGF effects patients with the following should not receive ramucirumab: non-healing wound/fracture, major surgery in prior 4 weeks, bleeding disorder or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

[k] **Choice of Chemotherapy** will be between oxaliplatin-based doublet (if eligible for oxaliplatin) or single agent capecitabine and fluorouracil; if neuropathy ≥ grade 2 develop during neoadjuvant phase, complete treatment with capecitabine and fluorouracil

[l] **Restaging** with pelvic MRI (if primary is present) and CT of chest and abdomen as well as pelvis (if pelvic MRI is not available)

DPYD Dihydropyrimidine Dehydrogenase

Rectal Cancer – Stage IV Unresectable, pMMR First Line Fit for Chemotherapy



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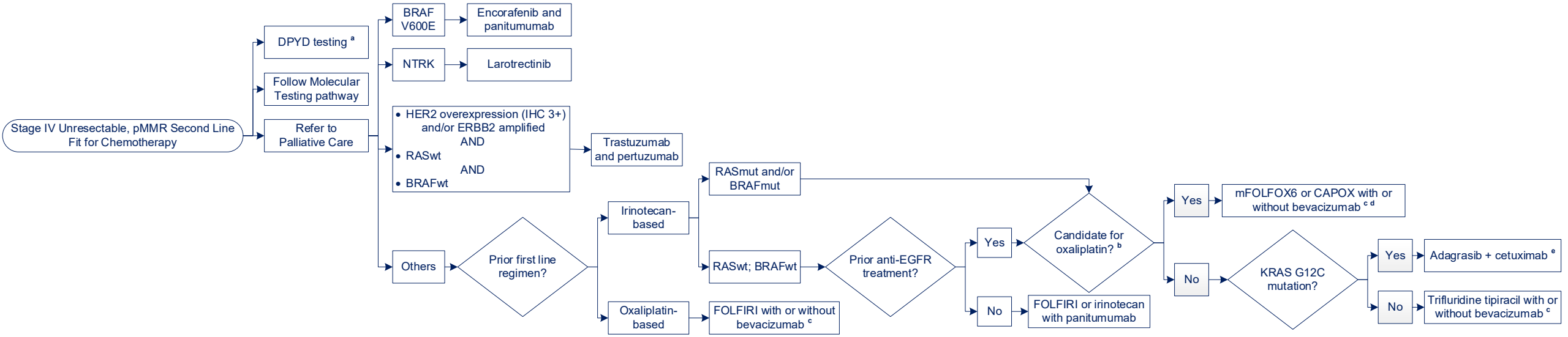
[b] **Candidate for Oxaliplatin** contraindication if any adjuvant treatment in the past 12 months or preexisting neuropathy >1 grade neuropathy; patient preference to avoid neuropathy

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

[d] **Candidate for Bevacizumab** received fluoropyrimidine and platinum agent in the first-line setting; 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
mut mutation
pMMR Proficient Mismatch Repair
wt wild type

Rectal Cancer – Stage IV Unresectable, pMMR Second Line Fit for Chemotherapy



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

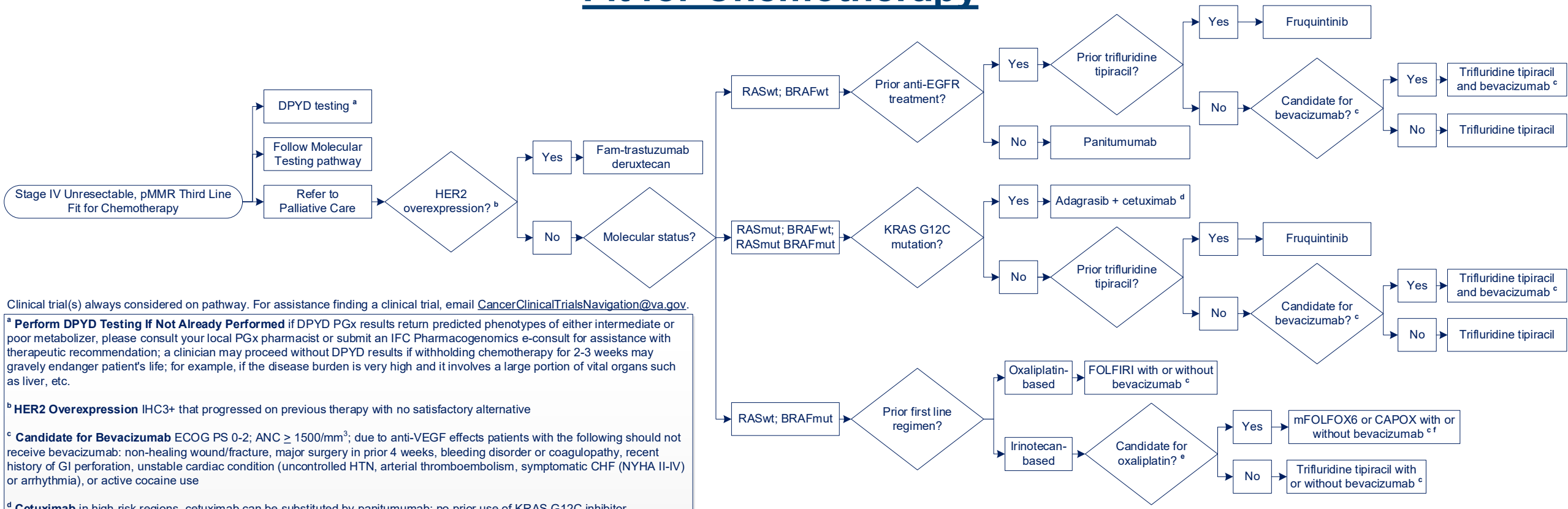
[c] **Candidate for Bevacizumab** ECOG PS 0-2; ANC ≥ 1500/mm^3; due to anti-VEGF effects patients with the following should not receive bevacizumab: non-healing wound/fracture, major surgery in prior 4 weeks, bleeding disorder or coagulopathy, recent history of GI perforation, unstable cardiac condition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

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

[e] **Cetuximab** in high-risk regions, cetuximab can be substituted by panitumumab; no prior use of KRAS G12C inhibitor

DPYD Dihydropyrimidine Dehydrogenase
EGFR Epidermal Growth Factor Receptor
mut Mutation
NTRK Neurotrophic Tyrosine Receptor Kinase
pMMR Proficient Mismatch Repair
wt Wild Type

Rectal Cancer – Stage IV Unresectable, pMMR Third Line Fit for Chemotherapy



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[b] **HER2 Overexpression** IHC3+ that progressed on previous therapy with no satisfactory alternative

[c] **Candidate for Bevacizumab** 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

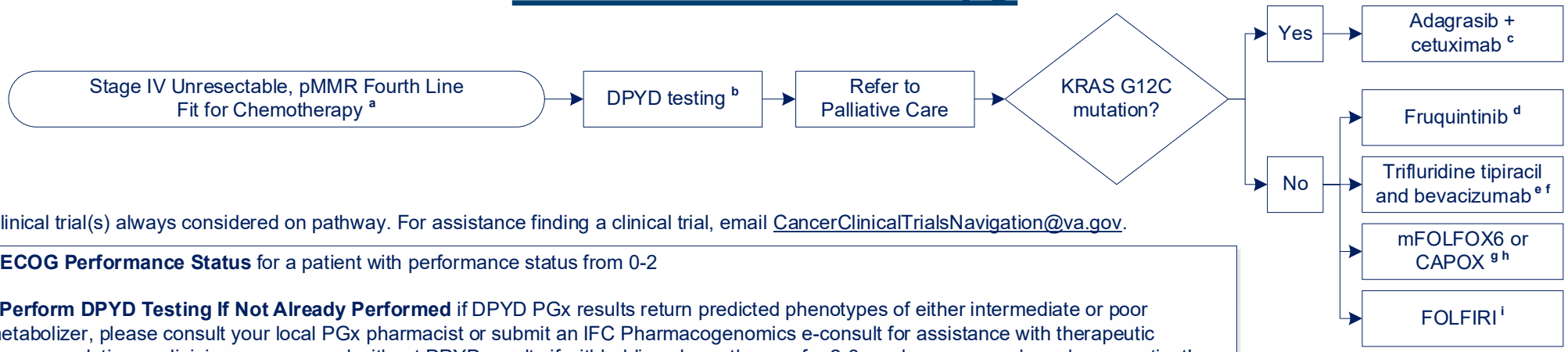
[d] **Cetuximab** in high-risk regions, cetuximab can be substituted by panitumumab; no prior use of KRAS G12C inhibitor

[e] **Capecitabine or Fluorouracil** consider DPYD testing to inform starting dose of fluorouracil or capecitabine in the shared decision making

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

DPYD Dihydropyrimidine Dehydrogenase
EGFR Epidermal Growth Factor Receptor
mut mutation
pMMR Proficient Mismatch Repair
wt wild type

Rectal Cancer – Stage IV Unresectable, pMMR Fourth Line Fit for Chemotherapy



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[a] **ECOG Performance Status** for a patient with performance status from 0-2

[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] **Cetuximab** in high-risk regions, cetuximab can be substituted by panitumumab; no prior use of KRAS G12C inhibitor

[d] **Fruquintinib** no prior failure to the treatment

[e] **Trifluridine Tipiracil** no prior failure to the treatment

[f] **Candidate for Bevacizumab** 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

[g] **mFOLFOX6 or CAPOX** well tolerated if used previously and duration from last treatment >12 months and and no ≥ grade 2 neuropathy

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

[i] **FOLFIRI** well tolerated if used previously and duration from last treatment >12 months

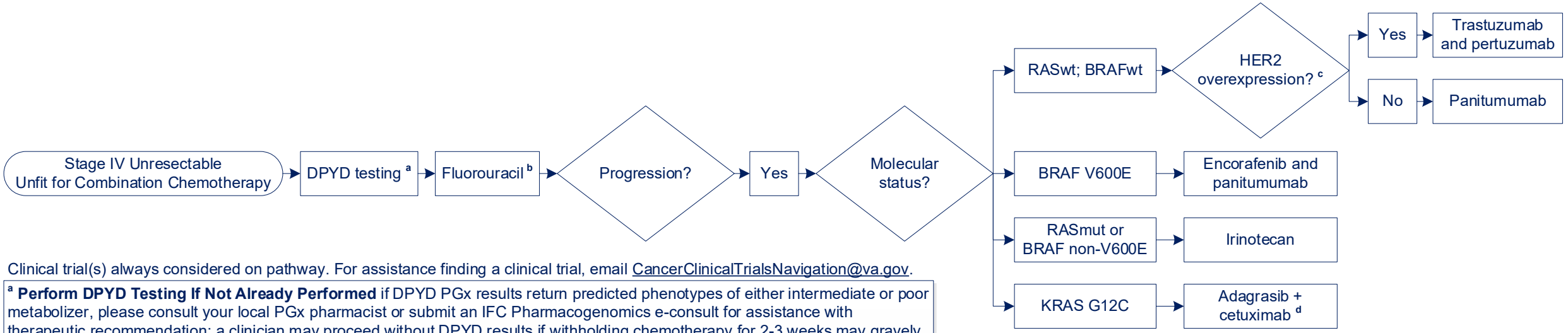
DPYD Dihydropyrimidine Dehydrogenase
pMMR Proficient Mismatch Repair

Rectal Cancer – Stage IV Unresectable, dMMR

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

dMMR Mismatch Repair Deficient
pMMR Proficient Mismatch Repair

Rectal Cancer – Stage IV Unresectable, Unfit for Chemotherapy



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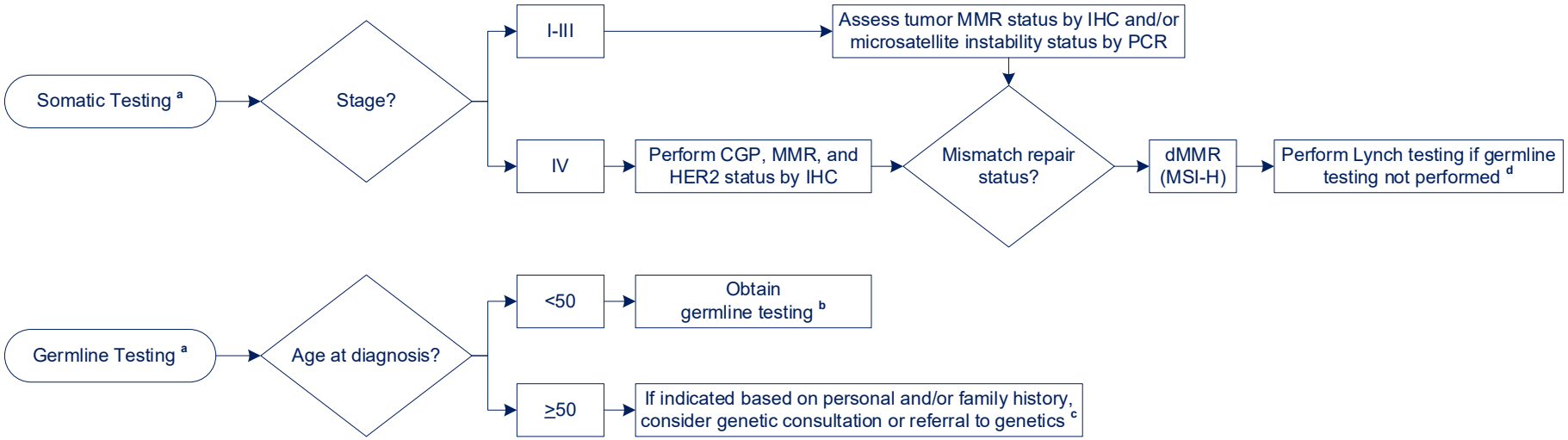
[b] **Fluorouracil** infusional 5-fluorouracil monotherapy is preferred, however for select patient unable to tolerate pump, capecitabine may be substituted if no issues with adherence, toxicity reporting, or severe renal impairment (CrCl<30 ml/min)

[c] **HER2 Overexpression** IHC3+ that progressed on previous therapy with no satisfactory alternative

[d] **Cetuximab** in high-risk regions, cetuximab can be substituted by panitumumab; no prior use of KRAS G12C inhibitor

DPYD Dihydropyrimidine Dehydrogenase
mut mutation
wt wild type

Rectal Cancer – Molecular Testing



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

[a] **Molecular Testing** perform for pathologically confirmed cancer

[b] **Germline Testing** an appropriate germline testing panel should include at minimum the following genes: APC; AXIN2; BMPR1A; CHEK2; EPCAM; GALNT12; GREM1; MLH1; MLH3; MSH2; MSH3; MSH6; MUTYH; NTHL1; PMS2; POLD1; POLE; PTEN; RNF43; SMAD4; STK11; and TP53

[c] **Personal and Family History** consider germline testing if significant personal and/or family history of multiple polyps, other Lynch syndrome or other hereditary cancer syndrome-associated cancers (e.g., colorectal, endometrial, gastric, ovarian, pancreas, urothelial, brain (usually glioblastoma), biliary tract, and small intestine, as well as sebaceous adenomas, sebaceous carcinomas, and keratoacanthomas as seen in Muir-Torre syndrome), or pathogenic or likely pathogenic variant in a gene associated with known hereditary cancer syndrome is present in the patient or a family member

[d] **Lynch Testing** the diagnostic Lynch genetic testing algorithm depends on the pattern of MLH1, MSH2, MSH6, and PMS2 expression by IHC; diagnostic Lynch genetic testing should be performed if there is loss of MSH2, MSH6, MSH2/MSH6, or PMS2 expression by IHC; if there is loss of MLH1 expression by IHC, *MLH1* promoter hypermethylation testing should be performed; *MLH1* hypermethylation suggests somatic mutation, but diagnostic Lynch genetic testing should be performed if *MLH1* is unmethylated in the context of MLH1 loss by IHC; a diagnostic Lynch genetic testing panel should include at minimum the following genes: *EPCAM*, *MLH1*, *MSH2*, *MSH6*, and *PMS2*

CGP Comprehensive Genomic Profiling
dMMR Mismatch Repair Deficient
IHC Immunohistochemistry
MMR Mismatch Repair
MSI-H Microsatellite Instability High
PCR Polymerase Chain Reaction

Rectal Cancer – Molecular Testing Table

Eligibility	Test Category	Test Type	Recommended Vendors	NPOP Coverage	Specimen Type
Rectal Cancer Stage I-III	IHC*	Mismatch repair (MMR) protein expression by IHC: MLH1, MSH2, MSH6, and PMS2.	Local VA or locally contracted vendor	No	Tumor Tissue
	PCR*	Microsatellite instability (MSI) status by PCR.	Regional VA Testing Center (GLA)	Yes	Tumor Tissue and Normal Tissue or Blood
	IHC	Consider BRAF V600E IHC if MLH1 or PMS2 expression is lost by IHC, or if MSI-H and IHC not performed. Mutated suggests somatic mutation. Unmutated calls for Methylation testing.	Local VA or locally contracted vendor	No	Tumor Tissue
	Molecular Testing	Consider *BRAF* V600E mutation testing if MLH1 or PMS2 expression is lost by IHC, or if MSI-H and IHC not performed. Mutated suggests somatic mutation. Unmutated calls for Methylation testing.	Local VA or locally contracted vendor	No	Tumor Tissue
	Methylation Testing	*MLH1* promoter hypermethylation testing (In the setting of loss of MLH1 or PMS2 expression by IHC). Hypermethylation suggests somatic mutation. Unmethylated calls for Germline Lynch testing.	Local VA or locally contracted vendor	No	Tumor Tissue
	Germline NGS***	If full germline testing not performed, perform Germline Lynch testing if: 1) MSH2 or MSH6 loss by IHC or 2) MLH1 or PMS2 loss by IHC and *MLH1* unmethylated or 3) MSI-H without IHC testing AND *BRAF* unmutated AND *MLH1* unmethylated	Fulgent Prevention Genetics	Yes Yes	Saliva, Blood
Rectal Cancer Stage IV	Somatic NGS	Comprehensive genomic profiling (CGP) including MSI.	Tempus Foundation Medicine	Yes Yes	Tumor Tissue*****, Blood
	IHC	HER2	Local VA or locally contracted vendor	No	Tumor Tissue
	FISH	Reflex to HER2 FISH if 2+ on IHC	Local VA or locally contracted vendor	No	Tumor Tissue
	IHC**	Mismatch repair (MMR) protein expression by IHC: MLH1, MSH2, MSH6, and PMS2.	Tempus	Yes (When ordered with CGP)	Tumor Tissue
	PCR**	Consider microsatellite instability (MSI) status by PCR if MSI by CGP is not performed or equivocal.	Regional VA Testing Center (GLA)	Yes	Tumor Tissue and Normal Tissue or Blood
	Methylation Testing	*MLH1* promoter hypermethylation testing (In the setting of loss of MLH1 or PMS2 expression by IHC). Hypermethylation suggests somatic mutation. Unmethylated calls for Lynch testing.	Local VA or locally contracted vendor	No	Tumor Tissue
	Germline NGS***	If full germline testing not performed, perform Germline Lynch testing if: 1) MSH2 or MSH6 loss by IHC or 2) MLH1 or PMS2 loss by IHC and *MLH1* unmethylated or 3) MSI-H without IHC testing AND *BRAF* unmutated AND *MLH1* unmethylated	Fulgent Prevention Genetics	Yes Yes	Saliva, Blood
Rectal Cancer Diagnosis Below the Age of 50	Germline NGS****	Full Germline Testing	Fulgent Prevention Genetics	Yes Yes	Saliva, Blood
Personal and/or Family History of Multiple Polyps, Other Lynch Syndrome or Other Hereditary Cancer Syndrome Associated Cancers), or Pathogenic or Likely Pathogenic Variant in a Gene Associated with Known Hereditary Cancer Syndrome is Present in the Patient or a Family Member	Germline NGS****	Full Germline Testing	Fulgent Prevention Genetics	Yes Yes	Saliva, Blood

* For Stage I-III, either MMR or MSI or Both can be performed

** For Stage IV, Both MMR and MSI should be performed; If MSI cannot be determined by CGP, then MSI by PCR can be performed

*** Germline Lynch testing should include at minimum the following genes: *EPCAM* (deletion), *MLH1, MSH2, MSH6, PMS2, POLE,* and *POLD1*

**** VA Common Hereditary POC panel or Equivalent Germline Test; Full Germline testing should include at minimum the following genes: APC; AXIN2; BMPR1A; CHEK2; EPCAM; GALNT12; GREM1; MLH1; MLH3; MSH2; MSH3; MSH6; MUTYH; NTHL1; PMS2; POLD1; POLE; PTEN; RNF43; SMAD4; STK11; and TP53; For genetic online ordering, refer to CCGS page for further details

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