

Oncology Clinical Pathways

Colon Cancer

March 2024 – V2.2024



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U.S. Department
of Veterans Affairs

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Colon 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 colon

Gulf War and Post 9/11 Veterans

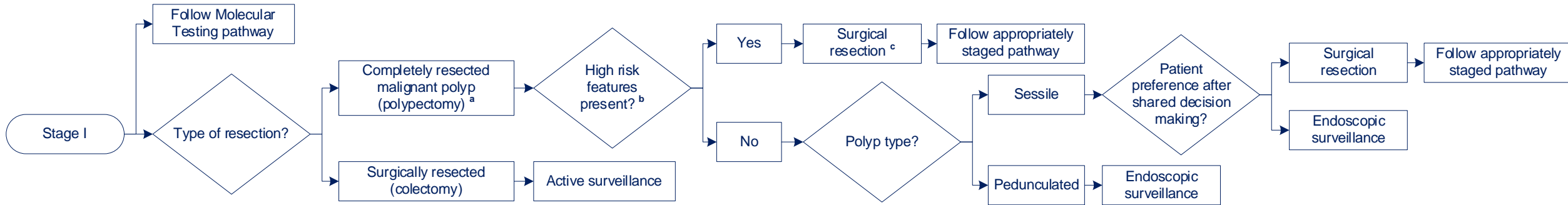
If the patient served on or after Sept. 11, 2001, in Afghanistan, Djibouti, Egypt, Jordan, Lebanon, Syria, Uzbekistan, or Yemen or if you served in the *Southwest Asia theater of operations, or Somalia, on or after Aug. 2, 1990, specific conditions include:

- 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 \(va.gov\)](https://www.va.gov)

Colon Cancer – Stage I



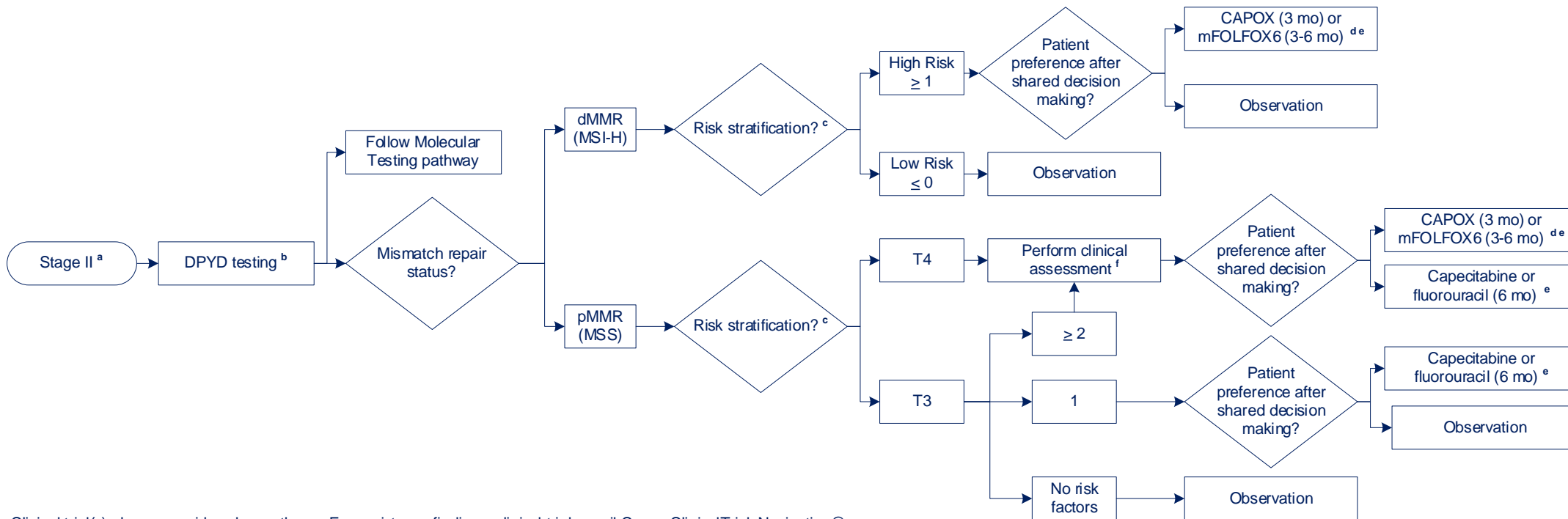
Clinical trial(s) always considered on pathway. For assistance finding a clinical trial, email CancerClinicalTrialsNavigation@va.gov.

^a **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

^c **Surgical Resection** defined as a formal oncologic segmental colectomy

Colon Cancer – Stage II



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

^a **Stage II** determined following surgical resection, with time to initiation of chemotherapy recommended to begin 6-8 weeks following surgery; delay beyond 3 months is likely to greatly reduce the efficacy of subsequent chemotherapy and should be weighed into decision making; late initiation of chemotherapy should be evaluated on a case by case basis

^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 **Risk Stratification:** high risk features include presence of clinical obstruction, localized tumor perforation, or poorly differentiated tumor (pMMR only), lymphovascular invasion, perineural invasion, <12 harvested lymph nodes, positive and/or close margin (≤ 1 mm in non-peritonealized margins), or high tumor budding (18/0.785 mm²)

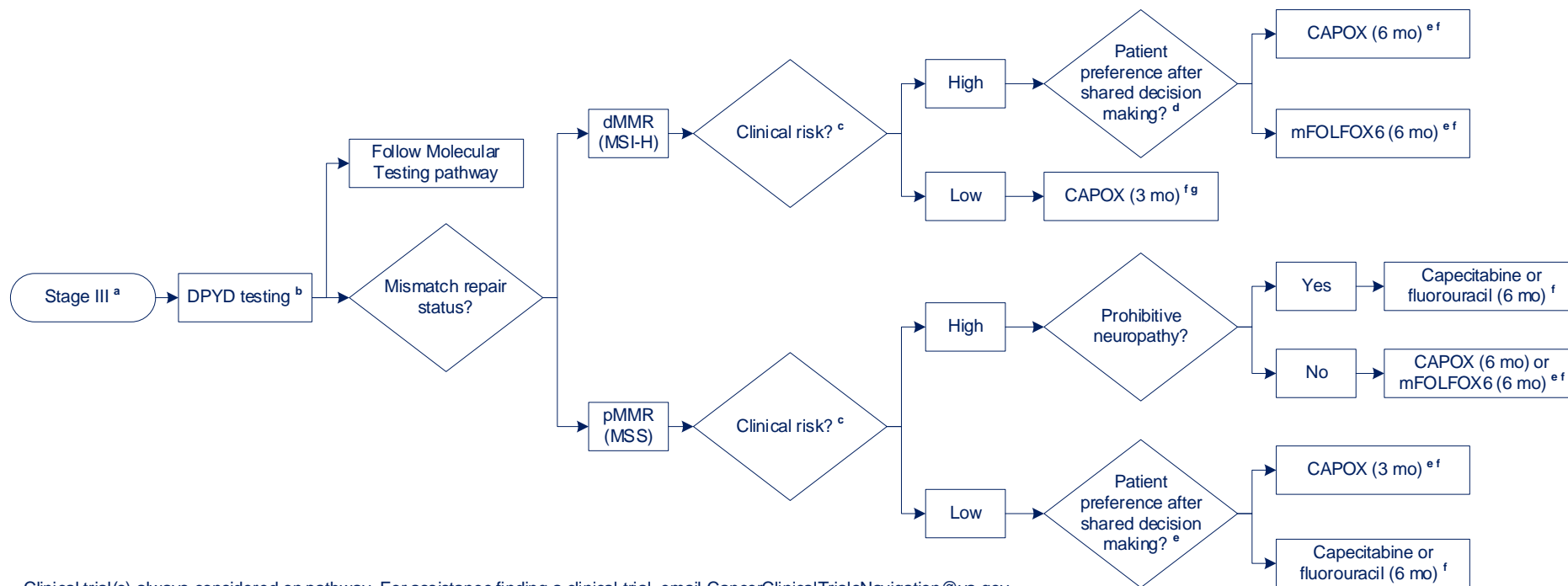
^d **Oxaliplatin-Based Regimens** risk of \geq Grade 3 neurotoxicity is lower with 3-month vs. 6-month; if \geq grade 2 neuropathy develops during treatment, may discontinue oxaliplatin after three months while continuing fluoropyrimidine to full course (6 months); for pMMR, the benefit of addition of oxaliplatin is unclear in patients aged > 70 due to paucity of data

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

^f **Clinical Assessment** determine presence of renal dysfunction, comorbidities, neuropathy, limited performance status, or limited life expectancy, as they would negatively impact the decision to use adjuvant chemotherapy

DPYD Dihydropyrimidine Dehydrogenase

Colon Cancer – Stage III



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

^a **Stage III** determined following surgical resection, with time to initiation of chemotherapy recommended to begin 6-8 weeks following surgery; delay beyond 3 months is likely to greatly reduce the efficacy of subsequent chemotherapy and should be weighed into decision making; late initiation of chemotherapy should be evaluated on a case by case basis

^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 **Clinical Risk** defines high risk as T4 and/or N2 (≥ 4 positive nodes) and low risk as T1-3 and N1

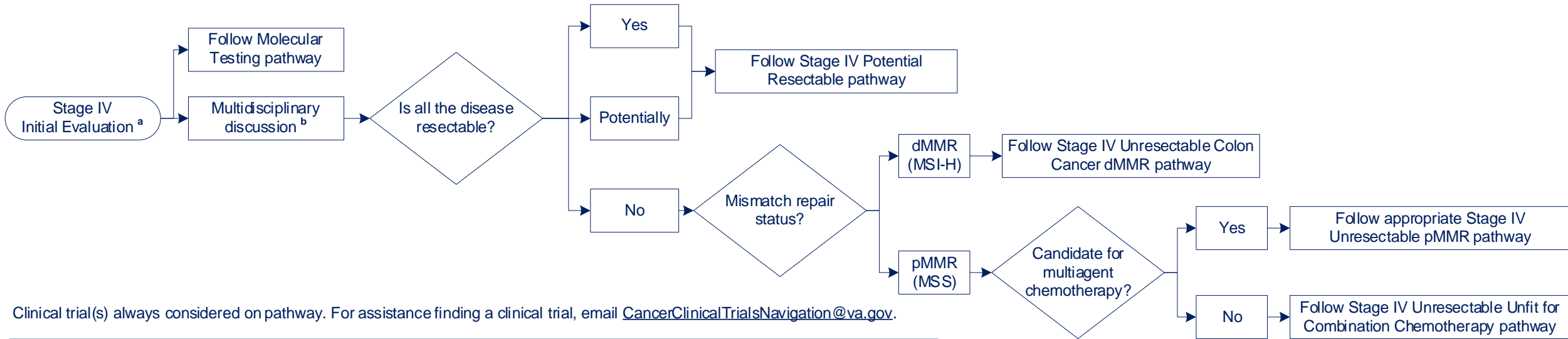
^d **If Preexisting Neuropathy**, single agent treatment may be an alternative for pMMR tumor; however, fluorouracil/capecitabine single agent treatment represents an inadequate option for dMMR tumors; observation may be appropriate for dMMR with significant baseline neuropathy (\geq grade 2)

^e **Oxaliplatin-Based Regimens** risk of \geq grade 3 neurotoxicity is lower with 3-month vs. 6-month; if $>$ grade 2 neuropathy develops, discontinue oxaliplatin while continuing fluoropyrimidine to full course; benefit of adding oxaliplatin is unclear in patients aged > 70 due to paucity of data

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

DPYD Dihydropyrimidine Dehydrogenase

Colon Cancer – Stage IV Initial Evaluation

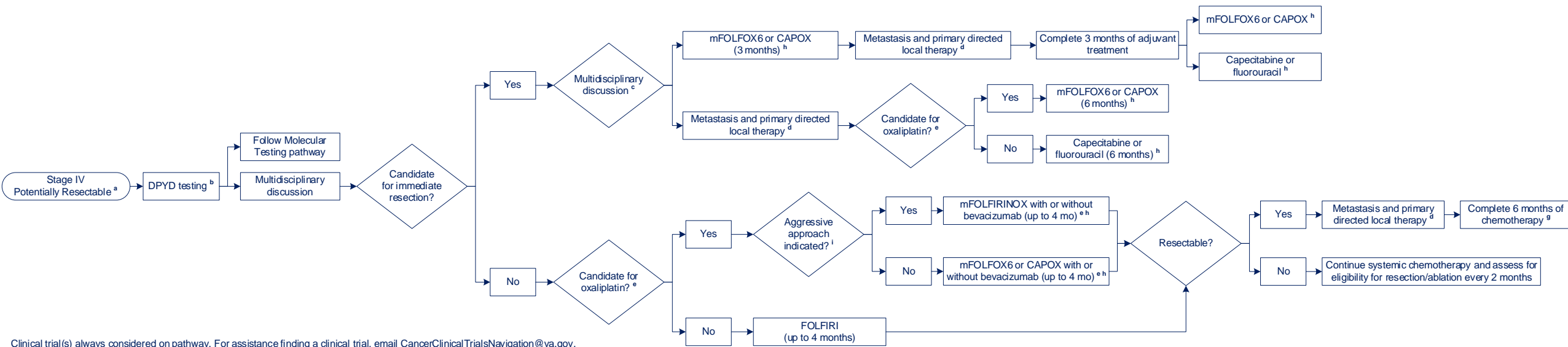


Clinical trial(s) always considered on pathway. For assistance finding a clinical trial, email CancerClinicalTrialsNavigation@va.gov.

^a **Stage IV** determined by clinical evaluation and imaging and/or pathological confirmation post diagnosis

^b **Multidisciplinary Discussion** refers to tumor board or with an expert or group of experts including but not limited to Medical Oncology, Radiation Oncology, Surgical Oncology, Thoracic Surgery, Interventional Radiology, Diagnostic Radiology, and/or Pathology

Colon Cancer – Stage IV Potentially Resectable



^a If Neuropathy \geq 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 refers to tumor board or with an expert or group of experts including but not limited to Medical Oncology, Radiation Oncology, Surgical Oncology, Thoracic Surgery, Interventional Radiology, Diagnostic Radiology, and/or Pathology

^d Metastasis-Directed Local Therapy options include surgery, radiation, and IR ablative techniques; surgery is preferred if feasible; resection of primary if present

^e Candidate for Oxaliplatin contraindication if any adjuvant treatment in the past 12 months or preexisting neuropathy >1 grade neuropathy

^f Candidate for Bevacizumab received fluoropyrimidine and platinum agent in the first-line setting; ECOG PS 0-2; ANC \geq 1500/mm³; 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

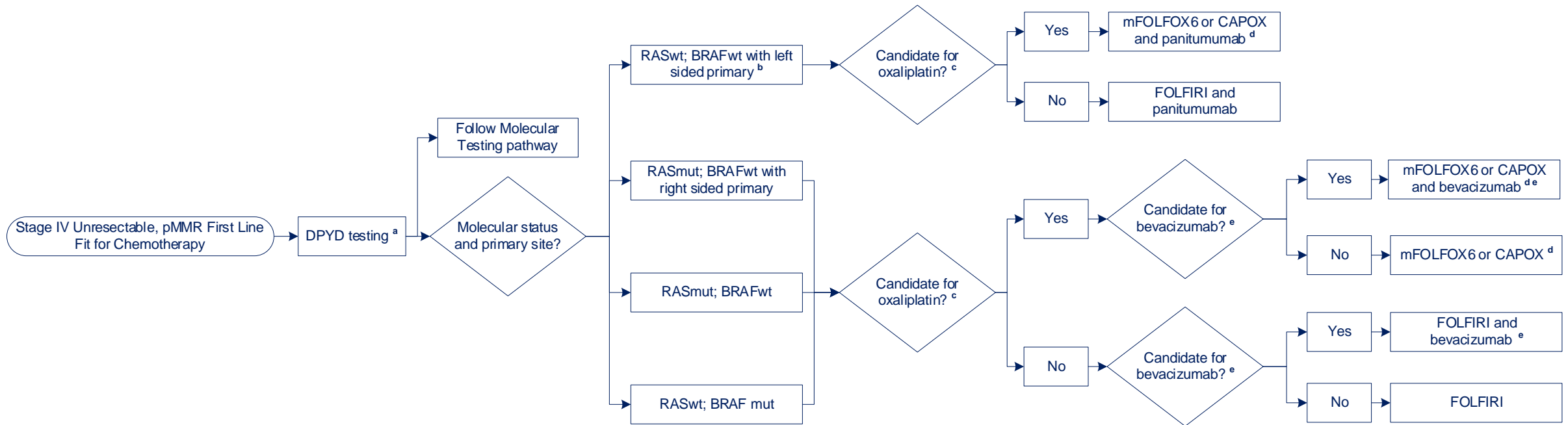
^g Choice of Chemotherapy will be between oxaliplatin-based doublet (if eligible for oxaliplatin) or single agent capecitabine and fluorouracil; if neuropathy \geq grade 2 develop during neoadjuvant phase, complete treatment with capecitabine and fluorouracil

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

ⁱ Aggressive Approach Indicated may be considered in very fit patients with excellent performance status and high disease burden and/or presence of BRAF mutation

DPYD Dihydropyrimidine Dehydrogenase

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



Clinical trial(s) 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 **Left Sided Primary** is defined as primary originating in splenic flexure and colon distal to that

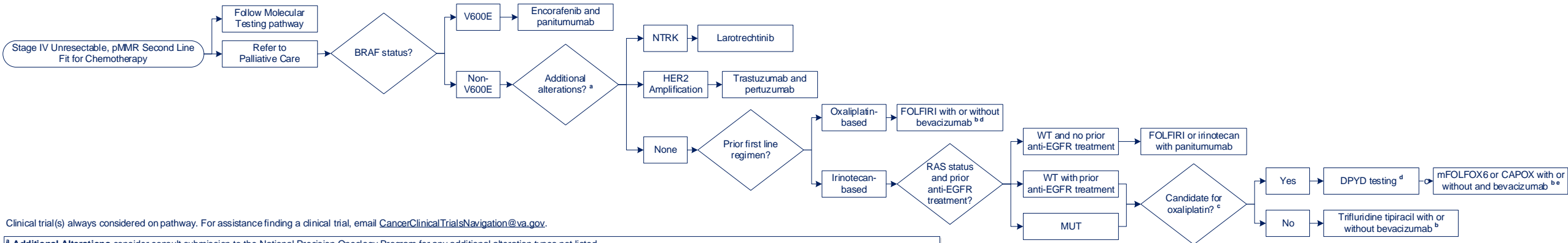
^c **Candidate for Oxaliplatin** contraindication if any adjuvant treatment in the past 12 months or preexisting neuropathy >1 grade neuropathy; patient preference to avoid neuropathy

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

^e **Candidate for Bevacizumab** received fluoropyrimidine and platinum agent in the first-line setting; ECOG PS 0-2; ANC $\geq 1500/\text{mm}^3$; 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

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



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

^a **Additional Alterations** consider consult submission to the National Precision Oncology Program for any additional alteration types not listed

^b **Candidate for Bevacizumab** received fluoropyrimidine and platinum agent in the first-line setting; ECOG PS 0-2; ANC \geq 1500/mm³; 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

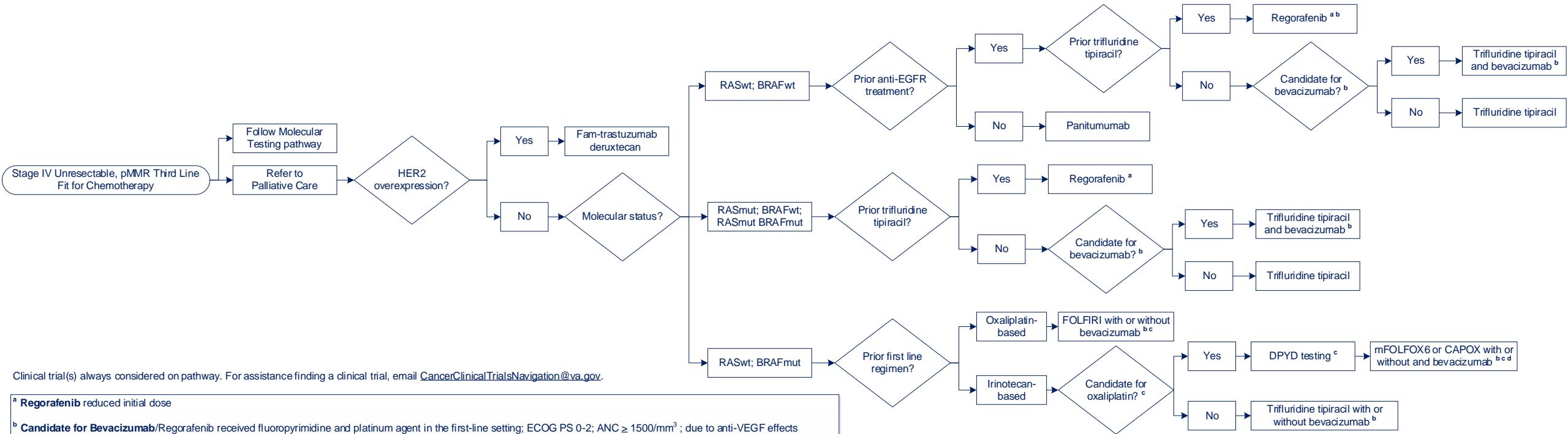
^c **Candidate for Oxaliplatin** contraindication if disease progression within 12 months of adjuvant treatment or preexisting neuropathy >1 grade neuropathy

^d **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.

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

DPYD Dihydropyrimidine Dehydrogenase

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



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

^a **Regorafenib** reduced initial dose

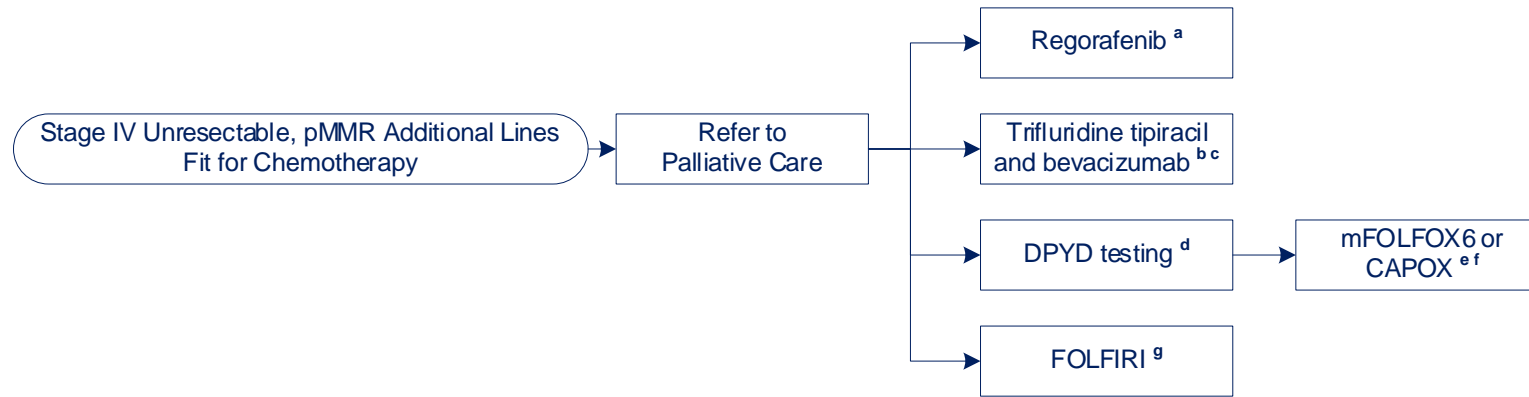
^b **Candidate for Bevacizumab/Regorafenib** received fluoropyrimidine and platinum agent in the first-line setting; ECOG PS 0-2; ANC \geq 1500/mm³; due to anti-VEGF effects patients with the following should not receive bevacizumab/regorafenib: non-healing wound/fracture, major surgery in prior 4 weeks, 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

^c **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.

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

DPYD Dihydropyrimidine Dehydrogenase

Colon Cancer – Stage IV Unresectable, pMMR Additional Lines Fit for Chemotherapy



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

^a **Candidate for Regorafenib** received fluoropyrimidine and platinum agent in the first-line setting; ECOG PS 0-2; ANC $\geq 1500/\text{mm}^3$; due to anti-VEGF effects patients with the following should not receive regorafenib: 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

^b **Trifluridine Tipiracil** no prior failure to the treatment

^c **Candidate for Bevacizumab** received fluoropyrimidine and platinum agent in the first-line setting; ECOG PS 0-2; ANC $\geq 1500/\text{mm}^3$; 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 **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.

^e **FOLFOX6 or CAPOX** well tolerated if used previously and duration from last treatment >12 months and no \geq grade 2 neuropathy

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

^g **FOLFIRI** well tolerated if used previously and duration from last treatment >12 months

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Colon Cancer – Stage IV Unresectable dMMR



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



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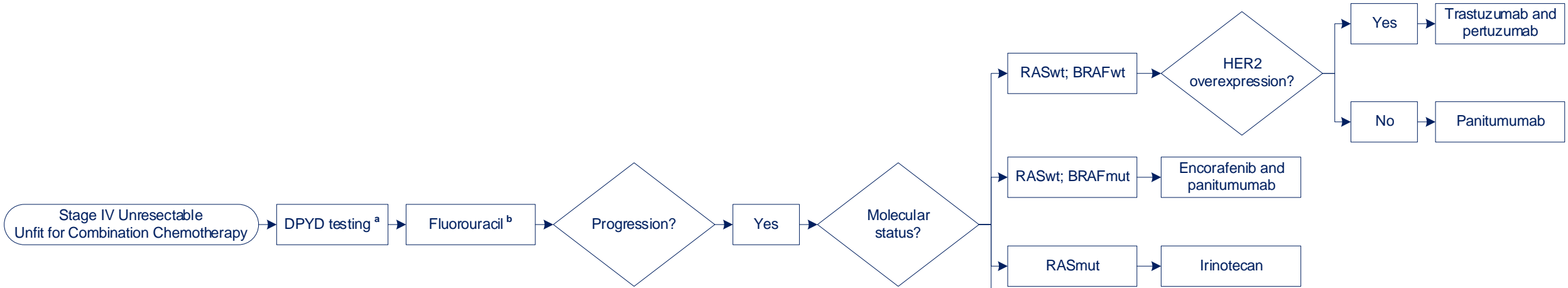
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Colon Cancer – Stage IV Unresectable Unfit for Combination Chemotherapy



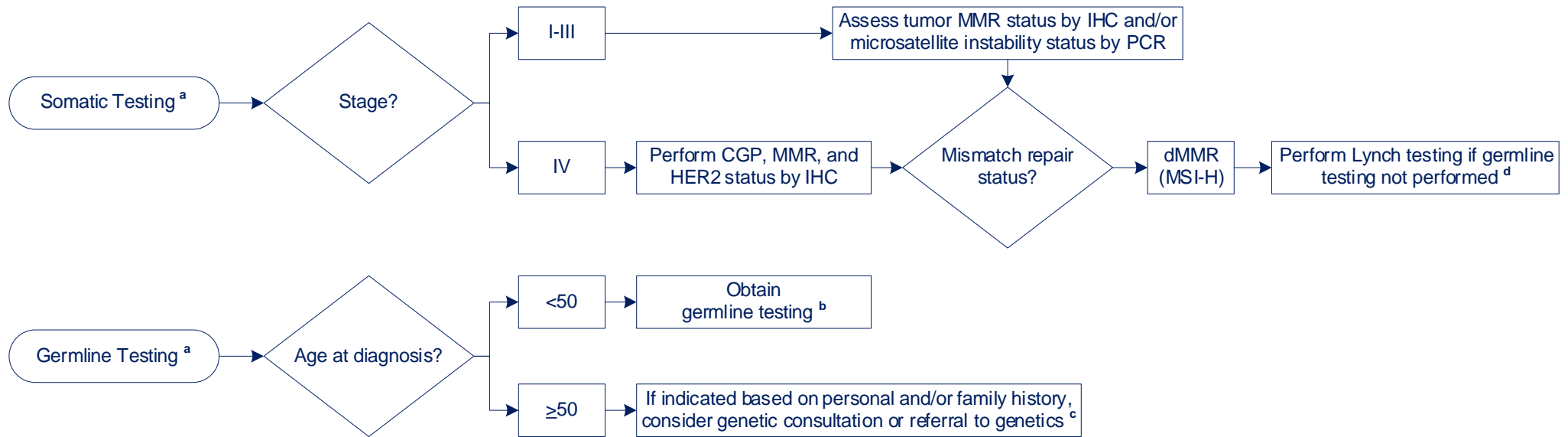
Clinical trial(s) always considered on pathway. For assistance finding a clinical trial, email CancerClinicalTrialsNavigation@va.gov.

^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 econsult for assistance with therapeutic recommendation; a clinician may proceed without DPYD results if withholding chemotherapy for 23 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 **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)

DPYD Dihydropyrimidine Dehydrogenase

Colon 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 keratocanthomas 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

Colon Cancer – Molecular Testing Table

| Eligibility | Test Category | Test Type | Recommended Vendors | NPOP Coverage | Specimen Type |
|--|---------------------|---|---------------------------------------|-----------------------------|---|
| 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 |
| 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 |
| 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



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