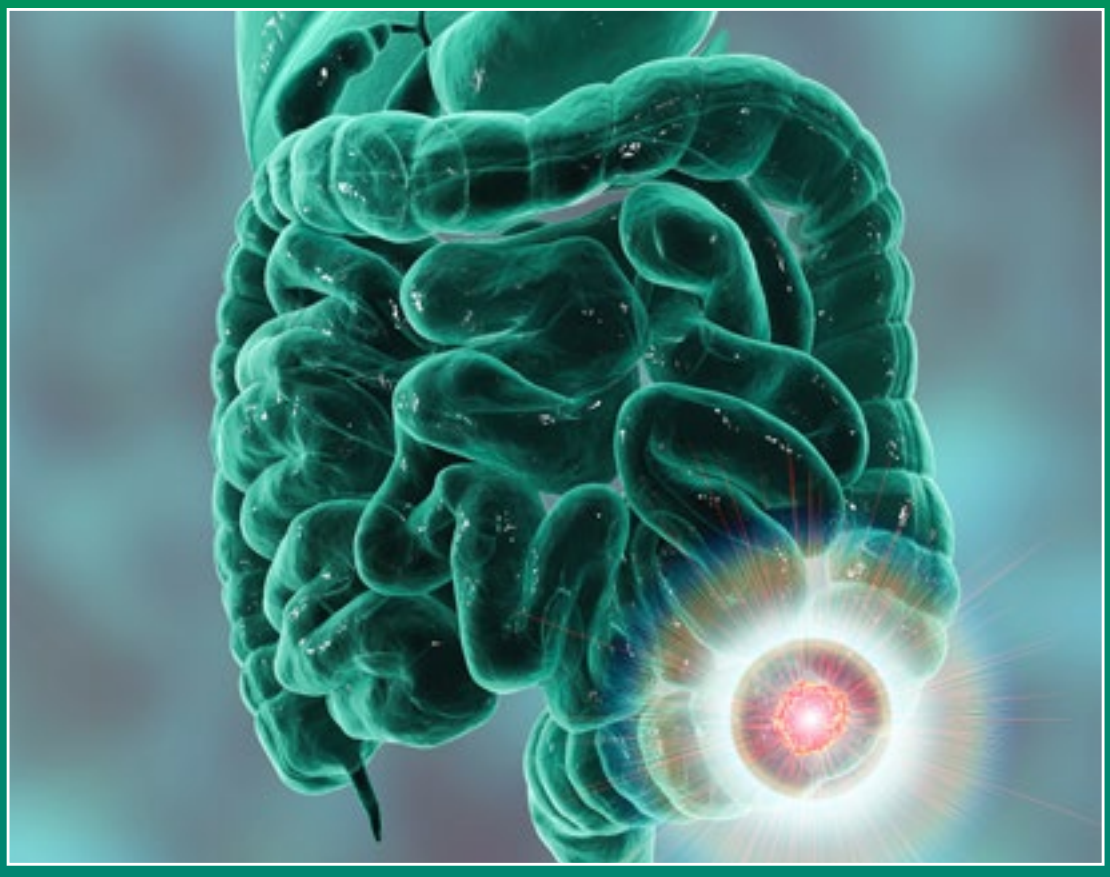
Advances in Diagnosis, Treatment of Early-Onset Colorectal Cancer



U.S. Medicine
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CHANGING THE PARADIGM IN FIRST-LINE TREATMENT

of mCRC for patients with newly diagnosed WT *RAS** left-sided mCRC

★ **NGS Testing for Patients Available via NPOP[1]**

★ **Vectibix® on VA Formulary†**

Scan here
to read about Vectibix® Clinical Study Results

Vectibix® (panitumumab)
100mg/5ml | 20mg/ml for injection

INDICATION AND LIMITATION OF USE

Vectibix® is indicated for the treatment of patients with wild-type *RAS* (defined as wild-type in both *KRAS* and *NRAS* as determined by an FDA-approved test for this use) metastatic colorectal cancer (mCRC): as first-line therapy in combination with FOLFOX, and as monotherapy following disease progression after prior treatment with fluoropyrimidine-, oxaliplatin-, and irinotecan-containing chemotherapy. Limitation of Use: Vectibix® is not indicated for the treatment of patients with *RAS*-mutant mCRC or for whom *RAS* mutation status is unknown.

IMPORTANT SAFETY INFORMATION

BOXED WARNING: DERMATOLOGIC TOXICITY

Dermatologic Toxicity: Dermatologic toxicities occurred in 90% of patients and were severe (NCI-CTC grade 3 and higher) in 15% of patients receiving Vectibix® monotherapy [see Dosage and Administration (2.3), Warnings and Precautions (5.1), and Adverse Reactions (6.1)].

Please see full Important Safety Information on adjacent page.

*Defined as wild type in both *KRAS* and *NRAS*.[2]
†Requires facility-level prior authorization. Review criteria for use.[3]
NGS = next-generation sequencing; NPOP = National Precision Oncology Program; mCRC = metastatic colorectal cancer; VA = Veterans Affairs; WT = wild type.

REFERENCES: **1.** U.S. Department of Veterans Affairs. National Oncology Program FAQs. https://www.cancer.va.gov/CANCER faq.asp. Accessed March 13, 2023. **2.** Vectibix® (panitumumab) prescribing information, Amgen. **3.** VA Formulary Search. https://www.pbm.va.gov. Accessed January 1, 2023.

IMPORTANT SAFETY INFORMATION CONT'D

- In Study 20020408, dermatologic toxicities occurred in 90% of patients and were severe (NCI-CTC grade 3 and higher) in 15% of patients with mCRC receiving Vectibix®. The clinical manifestations included, but were not limited to, acneiform dermatitis, pruritus, erythema, rash, skin exfoliation, paronychia, dry skin, and skin fissures.
- Monitor patients who develop dermatologic or soft tissue toxicities while receiving Vectibix® for the development of inflammatory or infectious sequelae. Life-threatening and fatal infectious complications including necrotizing fasciitis, abscesses, and sepsis have been observed in patients treated with Vectibix®. Life-threatening and fatal bullous mucocutaneous disease with blisters, erosions, and skin sloughing has also been observed in patients treated with Vectibix®. It could not be determined whether these mucocutaneous adverse reactions were directly related to EGFR inhibition or to idiosyncratic immune-related effects (eg, Stevens Johnson syndrome or toxic epidermal necrolysis). Withhold or discontinue Vectibix® for dermatologic or soft tissue toxicity associated with severe or life-threatening inflammatory or infectious complications. Dose modifications for Vectibix® concerning dermatologic toxicity are provided in the product labeling.
- Vectibix® is not indicated for the treatment of patients with colorectal cancer that harbor somatic *RAS* mutations in exon 2 (codons 12 and 13), exon 3 (codons 59 and 61), and exon 4 (codons 117 and 146) of either *KRAS* or *NRAS* and hereafter is referred to as "*RAS*."
- Retrospective subset analyses across several randomized clinical trials were conducted to investigate the role of *RAS* mutations on the clinical effects of anti-EGFR-directed monoclonal antibodies (panitumumab or cetuximab). Anti-EGFR antibodies in patients with tumors containing *RAS* mutations resulted in exposing those patients to anti-EGFR related adverse reactions without clinical benefit from these agents. Additionally, in Study 20050203, 272 patients with *RAS*-mutant mCRC tumors received Vectibix® in combination with FOLFOX and 276 patients received FOLFOX alone. In an exploratory subgroup analysis, OS was shorter (HR = 1.21, 95% CI: 1.01-1.45) in patients with *RAS*-mutant mCRC who received Vectibix® and FOLFOX versus FOLFOX alone.
- Progressively decreasing serum magnesium levels leading to severe (grade 3-4) hypomagnesemia occurred in up to 7% (in Study 20080763) of patients across clinical trials. Monitor patients for hypomagnesemia and hypocalcemia prior to initiating Vectibix® treatment, periodically during Vectibix® treatment, and for up to 8 weeks after the completion of treatment. Other electrolyte disturbances, including hypokalemia, have also been observed. Replete magnesium and other electrolytes as appropriate.
- In Study 20020408, 4% of patients experienced infusion reactions and 1% of patients experienced severe infusion reactions (NCI-CTC grade 3-4). Infusion reactions, manifesting as fever, chills, dyspnea, bronchospasm, and hypotension, can occur following Vectibix® administration. Fatal infusion reactions occurred in postmarketing experience. Terminate the infusion for severe infusion reactions.
- Severe diarrhea and dehydration, leading to acute renal failure and other complications, have been observed in patients treated with Vectibix® in combination with chemotherapy.
- Fatal and nonfatal cases of interstitial lung disease (ILD) (1%) and pulmonary fibrosis have been observed in patients treated with Vectibix®. Pulmonary fibrosis occurred in less than 1% (2/1467) of patients enrolled in clinical studies of Vectibix®. In the event of acute onset or worsening of pulmonary symptoms interrupt Vectibix® therapy. Discontinue Vectibix® therapy if ILD is confirmed.
- In patients with a history of interstitial pneumonitis or pulmonary fibrosis, or evidence of interstitial pneumonitis or pulmonary fibrosis, the benefits of therapy with Vectibix® versus the risk of pulmonary complications must be carefully considered.
- Exposure to sunlight can exacerbate dermatologic toxicity. Advise patients to wear sunscreen and hats and limit sun exposure while receiving Vectibix®.
- Serious cases of keratitis, ulcerative keratitis, and corneal perforation have occurred with Vectibix® use. Monitor for evidence of keratitis, ulcerative keratitis, or corneal perforation. Interrupt or discontinue Vectibix® therapy for acute or worsening keratitis, ulcerative keratitis, or corneal perforation.
- In an interim analysis of an open-label, multicenter, randomized clinical trial in the first-line setting in patients with mCRC, the addition of Vectibix® to the combination of bevacizumab and chemotherapy resulted in decreased OS and increased incidence of NCI-CTC grade 3-5 (87% vs 72%) adverse reactions. NCI-CTC grade 3-4 adverse reactions occurring at a higher rate in Vectibix®-treated patients included rash/acneiform dermatitis (26% vs 1%), diarrhea (23% vs 12%), dehydration (16% vs 5%), primarily occurring in patients with diarrhea, hypokalemia (10% vs 4%), stomatitis/mucositis (4% vs < 1%), and hypomagnesemia (4% vs 0).
- NCI-CTC grade 3-5 pulmonary embolism occurred at a higher rate in Vectibix®-treated patients (7% vs 3%) and included fatal events in three (< 1%) Vectibix®-treated patients. As a result of the toxicities experienced, patients randomized to Vectibix®, bevacizumab, and chemotherapy received a lower mean relative dose intensity of each chemotherapeutic agent (oxaliplatin, irinotecan, bolus 5-FU, and/or infusional 5-FU) over the first 24 weeks on study compared with those randomized to bevacizumab and chemotherapy.
- Vectibix® can cause fetal harm when administered to a pregnant woman. Advise pregnant women and females of reproductive potential of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment, and for at least 2 months after the last dose of Vectibix®.
- In monotherapy, the most commonly reported adverse reactions (≥ 20%) in patients with Vectibix® were skin rash with variable presentations, paronychia, fatigue, nausea, and diarrhea.
- The most commonly reported adverse reactions (≥ 20%) with Vectibix® + FOLFOX were diarrhea, stomatitis, mucosal inflammation, asthenia, paronychia, anorexia, hypomagnesemia, hypokalemia, rash, acneiform dermatitis, pruritus, and dry skin. The most common serious adverse reactions (≥ 2% difference between treatment arms) were diarrhea and dehydration.

Please see a brief summary of the Prescribing Information on the adjacent pages.

AMGEN

Vectibix® (panitumumab)

BRIEF SUMMARY OF FULL PRESCRIBING INFORMATION

WARNING: DERMATOLOGIC TOXICITY

Dermatologic Toxicity: Dermatologic Toxicities occurred in 90% of patients and were severe (NCI-CTC grade 3 or higher) in 15% of patients receiving Vectibix monotherapy [see Dosage and Administration (2.3), Warnings and Precautions (5.1) and Adverse Reactions (6.1)]

INDICATIONS AND USAGE

Metastatic Colorectal Cancer

Vectibix® is indicated for the treatment of patients with wild-type RAS (defined as wild-type in both *KRAS* and *NRAS* as determined by an FDA-approved test for this use) metastatic colorectal cancer (mCRC) [see Dosage and Administration (2.1)]:

- As first-line therapy in combination with FOLFOX *[see Clinical Studies (14.2)]*.
- As monotherapy following disease progression after prior treatment with fluoropyrimidine-, oxaliplatin-, and irinotecan-containing chemotherapy *[see Clinical Studies (14.1)]*.

Limitation of Use

Vectibix® is not indicated for the treatment of patients with *RAS*-mutant mCRC or for whom *RAS* mutation status is unknown *[see Dosage and Administration (2.1), Warnings and Precautions (5.2), and Clinical Pharmacology (12.1)]*.

DOSAGE AND ADMINISTRATION

Patient Selection

Prior to initiation of treatment with Vectibix®, assess *RAS* mutational status in colorectal tumors and confirm the absence of a *RAS* mutation in exon 2 (codons 12 and 13), exon 3 (codons 59 and 61), and exon 4 (codons 117 and 146) of both *KRAS* and *NRAS*. Information on FDA-approved tests for the detection of *RAS* mutations in patients with metastatic colorectal cancer is available at: http://www.fda.gov/CompanionDiagnostics.

Recommended Dose

The recommended dose of Vectibix® is 6 mg/kg, administered as an intravenous infusion over 60 minutes, every 14 days. If the first infusion is tolerated, administer subsequent infusions over 30 to 60 minutes. Administer doses higher than 1000 mg over 90 minutes *[see Dosage and Administration (2.4)]*. Appropriate medical resources for the treatment of severe infusion reactions should be available during Vectibix® infusions *[see Warnings and Precautions (5.4)]*.

Dose Modifications

Dose Modifications for Infusion Reactions *[see Warnings and Precautions (5.4) and Adverse Reactions (6.1, 6.3)]*

- Reduce infusion rate by 50% in patients experiencing a mild or moderate (grade 1 or 2) infusion reaction for the duration of that infusion.
- Terminate the infusion in patients experiencing severe infusion reactions. Depending on the severity and/or persistence of the reaction, permanently discontinue Vectibix®.

Dose Modifications for Dermatologic Toxicity *[see Boxed Warning, Warnings and Precautions (5.1), and Adverse Reactions (6.1, 6.3)]*

- Upon first occurrence of a grade 3 (NCI-CTC/CTCAE) dermatologic reaction, withhold 1 to 2 doses of Vectibix®. If the reaction improves to < grade 3, reinitiate Vectibix® at the original dose.
- Upon the second occurrence of a grade 3 (NCI-CTC/CTCAE) dermatologic reaction, withhold 1 to 2 doses of Vectibix®. If the reaction improves to < grade 3, reinitiate Vectibix® at 80% of the original dose.
- Upon the third occurrence of a grade 3 (NCI-CTC/CTCAE) dermatologic reaction, withhold 1 to 2 doses of Vectibix®. If the reaction improves to < grade 3, reinitiate Vectibix® at 60% of the original dose.
- Upon the fourth occurrence of a grade 3 (NCI-CTC/CTCAE) dermatologic reaction, permanently discontinue Vectibix®. Permanently discontinue Vectibix® following the occurrence of a grade 4 dermatologic reaction or for a grade 3 (NCI-CTC/CTCAE) dermatologic reaction that does not recover after withholding 1 or 2 doses.

Preparation and Administration

For intravenous infusion only. Do not administer Vectibix® as an intravenous push or bolus.

CONTRAINDICATIONS

None.

WARNINGS AND PRECAUTIONS

Dermatologic and Soft Tissue Toxicity

In Study 20020408, dermatologic toxicities occurred in 90% of patients and were severe (NCI-CTC grade 3 and higher) in 15% of patients with mCRC receiving Vectibix®.

The clinical manifestations included, but were not limited to, acneiform dermatitis, pruritus, erythema, rash, skin exfoliation, paronychia, dry skin, and skin fissures.

Monitor patients who develop dermatologic or soft tissue toxicities while receiving Vectibix® for the development of inflammatory or infectious sequelae. Life-threatening and fatal infectious complications including necrotizing fasciitis, abscesses, and sepsis have been observed in patients treated with Vectibix®. Life-threatening and fatal bullous mucocutaneous disease with blisters, erosions, and skin sloughing has also been observed in patients treated with Vectibix®. It could not be determined whether these mucocutaneous adverse reactions were directly related to EGFR inhibition or to idiosyncratic immune-related effects (e.g., Stevens-Johnson syndrome or toxic epidermal necrolysis). Withhold or discontinue Vectibix® for dermatologic or soft tissue toxicity associated with severe or life-threatening inflammatory or infectious complications *[see Boxed Warning and Adverse Reactions (6.1, 6.3)]*. Dose modifications for Vectibix® concerning dermatologic toxicity are provided *[see Dosage and Administration (2.3)]*.

Increased Tumor Progression, Increased Mortality, or Lack of Benefit in Patients with *RAS*-Mutant mCRC

Vectibix® is not indicated for the treatment of patients with colorectal cancer that harbor somatic *RAS* mutations in exon 2 (codons 12 and 13), exon 3 (codons 59 and 61), and exon 4 (codons 117 and 146) of either *KRAS* or *NRAS* and hereafter is referred to as *"RAS" [see Indications and Usage (1.1), Dosage and Administration (2.1), Clinical Pharmacology (12.1) and Clinical Studies (14)]*.

Retrospective subset analyses across several randomized clinical trials were conducted to investigate the role of *RAS* mutations on the clinical effects of anti-EGFR-directed monoclonal antibodies (panitumumab or cetuximab). Anti-EGFR antibodies in patients with tumors containing *RAS* mutations resulted in exposing those patients to anti-EGFR related adverse reactions without clinical benefit from these agents *[see Indications and Usage (1.1), and Clinical Pharmacology (12.1)]*.

Additionally, in Study 20050203, 272 patients with *RAS*-mutant mCRC tumors received Vectibix® in combination with FOLFOX and 276 patients received FOLFOX alone. In an exploratory subgroup analysis, OS was shorter (HR = 1.21, 95% CI: 1.01-1.45) in patients with *RAS*-mutant mCRC who received Vectibix® and FOLFOX versus FOLFOX alone *[see Indications and Usage (1.1)]*.

Electrolyte Depletion/Monitoring

Progressively decreasing serum magnesium levels leading to severe (grade 3-4) hypomagnesemia occurred in up to 7% (in Study 20080763) of patients across clinical trials. Monitor patients for hypomagnesemia and hypocalcemia prior to initiating Vectibix® treatment, periodically during Vectibix® treatment, and for up to 8 weeks after the completion of treatment. Other electrolyte disturbances, including hypokalemia, have also been observed. Replete magnesium and other electrolytes as appropriate.

Infusion Reactions

In Study 20020408, 4% of patients experienced infusion reactions and 1% of patients experienced severe infusion reactions (NCI-CTC grade 3-4). Infusion reactions, manifesting as fever, chills, dyspnea, bronchospasm, and hypotension, can occur following Vectibix® administration *[see Adverse Reactions (6.1, 6.3)]*. Fatal infusion reactions occurred in postmarketing experience. Terminate the infusion for severe infusion reactions *[see Dosage and Administration (2.3)]*.

Acute Renal Failure in Combination with Chemotherapy

Severe diarrhea and dehydration, leading to acute renal failure and other complications, have been observed in patients treated with Vectibix® in combination with chemotherapy.

Pulmonary Fibrosis/Interstitial Lung Disease (ILD)

Fatal and nonfatal cases of interstitial lung disease (ILD) (1%) and pulmonary fibrosis have been observed in patients treated with Vectibix®. Pulmonary fibrosis occurred in less than 1% (2/1467) of patients enrolled in clinical studies of Vectibix®. In the event of acute onset or worsening of pulmonary symptoms, interrupt Vectibix® therapy. Discontinue Vectibix® therapy if ILD is confirmed.

In patients with a history of interstitial pneumonitis or pulmonary fibrosis, or evidence of interstitial pneumonitis or pulmonary fibrosis, the benefits of therapy with Vectibix® versus the risk of pulmonary complications must be carefully considered.

Photosensitivity

Exposure to sunlight can exacerbate dermatologic toxicity. Advise patients to wear sunscreen and hats and limit sun exposure while receiving Vectibix®.

Ocular Toxicities

Serious cases of keratitis, ulcerative keratitis, and corneal perforation have occurred with Vectibix® use. Monitor for evidence of keratitis, ulcerative keratitis, or corneal perforation. Interrupt or discontinue Vectibix® therapy for acute or worsening keratitis, ulcerative keratitis, or corneal perforation.

Increased Mortality and Toxicity with Vectibix® in Combination with Bevacizumab and Chemotherapy

In an interim analysis of an open-label, multicenter, randomized clinical trial in the first-line setting in patients with mCRC, the addition of Vectibix® to the combination of bevacizumab and chemotherapy resulted in decreased OS and increased incidence of NCI-CTC grade 3-5 (87% vs 72%) adverse reactions. NCI-CTC grade 3-4 adverse reactions occurring at a higher rate in Vectibix®-treated patients included rash/acneiform dermatitis (26% vs 1%), diarrhea (23% vs 12%), dehydration (16% vs 5%), primarily occurring in patients with diarrhea, hypokalemia (10% vs 4%), stomatitis/mucositis (4% vs < 1%), and hypomagnesemia (4% vs 0). NCI-CTC grade 3-5 pulmonary embolism occurred at a higher rate in Vectibix®-treated patients (7% vs 3%) and included fatal events in three (< 1%) Vectibix®-treated patients.

As a result of the toxicities experienced, patients randomized to Vectibix®, bevacizumab, and chemotherapy received a lower mean relative dose intensity of each chemotherapeutic agent (oxaliplatin, irinotecan, bolus 5-FU, and/or infusional 5-FU) over the first 24 weeks on study compared with those randomized to bevacizumab and chemotherapy.

Embryo-fetal Toxicity

Based on data from animal studies and its mechanism of action, Vectibix® can cause fetal harm when administered to a pregnant woman. When given during organogenesis, panitumumab administration resulted in embryolethality in cynomolgus monkeys at exposures approximately 1.25 to 5-times the recommended human dose. Advise pregnant women and females of reproductive potential of the potential risk to the fetus. Advise females of reproductive potential to use effective contraception during treatment, and for at least 2 months after the last dose of Vectibix® *[see Use in Specific Populations (8.1, 8.3), Clinical Pharmacology (12.1)]*.

ADVERSE REACTIONS

The following adverse reactions are discussed in greater detail in other sections of the label:

- Dermatologic and Soft Tissue Toxicity *[see Boxed Warning, Dosage and Administration (2.3), and Warnings and Precautions (5.1)]*
- Increased Tumor Progression, Increased Mortality, or Lack of Benefit in *RAS*-Mutant mCRC *[see Indications and Usage (1.1) and Warnings and Precautions (5.2)]*
- Electrolyte Depletion/Monitoring *[see Warnings and Precautions (5.3)]*
- Infusion Reactions *[see Dosage and Administration (2.3), and Warnings and Precautions (5.4)]*
- Acute Renal Failure in Combination with Chemotherapy *[see Warnings and Precautions (5.5)]*
- Pulmonary Fibrosis/Interstitial Lung Disease (ILD) *[see Warnings and Precautions (5.6)]*
- Photosensitivity *[see Warnings and Precautions (5.7)]*
- Ocular Toxicities *[see Warnings and Precautions (5.8)]*
- Increased Mortality and Toxicity with Vectibix® in combination with Bevacizumab and Chemotherapy *[see Warnings and Precautions (5.9)]*

Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates in the clinical trials of a drug cannot be directly compared to rates in clinical trials of another drug and may not reflect the rates observed in practice. The adverse reaction information from clinical studies does, however, provide a

basis for identifying the adverse events that appear to be related to drug use and for approximating rates. Safety data are presented from two clinical trials in which patients received Vectibix®: Study 20020408, an open-label, multinational, randomized, controlled, monotherapy clinical trial (N = 463) evaluating Vectibix® with best supportive care (BSC) versus BSC alone in patients with EGFR-expressing mCRC and Study 20050203, a randomized, controlled trial (N = 1183) in patients with mCRC that evaluated Vectibix® in combination with FOLFOX chemotherapy versus FOLFOX chemotherapy alone. Safety data for Study 20050203 are limited to 656 patients with wild-type *KRAS* mCRC. The safety profile of Vectibix® in patients with wild-type *RAS* mCRC is similar with that seen in patients with wild-type *KRAS* mCRC.

Vectibix® Monotherapy

In Study 20020408, the most common adverse reactions (≥ 20%) with Vectibix® were skin rash with variable presentations, paronychia, fatigue, nausea, and diarrhea.The most common (> 5%) serious adverse reactions in the Vectibix® arm were general physical health deterioration and intestinal obstruction. The most frequently reported adverse reactions for Vectibix® leading to withdrawal were general physical health deterioration (n = 2) and intestinal obstruction (n = 2). For Study 20020408, the data described in Table 1 and in other sections below, except where noted, reflect exposure to Vectibix® administered to patients with mCRC as a single agent at the recommended dose and schedule (6 mg/kg every 2 weeks).

Table 1: Adverse Reactions (≥ 5% Difference) Observed in Patients Treated with Vectibix® Monotherapy and Best Supportive Care Compared to Best Supportive Care Alone (Study 20020408)

System Organ Class Preferred Term	Vectibix Plus Best Supportive Care (N=229)		Best Supportive Care (N=234)	
	Any Grade n (%)	Grade 3-4 n (%)	Any Grade n (%)	Grade 3-4 n (%)
Eye Disorders				
Growth of eyelashes	13 (6)			
Gastrointestinal Disorders				
Nausea	52 (23)	2 (< 1)	37 (16)	1 (< 1)
Diarrhea	49 (21)	4 (2)	26 (11)	
Vomiting	43 (19)	6 (3)	28 (12)	2 (< 1)
Stromatitis	15 (7)	2 (<1)		
General Disorders and Administration Site Conditions				
Fatigue	60 (26)	10 (4)	34 (15)	7 (3)
Mucosal inflammation	15 (7)	1 (< 1)	2 (< 1)	
Infections and Infestations				
Paronychia	57 (25)	4 (2)		
Respiratory, Thoracic, and Mediastinal Disorders				
Dyspnea	41 (18)	12 (5)	30 (13)	8 (3)
Cough	34 (15)	1 (< 1)	17 (7)	
Skin and Subcutaneous Tissue Disorders				
Erythema	150 (66)	13 (6)	2 (< 1)	
Pruritus	132 (58)	6 (3)	4 (2)	
Acneiform dermatitis	131 (57)	17 (7)	2 (< 1)	
Rash	51 (22)	3 (1)	2 (< 1)	
Skin fissures	45 (20)	3 (1)	1 (< 1)	
Exfoliative rash	41 (18)	4 (2)		
Acne	31 (14)	3 (1)		
Dry skin	23 (10)			
Nail disorder	22 (10)			
Skin exfoliation	21 (9)	2 (< 1)		
Skin ulcer	13 (6)	1 (< 1)		

Adverse reactions in Study 20020408 that did not meet the threshold criteria for inclusion in Table 1 were conjunctivitis (4.8% vs < 1%), dry mouth (4.8% vs 0%), pyrexia (16.6% vs 13.2%), chills (3.1% vs < 1%), pustular rash (4.4% vs 0%), papular rash (1.7% vs 0%), dehydration (2.6% vs 1.7%), epistaxis (3.9% vs 0%), and pulmonary embolism (1.3% vs 0%). In Study 20020408, dermatologic toxicities occurred in 90% of patients receiving Vectibix®. Skin toxicity was severe (NCI-CTC grade 3 and higher) in 15% of patients. Ocular toxicities occurred in 16% of patients and included, but were not limited to, conjunctivitis (5%). One patient experienced an NCI-CTC grade 3 event of mucosal inflammation. The incidence of paronychia was 25% and was severe in 2% of patients *[see Warnings and Precautions (5.1)]*.

In Study 20020408 (N = 229), median time to the development of dermatologic, nail, or ocular toxicity was 12 days after the first dose of Vectibix®; the median time to most severe skin/ocular toxicity was 15 days after the first dose of Vectibix®; and the median time to resolution after the last dose of Vectibix® was 98 days. Severe toxicity necessitated dose interruption in 11% of Vectibix®-treated patients *[see Dosage and Administration (2.3)]*.

Subsequent to the development of severe dermatologic toxicities, infectious complications, including sepsis, septic death, necrotizing fasciitis, and abscesses requiring incisions and drainage were reported.

Vectibix® in Combination with FOLFOX Chemotherapy

The most commonly reported adverse reactions (≥ 20%) in patients with wild-type *KRAS* mCRC receiving Vectibix® (6 mg/kg every 2 weeks) and FOLFOX therapy (N = 322) in Study 20050203 were diarrhea, stomatitis, mucosal inflammation, asthenia, paronychia, anorexia, hypomagnesemia, hypokalemia, rash, acneiform dermatitis, pruritus, and dry skin (Table 2). Serious adverse reactions (≥ 2% difference between treatment arms) in Vectibix®-treated patients with wild-type *KRAS* mCRC were diarrhea and dehydration. The commonly reported adverse reactions (≥ 1%) leading to discontinuation in patients with wild-type *KRAS* mCRC receiving Vectibix® were rash, paresthesia, fatigue, diarrhea, acneiform dermatitis, and hypersensitivity. One grade 5 adverse reaction, hypokalemia, occurred in a patient who received Vectibix®.

Table 2: Adverse Reactions (≥ 5% Difference) Observed in Patients with Wild-type K*RAS* Tumors Treated with Vectibix® and FOLFOX Chemotherapy Compared to FOLFOX Chemotherapy Alone (Study 20050203)

System Organ Class Preferred Term	Vectibix® Plus FOLFOX (n = 322)		FOLFOX Alone (n = 327)	
	Any Grade n (%)	Grade 3-4 n (%)	Any Grade n (%)	Grade 3-4 n (%)
Eye Disorders				
Conjunctivitis	58 (18)	5 (2)	10 (3)	
Gastrointestinal Disorders	5 (2)	10 (3)		
Diarrhea	201 (62)	59 (18)	169 (52)	29 (9)
Stromatitis	87 (27)	15 (5)	42 (13)	1 (<1)
General Disorders and Administration Site Conditions				
Mucosal inflammation	82 (25)	14 (4)	53 (16)	1 (<1)
Asthenia	79 (25)	16 (5)	62 (19)	11 (3)
Infections and Infestations				
Paronychia	68 (21)	11 (3)		
Metabolism and Nutrition Disorders				
Anorexia	116 (36)	14 (4)	85 (26)	6 (2)
Hypomagnesemia	96 (30)	21 (7)	26 (8)	1 (< 1)
Hypokalemia	68 (21)	32 (10)	42 (13)	15 (5)
Dehydration	26 (8)	8 (2)	10 (3)	5 (2)
Respiratory, Thoracic, and Mediastinal Disorders				
Epistaxis	46 (14)		30 (9)	
Skin and Subcutaneous Tissue Disorders				
Rash	179 (56)	55 (17)	24 (7)	1 (< 1)
Acneiform dermatitis	104 (32)	33 (10)		
Pruritus	75 (23)	3 (< 1)	14 (4)	
Dry skin	68 (21)	5 (2)	13 (4)	
Erythema	50 (16)	7 (2)	14 (4)	
Skin fissures	50 (16)	1(<1)	1(<1)	
Alopecia	47 (15)		30 (9)	
Acne	44 (14)	10 (3)	1 (< 1)	
Nail disorder	32 (10)	4 (1)	4 (1)	
Palmar-plantar erythrodysesthesia syndrome	30 (9)	4 (1)	9 (3)	2 (< 1)

Adverse reactions that did not meet the threshold criteria for inclusion in Table 2 were flushing (3% vs < 1%), abdominal pain (28% vs 23%), localized infection (3.7% vs < 1%), cellulitis (2.5% vs 0%), hypocalcemia (5.6% vs 2.1%), and deep vein thrombosis (5.3% vs 3.1%).

Infusion Reactions

Infusional toxicity manifesting as fever, chills, dyspnea, bronchospasm or hypotension was assessed within 24 hours of an infusion during the clinical study. Vital signs and temperature were measured within 30 minutes prior to initiation and upon completion of the Vectibix® infusion. The use of premedication was not standardized in the clinical trials. Thus, the utility of premedication in preventing the first or subsequent episodes of infusional toxicity is unknown. Across clinical trials of Vectibix® monotherapy, 3% (24/725) experienced infusion reactions of which < 1% (3/725) were severe (NCI-CTC grade 3-4). In one patient, Vectibix® was permanently discontinued for a serious infusion reaction *[see Dosage and Administration (2.2, 2.3)]*.

Immunogenicity

As with all therapeutic proteins, there is potential for immunogenicity. The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors, including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to panitumumab in the studies described below with the incidence of antibodies to other products may be misleading.

The immunogenicity of Vectibix® has been evaluated using two different screening immunoassays for the detection of binding anti-panitumumab antibodies: an acid dissociation bridging enzyme-linked immunosorbent assay (ELISA) detecting high-affinity antibodies and a Biacore® biosensor immunoassay detecting both high- and low-affinity antibodies. For patients whose sera tested positive in screening immunoassays, an in vitro biological assay was performed to detect neutralizing antibodies.

Monotherapy: The incidence of treatment-emergent binding anti-panitumumab antibodies was 0.5% (7/1295) as detected by ELISA and 5.3% (68/1295) as detected by the Biacore® assay. The incidence of neutralizing anti-panitumumab antibodies was 0.8% (11/1295). There was no evidence of altered pharmacokinetics or safety profiles in patients who developed antibodies to panitumumab.

In combination with chemotherapy: The incidence of treatment-emergent binding anti-panitumumab antibodies was 0.9% (12/1297) as detected by the ELISA and 0.7% (9/1296) as detected by the Biacore® assay. The incidence of neutralizing anti-panitumumab antibodies was 0.2% (2/1297). No evidence of an altered safety profile was found in patients who developed antibodies to panitumumab.

Postmarketing Experience

The following adverse reactions have been identified during post-approval use of Vectibix®. Because these reactions are reported in a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

- **Skin and subcutaneous tissue disorders:** Skin necrosis, angioedema, life-threatening and fatal bullous mucocutaneous disease *[see Boxed Warning, Dosage and Administration (2.3), and Warnings and Precautions (5.1)]*
- **Immune system disorders:** Infusion reaction *[see Dosage and Administration (2.3) and Warnings and Precautions (5.4)]*
- **Eye disorders:** Keratitis/ulcerative keratitis *[see Warnings and Precautions (5.8)]*

USE IN SPECIFIC POPULATIONS

Pregnancy

Risk Summary

Based on data from animal studies and its mechanism of action, Vectibix® can cause fetal harm when administered to pregnant women *[see Clinical Pharmacology (12.1)]*. Limited available data on the use of Vectibix® in pregnant women are not sufficient to inform a risk of adverse pregnancy-related outcomes. Vectibix® is a human IgG monoclonal antibody and may be transferred across the placenta during pregnancy. Reproduction studies in cynomolgus monkeys treated with 1.25 to 5 times the recommended human dose of panitumumab resulted in significant embryolethality and abortions; however, no other evidence of teratogenesis was noted in offspring *[see Data]*. Advise pregnant women of the potential risk to the fetus. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively. The estimated background risk of major birth defects and miscarriage for the indicated population is unknown.

Data

Animal Data

Based on animal models, EGFR is involved in prenatal development and may be essential for normal organogenesis, proliferation, and differentiation in the developing embryo. Pregnant cynomolgus monkeys were treated weekly with panitumumab during the period of organogenesis (gestation day [GD] 20-50). While no panitumumab was detected in serum of neonates from panitumumab-treated dams, anti-panitumumab antibody titers were present in 14 of 27 offspring delivered at GD 100. There were no fetal malformations or other evidence of teratogenesis noted in the offspring; however, significant increases in embryolethality and abortions occurred at doses of approximately 1.25 to 5 times the recommended human dose (based on body weight).

Lactation

Risk Summary

There are no data on the presence of panitumumab in human milk or the effects of panitumumab on the breastfed infant or on milk production. Human IgG is present in human milk, but published data suggest that breast milk antibodies do not enter the neonatal and infant circulation in substantial amounts. Because of the potential for serious adverse reactions in breastfed infants from Vectibix®, advise women not to breastfeed during treatment with Vectibix® and for 2 months after the final dose.

Females and Males of Reproductive Potential

Contraception

Females

Vectibix® can cause fetal harm when administered to a pregnant woman *[see Use in Specific Populations (8.1)]*. Advise females of reproductive potential to use effective contraception during treatment with Vectibix® and for 2 months after the last dose of Vectibix®.

Infertility

Females

Based on results from animal fertility studies conducted in female cynomolgus monkeys, Vectibix® may reduce fertility in females of reproductive potential. The effects in animal studies were reversible *[see Nonclinical Toxicology (13.1)]*.

Pediatric Use

The safety and effectiveness of Vectibix® have not been established in pediatric patients.
The pharmacokinetics of panitumumab at doses ranging from 2.5 mg/kg intravenous weekly, 6 mg/kg intravenous every 2 weeks, or 9 mg/kg intravenous every 3 weeks were evaluated in 28 pediatric patients. Panitumumab exposures were comparable in adult and adolescent patients of 12 to 17 years of age. Limited data suggested that pediatric patients of 2 to < 12 years of age had lower panitumumab exposure and higher clearance than that in adolescent patients following 6 mg/kg intravenous administration of Vectibix®. There was no evidence of an anti-tumor treatment effect in these patients.

Geriatric Use

Of the 737 patients who received Vectibix® monotherapy in Study 20020408 and 20080763, 36% were 65 and over while 8% were 75 and over. No overall differences in safety or efficacy were observed in elderly patients (≥ 65 years of age) treated with Vectibix® monotherapy. Of the 322 patients in Study 20050203 who received Vectibix® plus FOLFOX, 128 (40%) were 65 and over while 8% were 75 and over. Patients older than 65 years of age experienced an increased incidence of serious adverse events (52% vs 36%) and an increased incidence of serious diarrhea (15% vs 5%) as compared to younger patients.

OVERDOSAGE

Doses up to approximately twice the recommended therapeutic dose (12 mg/kg) resulted in adverse reactions of skin toxicity, diarrhea, dehydration, and fatigue.

Amgen Inc.
One Amgen Center Drive
Thousand Oaks, CA 91320-1799 USA Patent: http://pat.amgen.com/vectibix/

Clinicians Puzzled by Sharp Rise In Colorectal Cancer Patients Who Are Younger Than 50

ROCHESTER, MN—Colorectal cancer (CRC) is the third-most-common cancer globally and ranks second as the most-common cause of cancer-related mortality. Until recent decades, it was viewed as primarily a disease of the elderly, with average occurrence in their late 60s for men and early 70s for women.

What has puzzled researchers and clinicians in recent years, however, is the troubling increase in the incidence of CRC in adults younger than age 50 in the United States and in other high-income countries. A study last year in the *New England Journal of Medicine* pointed out that early-onset CRC now makes up about 10% of new cases of the cancer. An increase in mortality of younger patients has accompanied the rising trend.[1]

The American Cancer Society reported that, among older adults, cancer death rates continued to decline 0.6% in those 50 to 64 and 2.6% in those 65 and older from 2013-2017, although not as rapidly as from 2004-2013, when the rates were 1% and 3.3%, respectively.

On the other hand, CRC death rates have increased in individuals younger than 50 years of age by 1.3% per year, since 2004.

"The concurrent increase in early-onset colorectal cancer and decline in later-onset cases have shifted the median age at diagnosis from 72 years in the early 2000s to 66 years at present," according to the *NEJM* review from the Mayo Clinic's Frank A. Sinicrope, MD. "In the next 10 years, it is estimated that 25% of rectal cancers and 10 to 12% of colon cancers will be diagnosed in persons younger than 50 years of age."

Projections are that early-onset colorectal cancer will double in younger patients, who often present with more advanced disease because of delayed diagnosis.

Because of recommendations lowering the age of screening from 50 to 45, the Military Health System will have 200,000 additional beneficiaries who need to undergo testing, according to Chin Hee Kim, MD, deputy chief of specialty care support of the DHA Directorate of Medical Affairs.

Interestingly, colorectal cancer in younger patients appears to have different clinical features than later-onset disease. "Early-onset colorectal cancers are most commonly detected in the rectum, followed by the distal colon; more than 70% of early-onset colorectal cancers are in the left colon at presentation," the *NEJM* article advised. "By comparison, later-onset colorectal cancers (those diagnosed in patients ≥50 years of age) occur at similar frequencies in the proximal colon and distal colorectum."

The VA has played a key role in researching early onset colorectal cancer. A study in 2020 noted that the reasons for rising EOCRC incidence and mortality continued to be perplexing. "Some have hypothesized that the rising trend may be related to common or increasingly prevalent modifiable behaviors, such as excess body weight, low physical activity, and diabetes mellitus," wrote the authors from the University of California San Diego, the VA San Diego Healthcare System and colleagues. "Additionally, non-modifiable risk factors such as race/ethnicity may be associated with EOCRC compared to later-onset CRC"

With results published in the journal *Gastroenterology*, the researchers conducted a case-control study of U.S. veterans 18 to 49 years old who underwent colonoscopy examinations from 1999 through 2014. The study team identified EOCRC cases from a national cancer registry, while cancer-free veterans, determined by baseline colonoscopy through three years of follow-up, made up the control group.[2]

Data on age, sex, race/ethnicity, body weight, body mass index (BMI), diabetes, smoking status and aspirin use were collected for the study which, for final analysis, included 651 EOCRC cases and 67,416 controls. Median age of participants was 45.3 years, and 82.3% were male.

Results indicated that a higher proportions of cases were older, male, current smokers, nonaspirin users who had lower BMIs, compared with the controls. In adjusted analyses, the researchers determined that increasing age and male sex were significantly associated with increased risk of EOCRC, but

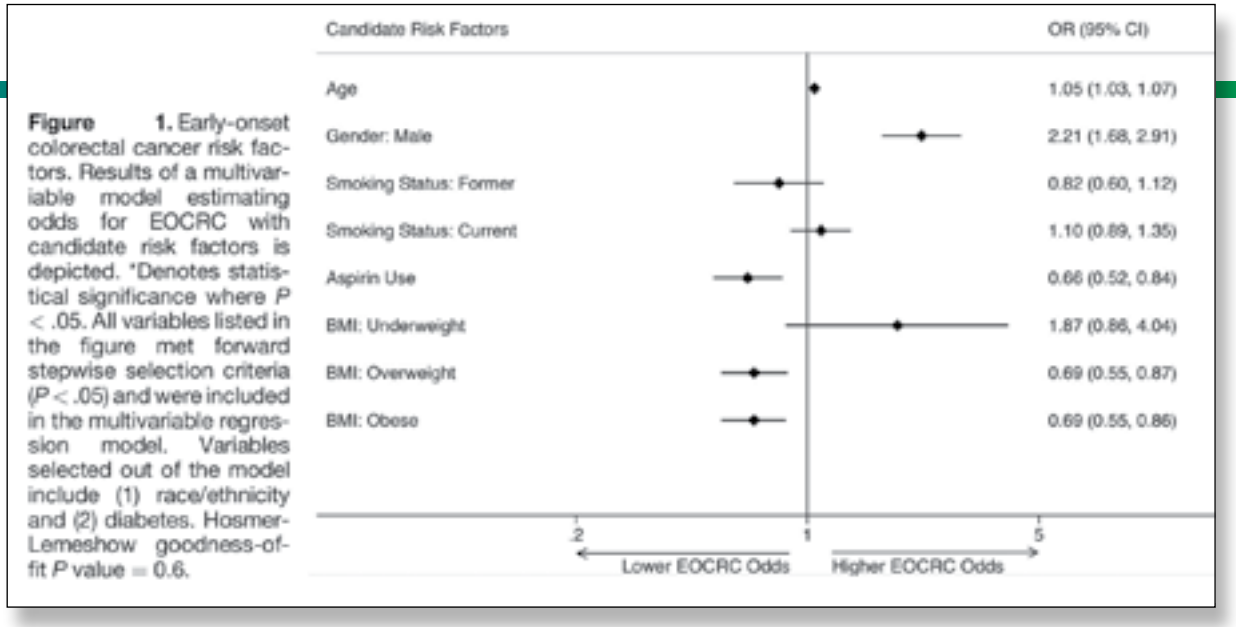


Figure 1. Early-onset colorectal cancer risk factors. Results of a multivariable model estimating odds for EOCRC with candidate risk factors is depicted. *Denotes statistical significance where $P < .05$. All variables listed in the figure met forward stepwise selection criteria ($P < .05$) and were included in the multivariable regression model. Variables selected out of the model include (1) race/ethnicity and (2) diabetes. Hosmer-Lemeshow goodness-of-fit P value = 0.6.

Source: Low EE, Demb J, Liu L, Earles A, Bustamante R, Williams CD, Provenzale D, Kaltenbach T, Gawron AJ, Martinez ME, Gupta S. Risk Factors for Early-Onset Colorectal Cancer. Gastroenterology. *2020 Aug;159(2):492-501.e7. doi: 10.1053/j.gastro.2020.01.004. Epub 2020 Jan 9. PMID: 31926997; PMCID: PMC7343609*

aspirin use and being overweight or obese (relative to normal BMI) were significantly associated with decreased odds of EOCRC.

Weight Loss Early Sign

"In post hoc analyses, weight loss of 5 kg or more within the 5-year period preceding colonoscopy was associated with higher odds of EOCRC (odds ratio 2.23; 95% CI 1.76-2.83)," they explained, adding, "Weight loss may be an early clinical sign of EOCRC. More-intense efforts are required to identify the factors that cause EOCRC and signs that can be used to identify individuals at highest risk."

Researchers from the Rocky Mountain Regional VAMC were involved in the development of new guidelines by the international Delphi Initiative for Early-Onset Colorectal Cancer (DIRECt).

"Patients with early-onset colorectal cancer (eoCRC) are managed according to guidelines that are not age-specific. A multidisciplinary international group (DIRECt), composed of 69 experts, was convened to develop the first evidence-based consensus recommendations for eoCRC," according to a report in *Clinical Gastroenterology & Hematology*.[3]

The DIRECt group produced 31 statements in seven areas of interest:

- diagnosis,
- risk factors,
- genetics,
- pathology-oncology,
- endoscopy,
- therapy and
- supportive care.

The panel reported a strong consensus that all individuals younger than 50 should undergo CRC risk stratification and prompt symptom assessment. In addition, it emphasized that all newly diagnosed eoCRC patients should receive germline genetic testing and that is best to occur before surgery. "On the basis of current evidence, endoscopic, surgical, and oncologic treatment of eoCRC should not differ from later-onset CRC, except for individuals with pathogenic or likely pathogenic germline variants," the guideline authors wrote. "The evidence on chemotherapy is not sufficient to recommend changes to established therapeutic protocols. Fertility preservation and sexual health are important to address in eoCRC survivors. The DIRECt group highlighted areas with knowledge gaps that should be prioritized in future research efforts, including age at first screening for the general population, use of fecal immunochemical tests, chemotherapy, endoscopic therapy, and post-treatment surveillance for eoCRC patients."

[1] Sinicrope FA. Increasing Incidence of Early-Onset Colorectal Cancer. *N Engl J Med.* 2022 Apr 21;386(16):1547-1558. doi: 10.1056/NEJMra2200869. PMID: 35443109.

[2] Low EE, Demb J, Liu L, Earles A, Bustamante R, Williams CD, Provenzale D, Kaltenbach T, Gawron AJ, Martinez ME, Gupta S. Risk Factors for Early-Onset Colorectal Cancer. *Gastroenterology*. 2020 Aug;159(2):492-501.e7. doi: 10.1053/j.gastro.2020.01.004. Epub 2020 Jan 9. PMID: 31926997; PMCID: PMC7343609.

[3] Cavestro GM, Mannucci A, Balaguer F, Hampel H, et. al.; Collaborative Group of the Americas on Inherited Gastrointestinal Cancer; European Hereditary Tumour Group, and the International Society for Gastrointestinal Hereditary Tumours. Delphi Initiative for Early-Onset Colorectal Cancer (DIRECt) International Management Guidelines. *Clin Gastroenterol Hepatol*. 2022 Dec 20:S1542-3565(22)01171-5. doi: 10.1016/j.cgh.2022.12.006. Epub ahead of print. PMID: 36549470.

Primary Tumor Sidedness Increasingly Important in CRC Diagnosis, Treatment

ALBANY, NY—In colorectal cancer, left-sided colorectal cancer (LCC) is associated with better survival compared to right-sided colon cancer (RCC) in metastatic disease, according to a study involving VA researchers.

Past studies have indicated that older patients with Stage IV left-sided colorectal responded better to treatment and had improved overall survival. But is that also true for patients younger than 50 who have early onset colorectal cancer (EOCC)?

The VA study, which involved 65,940 CRC cases from the National VA Cancer Cube Registry (2001-2015), suggested it is, but only in a limited situation. Results were published in *Cancer Medicine.*[1]

Authors from the Stratton VAMC in Albany, NY, and colleagues from the Karmanos Cancer Institute and Wayne State University, both in Detroit; Albany, NY, Medical College, and the University of Maryland in Baltimore advised that EOCRC accounts for 3.18% of cases at the VA. That's lower than the 11% derived from the National Cancer Data Base.

"The lower fraction of EOCRC observed in our study can be accounted for by the higher incidence of malignancies in veterans than the general population," they explained. "On average, veterans are more likely to be older, smoke, drink alcohol, and to have been exposed to Agent Orange."

The researchers found that, "while CRC is almost twice as likely to originate from the left colon in the overall population, EOCRC is almost three times as likely to arise from the left side (L:R ratio 2.84). This ratio is highest for cases diagnosed in patients in their 30s (L:R of 3.44)."

As for survival, LCC is associated with better OS than RCC only in Stage IV for the younger patients compared to the overall population, where LCC is associated with better OS in all stages except Stage II. "The better prognosis of stage II RCC might be due to the high incidence of mismatch repair deficient tumors in this subpopulation," the study pointed out.

"A consensus is emerging that EOCRC is a pathologically, epidemiologically, anatomically, and biologically different disease than late-onset CRC," the researchers suggested.

The database included 2,096 EOCRC cases, defined as CRC diagnosed at younger than 50 years old. Using ICD codes, the study team defined RCC as from the cecum to the hepatic flexure (C18.0-C18.3), and LCC from the splenic flexure to the rectum (C18.5-18.7; C19 and C20).

Results indicated that EOCRC is far more likely to originate from the left side (66.65% LCC in EOCRC vs. 58.77% in CRC). "Overall, LCC has better 5-year Overall Survival (OS) than RCC in stages I (61.67% vs. 58.01%) and III (46.1% vs. 42.1%) and better 1-year OS in stage IV (57.79% vs. 49.49%)," the researchers reported. "Stage II RCC has better 5-year OS than LCC (53.39% vs. 49.28%). In EOCRC, there is no statistically significant difference between LCC and RCC in stages I-III. Stage IV EOCRC patients with LCC and RCC have a 1-year OS of 73.23% and 59.84%, respectively."

Background information in the article called the increase in EORCC cases "alarming," adding, "Since 1975, there has been a 67% increase in the incidence of CRC in patients between the ages 20-49.In 2020, approximately 12% of newly diagnosed CRC cases are expected to occur in individuals under the age of 50 (17,930/147,950). Most strikingly, the fastest rise in incidence was observed in the youngest age group (20-29 years old)."

One result has been a recommendation by the American Cancer Society to lower the age of screening for people at average risk to 45.

"Screening aside, the oncology community has recognized EOCRC as an emerging unmet need," the researchers wrote. "Specific challenges in EOCRC include a lack of understanding of the etiological drivers behind this epidemiologic increase and unfamiliarity with survivorship issues in young adults6 and a dearth of data about whether standard treatments apply to this subset."

Left-Sided Tumors

As to what is causing the increase in early-onset colon cancer, the reasons are not clear. "Interestingly, the rise in EOCRC is driven by left-sided tumors. Additionally, a site-specific distinct molecular signature in EOCRC is emerging.

Some studies suggested various potential risk factors for EOCRC as diet, stress, gut microbiota, and many others," they added.

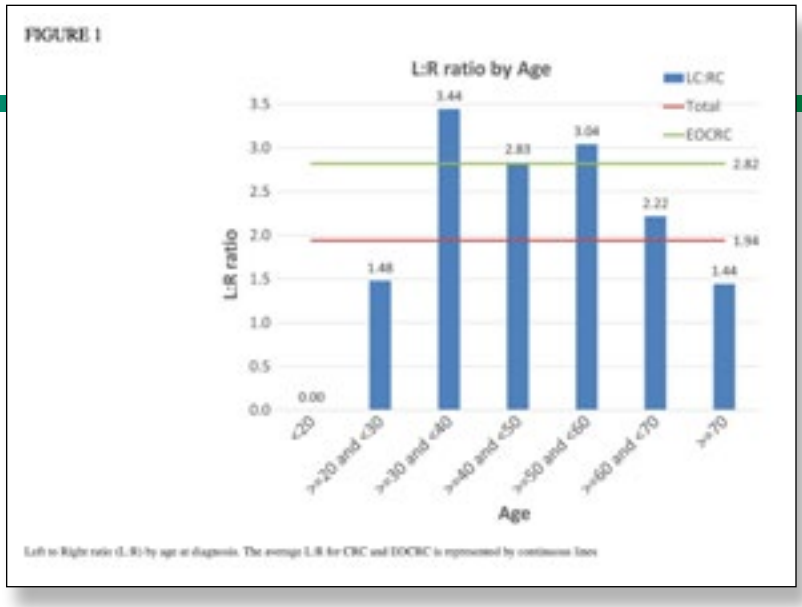
Touted as the first review of primary tumor sidedness (PTS) at the VA, the study noted that, while VA patients are primarily white and male, RCC is more likely to arise in women, Blacks, and the elderly. Right-sided colon cancer also tended to present at a more-advanced stage.

The article also pointed out that symptoms of CRC differ by tumor location. "Symptoms more characteristic of RCC are anemia and vague abdominal pain, while LCC usually presents with hematochezia, change in bowel habits, and is more likely to cause obstruction," the study team noted. "This difference is thought to be due in part to the larger luminal diameter of the cecum and consistency of the bowel contents, as the tumors need to grow large enough to cause obstructive symptoms. Traditionally, this anatomical discrepancy was thought to explain the shortened survival associated with RCC. The predominance of RCC in specific epidemiologic subpopulations (Blacks, women, and elderly) belies that explanation."

A new study from Brigham and Women's Hospital and Harvard Medical School also underscored the importance of colorectal cancer and how that affects tumor molecular features.

"The pathogenic effect of colorectal tumor molecular features may be influenced by several factors, including those related to microbiota, inflammation, metabolism, and epigenetics, which

FIGURE 1



Source: Azar I, Al Masalmeh N, Esfandiarifard S, Virk G, Kiwan W, Frank Shields A, Mehdi S, Philip PA. The impact of primary tumor sidedness on survival in early-onset colorectal cancer by stage: A National Veterans Affairs retrospective analysis. Cancer Med. *2021 May;10(9):2987-2995. doi: 10.1002/cam4.3757. Epub 2021 Apr 2. PMID: 33797856; PMCID: PMC8085929.*

may change along colorectal segments," according to the article in the *Journal of Gastroenterology*. "We hypothesized that the prognostic association of colon cancer location might differ by tumor molecular characteristics."[2]

The international study team used a consortium dataset of 13,101 colorectal cancer cases, including 2,994 early-onset cases, to analyze how detailed tumor location stratified by statuses of microsatellite instability (MSI), CpG island methylator phenotype (CIMP) and KRAS and BRAF oncogenic mutation affected survival.

"There was a statistically significant trend for better colon cancer-specific survival in relation to tumor location from the cecum to sigmoid colon (P_{trend} = 0.002), excluding the rectum," they wrote. "The prognostic association of colon location differed by MSI status ($P_{interaction}$ = 0.001). Non-MSI-high tumors exhibited the cecum-to-sigmoid trend for better colon cancer-specific survival [P_{trend} < 0.001; multivariable hazard ratio (HR) for the sigmoid colon (vs. cecum), 0.80; 95% confidence interval (CI) 0.70-0.92], whereas MSI-high tumors demonstrated a suggestive cecum-to-sigmoid trend for worse survival (P_{trend} = 0.020; the corresponding HR, 2.13; 95% CI 1.15-3.92). The prognostic association of colon tumor location also differed by CIMP status ($P_{interaction}$ = 0.003) but not significantly by age, stage, or other features. Furthermore, MSI-high status was a favorable prognostic indicator in all stages."

Those authors called for large-scale studies to examine detailed colonic subsites in molecular oncology research.

[1] Azar I, Al Masalmeh N, Esfandiarifard S, Virk G, Kiwan W, Frank Shields A, Mehdi S, Philip PA. The impact of primary tumor sidedness on survival in early-onset colorectal cancer by stage: A National Veterans Affairs retrospective analysis. *Cancer Med.* 2021 May;10(9):2987-2995. doi: 10.1002/cam4.3757. Epub 2021 Apr 2. PMID: 33797856; PMCID: PMC8085929.

[2] Ugai T, Akimoto N, Haruki K, Harrison TA, et. al. Prognostic role of detailed colorectal location and tumor molecular features: analyses of 13,101 colorectal cancer patients including 2994 early-onset cases. *J Gastroenterol.* 2023 Jan 17. doi: 10.1007/s00535-023-01955-2. Epub ahead of print. PMID: 36648535.

Tumor Location Increasingly Important For Determining Optimal CRC Treatments

CHICAGO—Traditionally, treatment for colon cancer has been based primarily on the stage, but other issues—especially location—are becoming increasingly important.

According to the American Cancer Society, patients whose cancer hasn't metastasized usually have surgery as the first-line treatment but may have adjuvant treatment with chemotherapy for several months.

By Stage IV, colon cancer has spread from the colon to distant organs and tissues, usually the liver but also the lungs, brain, peritoneum (the lining of the abdominal cavity) or to distant lymph nodes. At that point, according to the cancer society, surgery is unlikely, and patients usually are treated with chemotherapyTh and/or targeted therapies, most likely to include one or more of the following:

- FOLFOX: leucovorin, 5-FU, and oxaliplatin (Eloxatin)
- FOLFIRI: leucovorin, 5-FU, and irinotecan (Camptosar)
- CAPEOX or CAPOX: capecitabine (Xeloda) and oxaliplatin
- FOLFOXIRI: leucovorin, 5-FU, oxaliplatin, and irinotecan
- One of the above combinations, plus either a drug that targets VEGF, (bevacizumab [Avastin], ziv-aflibercept [Zaltrap], or ramucirumab [Cyramza]) or a drug that targets EGFR (cetuximab [Erbitux] or panitumumab [Vectibix])
- 5-FU and leucovorin, with or without a targeted drug
- Capecitabine, with or without a targeted drug
- Irinotecan, with or without a targeted drug
- Cetuximab alone
- Panitumumab alone
- Regorafenib (Stivarga) alone
- Trifluridine and tipiracil (Lonsurf)

For patients with cancer cell changes in genes or proteins, targeted therapy drugs might be an option. The ACS advised that might include drugs that target blood vessel formation, such as vascular endothelial growth factor (VEGF), halting their action. In other cases, drugs targeting epidermal growth factor receptor (EGFR) are used. Limited research has been done on which type works better in which situation.

Tumor Location

Emerging research on the importance of tumor location is affecting some of those regimens, however. "Primary tumor sidedness (PTS) is an independent prognostic factor in metastatic CRC," wrote the authors of a VA study published in *Cancer Medicine*. "PTS is also a predictive factor for response to EGFR inhibition in stage IV CRC, and laterality has been incorporated in the current version of National Comprehensive Cancer Network (NCCN) guidelines as a surrogate for response."[1]

The study pointed out that past research on FOLFOX/FOLFIRI in combination with bevacizumab versus cetuximab found that right-sided colon cancer (RCC) benefits less from cetuximab than left-sided colon cancer (LCC).

"Embryologically, the right colon is derived from the midgut, while the left colon arises from the hindgut suggesting varied tumor biology," the researchers added. "Hence, tumors arising from different embryological states are associated with distinct genetic drivers (RCC: BRAF mutation, MMRd, CpG island methylator phenotype CIMP vs. LCC: chromosomal instability, KRAS mutation, APC mutations), and ultimately different responses to systemic therapies."

That study determined that, in early onset colorectal cancer, which occurs before age 50, patients with RCC have significantly worse survival than LCC in the metastatic setting (1-year OS-RCC: 59.84% vs. LCC: 73.23%; $p = 0.0086$). In the nonmetastatic setting, however, they found no statistically significant difference in 5-year overall survival at any stage.

New research from the Phase 3 PARADIGM trial could prove to be practice-changing, however, for treatment of some types of left-sided colorectal cancer. Early results were presented at the 2022 American Society of Clinical Oncology meeting in Chicago.

PARADIGM was the first prospective trial to test the superiority of panitumumab(PAN) vs. bevacizumab (BEV) combined with standard doublet first-line chemotherapy—mFOLFOX6—for patients with RAS wild-type (WT) metastatic colorectal cancer and left-sided primary tumors.[2]

The open-label, multicenter trial was conducted in Japan and randomly selected patients with chemotherapy-naive RAS WT metastatic colorectal cancer to PAN + mFOLFOX6 or BEV + mFOLFOX6.

Researchers randomized 823 patients from May 2015 to June 2017, with 400 patients ultimately receiving PAN and 402 patients receiving BEV in the full-analysis set (FAS) population. Most of the patients, 312 and 292, respectively, had left-sided primary tumors.

The study team analyzed overall survival (OS) after 448 OS events in left-sided patients with a median follow-up of 61 months. Results indicated that PAN "significantly improved OS vs. BEV in both populations: left-sided (HR, 0.82; 95.798% CI, 0.68-0.99, p = 0.031, which crossed the boundary of significance [0.042]), and FAS (HR, 0.84; 95% CI, 0.72-0.98; p = 0.030, with < 0.05 as the boundary)."

Researchers reported at ASCO that progression-free survival was comparable between treatment groups, but RR and R0 resection rates were higher with PAN compared with BEV. The hazard ratio for overall survival in the right-sided population was 1.09, they added, and no new safety signal was observed.

"PAN significantly improved OS vs. BEV in combination with mFOLFOX6 in patients with *RAS* WT and left-sided mCRC, establishing a standard first-line combination regimen for this population," the authors concluded.

PARADIGM efficacy outcomes.

	PAN + mFOLFOX6	BEV + mFOLFOX6	HR (CI)[a]	*Pp* value
Left-sided tumor population	n=312	n=292		
Median OS, mo	37.9 (34.1-42.6)	34.3 (30.9-40.3)	0.82 (0.68-0.99)	0.031
Median PFS, mo	13.7 (12.7-15.3)	13.2 (11.4-14.5)	0.98 (0.82-1.17)	
RR, %	80.2 (75.3-84.5)	68.6 (62.9-74.0)		
R0 resection, %	18.3 (14.1-23.0)	11.6 (8.2-15.9)		
FAS population	n=400	n=402		
Median OS, mo	36.2 (32.0-39.0)	31.3 (29.3-34.1)	0.84 (0.72-0.98)	0.030
Median PFS, mo	12.9 (11.3-13.6)	12.0 (11.3-13.5)	1.01 (0.87-1.18)	
RR, %	74.9 (70.3-79.1)	67.3 (62.4-71.9)		
R0 resection, %	16.5 (13.0-20.5)	10.9 (8.1-14.4)		

Source: Yoshino T, Eatanabe J, Shitara K, Yasul H, et. al. Panitumumab (PAN) plus mFOLFOX6 versus bevacizumab (BEV) plus mFOLFOX6 as first-line treatment in patients with RAS wild-type (WT) metastatic colorectal cancer (mCRC): Results from the phase 3 PARADIGM trial. .J Clin Oncol. *2022. 40, no. 17_ suppl (June 10, 2022) LBA1-LBA1. Published online June 08, 2022.*

In an updated version from November, the authors wrote that first-line chemotherapy combined with panitumumab significantly improved overall survival compared with first-line chemotherapy combined with bevacizumab among patients with left-sided tumors (median overall survival, 37.9 months vs. 34.3 months; hazard ratio [HR] for death, 0.82), and in the overall population (median overall survival, 36.2 vs. 31.3 months; HR for death, 0.84).

The PARADIGM study was the first to compare an anti-EGFR antibody, panitumumab, with an anti-VEGF antibody, bevacizumab when added to standard chemotherapy for patients with RAS wild-type disease and left-sided primary tumor. It followed two other trials, CALGB 80405 and the European FIRE-3, that sought to determine whether first-line chemotherapy should be combined with anti-EGFR or anti-VEGF antibodies in combination with the FOLFOX chemotherapy protocol, but looked at a more limited group of patients—those with left-sided colon tumors and without mutations in the RAS genes (KRAS and NRAS wild-type).

[1] Azar I, Al Masalmeh N, Esfandiarifard S, Virk G, Kiwan W, Frank Shields A, Mehdi S, Philip PA. The impact of primary tumor sidedness on survival in early-onset colorectal cancer by stage: A National Veterans Affairs retrospective analysis. *Cancer Med.* 2021 May;10(9):2987-2995. doi: 10.1002/cam4.3757. Epub 2021 Apr 2. PMID: 33797856; PMCID: PMC8085929.

[2] Yoshino T, Eatanabe J, Shitara K, Yasul H, et. al. Panitumumab (PAN) plus mFOLFOX6 versus bevacizumab (BEV) plus mFOLFOX6 as first-line treatment in patients with RAS wild-type (WT) metastatic colorectal cancer (mCRC): Results from the phase 3 PARADIGM trial. *.J Clin Oncol.* 2022. 40, no. 17_suppl (June 10, 2022) LBA1-LBA1. Published online June 08, 2022.

Colorectal Cancer Screening Has Changed Significantly in Recent Years

ROCKVILLE, MD—In recent years, the protocols for colorectal cancer screening have undergone some significant changes.

One reason is the growing issue of early-onset colorectal cancer in patients 50 and younger. That prompted the U.S. Preventive Services Task Force to lower the age for which screening is recommended from 50 to 45.[1]

"Colorectal cancer is most frequently diagnosed among persons aged 65 to 74 years," the panel wrote. "It is estimated that 10.5% of new colorectal cancer cases occur in persons younger than 50 years. Incidence of colorectal cancer (specifically adenocarcinoma) in adults aged 40 to 49 years has increased by almost 15% from 2000-2002 to 2014-2016. In 2016, 25.6% of eligible adults in the U.S. had never been screened for colorectal cancer and in 2018, 31.2% were not up to date with screening."

That meant about 21 million Americans became eligible for screening. In the Military Health System, the estimated effect of the lower age recommendation means more than 200,000 additional beneficiaries will need to be screened for CRC, according to Chin Hee Kim, MD, deputy chief of specialty care support of the Defense Health Agency Directorate of Medical Affairs.

The new DHA guidelines offer a range of CRC screening options, including expanding the use of a stool-based test, the fecal immunochemical test (FIT) as an alternative to a colonoscopy.

A recent VA study discussed the challenges of screening during the height of the COVID-19 pandemic and how backlogs in high-volume gastrointestinal endoscopic procedures, such as colonoscopy, occurred.[2]

The recent report in the journal *Gastroenterology* pointed out that the inability to perform that screening is projected to lead to a rise in avoidable colorectal cancers. "Almost one-third of colonoscopies performed in Veterans Health Administration (VHA), the largest integrated health system in the United States, are for screening," according to the authors from the VA Ann Arbor, MI, Healthcare System and the University of Michigan Health System.

The article advised, however, that colonoscopy is not the only option for colorectal cancer screening. It explained that the USPSTF recommends several different testing modalities, including annual FIT as alternatives to colonoscopy for average-risk screening.

"Future work should focus on developing multilevel implementation strategies to provide facilities with effective tools to enhance uptake and sustainability of stool-based CRC screening to reduce colonoscopy demand and improve overall endoscopy access for high-need patients, particularly in integrated healthcare systems and other settings with limited endoscopy access," the authors emphasized.

Their recommendations were based on a recent simulation study that projected how increased FIT-based screening during COVID-19 could mitigate the consequences of reduced screening rates on CRC outcomes during the pandemic.

The study found that, systemwide, a 9.3% decrease (95% confidence interval [CI], -10.5% to -8.1%) in the mean (adjusted) facility-level proportion of screening procedures pre-COVID and COVID occurred. "Most facilities modestly decreased screening colonoscopy use in the COVID period, with wide variation across facilities (interquartile range, -14.8% to -4.6%)," the authors wrote. "At the same time, average monthly FIT volume increased by 7.9% before and after COVID-19 (pre-COVID, 31,604 FIT per month; COVID, 34,109 FIT per month)."

"Although we found a modest (9.3%) decrease in the overall proportion of screening procedures by the fourth quarter of 2020, VHA facilities clearly did not maximize the opportunity to accomplish a marked, systemwide reduction in screening colonoscopy demand by shifting to an underused, evidence-based alternative screening modality (FIT)," the authors concluded. "This occurred despite a national VHA policy directive strongly encouraging widespread adoption of a stool-based CRC screening strategy to enhance overall endoscopy access."

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VA PARTICIPATED IN RESEARCH EXAMINING MAJOR, MINOR COLONOSCOPY RISKS

DURHAM, NC—Colonoscopies are not without risk, yet data are limited regarding the procedures' long-term adverse effects.

A Durham, NC, VA Healthcare System-led study sought to describe adverse events during follow-up in a colonoscopy screening program after the baseline examination. With researchers from VAMCs in Portland, OR, and Perry Point, MD, as well as other academic institutions, they also examined factors associated with increased risk.

The study, which was published in *Gastrointestinal Endoscopy,* included 3,121 asymptomatic veterans 50 to 75 years who underwent screening colonoscopy between 1994 and 1997. For purposes of the research, periprocedure adverse events requiring significant intervention were defined as major events—other events were considered minor—and were tracked during follow-up for at least 10 years.[1]

Results indicated that, of 3,727 follow-up examinations in 1,983 participants, adverse events occurred in 105 examinations (2.8%) in 93 individuals. Of those, 22 were major and 87 were minor events.

"Incidence of major events (per 1,000 examinations) remained relatively stable over time, with 6.1 events at examination two, 4.8 at examination three, and 7.2 at examination four," the authors pointed out. "Examinations with major events included one perforation, three GI bleeds requiring intervention, and 17 cardiopulmonary events."

The authors also noted that a history of prior colonoscopic adverse events was associated with an increased risk of events (major or minor) during follow-up (OR, 2.7; 95% confidence interval, 1.6-4.6).

"Long-term programmatic screening and surveillance was safe, as major events were rare during follow-up.," the researchers concluded. "However, serious cardiopulmonary events were the most common major events. These results highlight the need for detailed assessments of comorbid conditions during routine clinical practice, which could help inform individual decisions regarding the utility of ongoing colonoscopy follow-up."

Another recent study in the Digestive and Liver Disease journal also looked at incidence, risk and protective factors of symptoms after colonoscopy. The Italian study involved researchers from Stonybrook University in New York.[2]

Its focus was on minor adverse events which may develop after colonoscopy, and the prospective study was conducted in 10 Italian hospitals. Defined as the main outcome was a cumulative score combining 10 gastrointestinal (GI) symptoms occurring the week following colonoscopy.

Researchers reported that, of 793 patients included in the analysis, 361 (45.5%) complained about the new onset of at least one GI symptom after the exam. One symptom was reported by 202 (25.5%), and two or more symptoms by 159 (20.1%). The authors said that newly developed symptoms more frequently reported were epigastric/abdominal bloating (32.2%), pain (17.3%), and dyspeptic symptoms (17.9%). Symptoms were associated with:

- female sex (odds ratio [OR]=2.54),
- increasing number of symptoms developed during bowel preparation intake (OR=1.35) and
- somatic symptoms (OR=1.27).

"An inverse association was observed with better mood (OR=0.74)," the authors wrote. "A high-risk profile was identified, represented by women with bad mood and somatic symptoms (OR=8.81)."

The authors concluded that about half of the patients develop de novo GI symptoms following colonoscopy. "Improving bowel preparation tolerability may reduce the incidence of post-colonoscopy symptoms, especially in more vulnerable patients," they suggested.

[1] Kobe EA, Sullivan BA, Qin X, Redding TS 4th, et. al. Longitudinal assessment of colonoscopy adverse events in the prospective Cooperative Studies Program no. 380 colorectal cancer screening and surveillance cohort. Gastrointest Endosc. 2022 Sep;96(3):553-562.e3. doi: 10.1016/j.gie.2022.04.1343. Epub 2022 May 7. PMID: 35533738.

[2] Collatuzzo G, Boffetta P, Radaelli F, Cadoni S, Hassan C, et. al. Incidence, risk and protective factors of symptoms after colonoscopy. Dig Liver Dis. 2022 Sep 22:S1590-8658(22)00651-X. doi: 10.1016/j.dld.2022.08.025. Epub ahead of print. PMID: 36154988.

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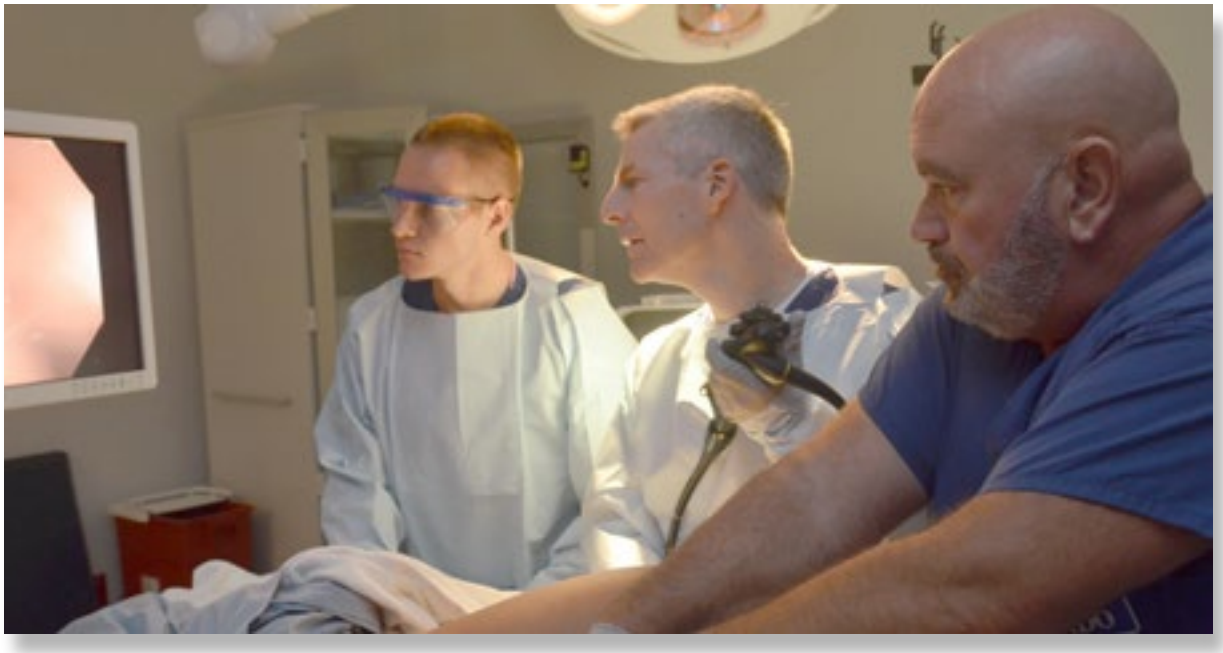

Capt. John Bassett (middle), a gastroenterologist at Naval Hospital Jacksonville, along with hospitalman Wesley Ward (left) and Robert Hauser (right), an endoscopy technician, performed a colonoscopy on a patient in 2018. —U.S. Navy photo by Jacob Sippel

VA has been recognized for achieving CRC screening rates that surpass the national benchmark of 80%. It also has been found to be free of many of the racial/ethnic CRC screening disparities that occur in healthcare settings throughout the United States. In the VA healthcare system, Hispanic and Black veterans have similar or higher CRC screening rates than whites.

[1] US Preventive Services Task Force. Screening for Colorectal Cancer: US Preventive Services Task Force Recommendation Statement. *JAMA*. 2021;325(19):1965–1977. doi:10.1001/jama.2021.6238

[2] Adams MA, Kurlander JE, Gao Y, Yankey N, Saini SD. Impact of Coronavirus Disease 2019 on Screening Colonoscopy Utilization in a Large Integrated Health System. *Gastroenterology*. 2022 Jun;162(7):2098-2100.e2. doi: 10.1053/j.gastro.2022.02.034. Epub 2022 Feb 24. PMID: 35219698; PMCID: PMC8867975.

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