



REASONS FOR HOPE

Advances in the management of colorectal cancer

By Eleanor Mayfield

Laura Hauser was 34, a busy mom of a five-year-old and a seven-year-old, with a full-time job and a business on the side.

“When I saw my OB-GYN for my annual checkup, I mentioned that I’d noticed blood in my stool,” she recalls. “She pushed me to get a colonoscopy, just for peace of mind. So I did, and after I woke up the doctor came in and said, ‘We found something—we think it’s cancer.’”

Worse news arrived just days before she was scheduled to have surgery: the cancer had spread to her liver.

Laura, of Wesley Chapel, Florida, near Tampa, is an atypical colorectal cancer patient. Of the more than 132,000 people in the United States whom the American Cancer Society estimates will receive a diagnosis

of colorectal cancer (CRC) in 2015, nine out of 10 will be 50 or older. But while rates of CRC have been steadily declining in that age group—most likely because of effective screening—for reasons that aren’t clear, more people ages 20 to 49 are being diagnosed with the disease.^{1,2}

In another sense, Laura may represent a new face of advanced CRC—that of a chronic condition that many people live with for years. Six years after her diagnosis, after multiple surgeries and rounds of chemotherapy, a stint in a clinical trial, and more chemotherapy, Laura is not letting the disease slow her down—and she is not alone. “I’ve met people who are 12 years out from a Stage IV CRC diagnosis,” she says.

Advances such as new medications, minimally invasive surgical techniques, and personalized treatment regimens

are helping CRC survivors live longer and better.

“The era of one-size-fits-all care for CRC is over,” says Steven Nurkin, MD, assistant professor of oncology at Roswell Park Cancer Institute in Buffalo, New York. “No two patients are the same, and every patient should expect to be offered treatment options appropriate to the characteristics of their disease.”

Dr. Nurkin specializes in CRC surgery using small instruments and incisions that, he says, result in less pain and a faster recovery without tradeoffs in survival or risk of cancer recurrence. Moreover, with advances in techniques such as sphincter-preserving surgery, says Dr. Nurkin, most patients should not need a permanent colostomy.

New drugs and new understanding of how to target treatment to specific features of patients’ tumors are



Laura Hauser and husband, Richard

transforming chemotherapy for CRC, says Wells Messersmith, MD, associate professor of medical oncology at the University of Colorado Cancer Center in Aurora.

“Usually, we give a drug to 100 people, knowing it will help at most 10 or 20 of them,” says Dr. Messersmith. “Now, at least with some drugs, we can identify the 10 or 20 patients most likely to benefit from treatment based on their tumors’ molecular and genetic characteristics.”

Powerful new tests that scan tumor samples for the presence of hundreds of molecular or genetic changes help doctors match patients with treatments more likely to work and avoid those that probably will not (see sidebar “Resources, page 42”).

Taken together these advances provide reasons for hope for those facing a CRC diagnosis.

“SO GRATEFUL”

When Laura’s tumor showed signs of growth after several months in a clinical trial (TAS-102 trial), her doctor switched her to a standard chemotherapy regimen plus a recently approved drug, Zaltrap® (ziv-aflibercept). Her children, now 11 and 13, and her husband, Richard, keep her going, she says. In early 2015, hooked up to her chemo pump, she celebrated her fortieth birthday at a party with family and friends.

“I wasn’t happy about being on chemo at my birthday party,” she says, “but I also felt so grateful to have made it to that milestone.”



COLORECTAL CANCER TREATMENT PRIMER

Treatment advances are encouraging, but the volume of information about tests, treatments, and trials can be overwhelming. Here is what you should know if you or someone you love is facing CRC today.

COLORECTAL CANCER

ALPHABET SOUP:

Abbreviations You Need to Know

CAPIRI or XELIRI

A combination of the drugs Xeloda® (capecitabine) and Camptosar® (irinotecan), used to treat advanced colorectal cancer

CAPOX or XELOX

A combination of the drugs Xeloda (capecitabine) and Eloxatin® (oxaliplatin), used to treat advanced colorectal cancer

DNA

A substance in cells that passes genetic information from parents to children

EGFR

A protein on the surface of some cells that stimulates the cells to divide. Many cancer cells have too much EGFR, which fuels their growth. Drugs such as Erbitux® (cetuximab) and Vectibix® (panitumumab) try to stop cancer cell growth by blocking EGFR.

FOLFIRI

A combination of folinic acid (or leucovorin), fluorouracil, and irinotecan, used to treat advanced colorectal cancer

FOLFOX

A combination of folinic acid (or leucovorin), fluorouracil, and oxaliplatin, used to treat advanced colorectal cancer

KRAS (“kay-rass”)

A gene that may cause cancer when mutated. It makes the KRAS protein, which among other functions helps cells grow. A normal (not mutated) KRAS gene is called “wild type.” Research has shown that the EGFR-blocking drugs Erbitux and Vectibix do not work for colorectal cancer patients whose tumors have a KRAS mutation.³

NRAS (“en-rass”)

A gene similar to KRAS. A recent study found that Erbitux and Vectibix are ineffective against tumors that have a normal KRAS gene but a mutation in NRAS⁴

VEGF (“vedge-eff”)

A protein that stimulates blood vessels to form. Tumors need blood vessels to grow. Some drugs try to stop cancer cell growth by blocking VEGF.



NEW DRUGS FOR ADVANCED CRC

- STIVARGA® (regorafenib) was approved by the US Food and Drug Administration (FDA) in 2012 to treat advanced CRC when other treatments have stopped working. It blocks VEGF and other proteins that help cancer cells grow. Patients treated with Stivarga plus symptom management survived more than six months on average, compared with five months for those who received a placebo plus symptom management.⁵
- ZALTRAP® (ziv-aflibercept) got the FDA's nod in 2012 for use with FOLFIRI to treat advanced CRC that has worsened after treatment, with a regimen that included oxaliplatin. Patients treated with FOLFIRI plus Zaltrap survived more than 13 months on average, compared with 12 months for patients receiving FOLFIRI plus a placebo.⁶
- The investigational drug TAS-102 is being tested for treatment of advanced CRC after at least two previous treatments have stopped working. In early trial results, TAS-102 extended survival by 32 percent and reduced by 52 percent the risk that the cancer would worsen compared with a placebo and symptom management. Half the patients in the trial had received four or more previous treatments.⁷ TAS-102 is awaiting FDA approval. Patients with metastatic CRC may be eligible to enroll in an ongoing expanded access study of TAS-102. Information is available at clinicaltrials.gov/ct2/show/NCT02286492 or by calling (855) 598-8259.
- The investigational drug

XILONIX™, a humanized anti-inflammatory antibody, is being tested in patients with advanced CRC for its ability to inhibit tumor growth and metastasis by interrupting crucial signals needed for cancer to spread. The drug may also help improve fatigue, muscle loss,

and anxiety caused by tumor-related inflammation.⁸ A pivotal Phase III trial of Xilonix—the Xilonix Colorectal Cancer Immunotherapy Treatment Evaluation (XCITE)—is now under way. For more information visit xcitecolontrial.com.

NEWLY DIAGNOSED: QUESTIONS TO ASK YOUR DOCTOR

❖ HOW MANY PATIENTS WITH THE TYPE OF CANCER I HAVE DO YOU SEE?

Consider seeking out a doctor who specializes in colorectal cancer or gastrointestinal cancers.

❖ WHAT TYPE OF MOLECULAR AND GENETIC TESTING DO YOU RECOMMEND?

Every patient's tumor should be tested for genetic changes that may influence treatment options, says Dr. Messersmith. But be aware that these tests can also generate unhelpful information and may not always make appropriate treatment recommendations. Review the test results carefully with your doctor.

❖ SHOULD I BE TESTED TO FIND OUT IF COLORECTAL CANCER RUNS IN MY FAMILY?

Between 5 percent and 10 percent of patients with CRC have inherited genetic changes that increase their risk of this and other cancers. If anyone else in your family has had CRC, especially if he or she was diagnosed when younger than 45, talk with your doctor about being tested for familial forms of the disease.

❖ AM I A CANDIDATE FOR SURGERY? IF SO, CAN SURGERY BE DONE IN A MINIMALLY INVASIVE WAY? IS MY SURGEON AN EXPERT IN THESE TECHNIQUES?

Minimally invasive surgical techniques can get the job done with fewer complications for the patient, but surgeons need specific training to use these techniques, says Dr. Nurkin.

❖ CAN I GET A SECOND OPINION?

Most patients benefit from a second opinion; this is especially true if your doctor is part of a small practice and does not work with a team of other cancer specialists, does not recommend molecular testing, or does not mention minimally invasive surgery. A second opinion may confirm the treatment offered during your initial consultation or provide other options.

❖ SHOULD I CONSIDER ENROLLING IN A CLINICAL TRIAL?

Patients in clinical trials have access to the newest cancer therapies, which may be more effective than standard treatment. Taking part in clinical trials also helps develop new treatments for future patients.



CANCER CLINICAL TRIALS: SEPARATING FACT FROM MYTH

Without clinical trials there would be no advances in cancer treatment. Yet, according to the National Cancer Institute, for every 100 patients with cancer who could enroll in a clinical trial, only about three do so.⁹ Many people have misconceptions about cancer clinical trials. Here are the facts.

Are clinical trials a last resort?

Clinical trials are an option for advanced cancer when standard treatments have not worked, but they are offered for every stage of cancer as well as for cancer prevention.

Are the treatments offered in clinical trials unproven?

All new treatments are unproven before they are tested in clinical trials. Every potential new treatment goes through extensive lab testing before being tried in people. Every trial follows a detailed plan, and doctors watch participants closely for adverse effects.

Are patients in clinical trials “guinea pigs”?

The “informed consent” process explains the reasons for the trial,

the potential risks and benefits, and your rights. The medical team will keep you informed about what happens during the trial. In one survey 97 percent of clinical trial participants said the care they received was very good and they were treated with dignity and respect.¹⁰

Can I leave a trial if I change my mind?

You can change your mind and leave a trial at any time. Your doctor will continue to treat you with the best available standard treatment.

Will I get a sugar pill or no treatment?

In most trials you will receive either the best standard treatment or a new treatment that might be better. Sometimes you may receive

standard treatment plus a new treatment. Placebos may be used when no standard treatment exists or in cases of advanced cancer when all standard treatments have failed.

Will my insurance cover it?

Many states require health insurers to cover the costs of treatment in clinical trials. Medicare has covered these costs since 2000. Certain conditions usually apply. Learn more at cancer.gov/clinicaltrials/learningabout/payingfor/insurance-coverage.

Will I have to travel far from home?

In many clinical trials, you can receive treatment at your local hospital or your doctor’s office.

EMILY’S STORY “I CONSIDER MYSELF VERY LUCKY.”

Emily Gruttadauria was newly married and about to leave on her honeymoon when she noticed blood in her stool. At first she blamed a recurrence of hemorrhoids, but when the problem persisted, she saw her doctor, who recommended a colonoscopy.

The colonoscopy found a polyp so large only part of it could be removed. “They told me the biopsy showed cancerous cells,” Emily recalls. She was 27 years old.

At Roswell Park Cancer Institute in Buffalo, near Emily’s home in Cheektowaga, New York, a second biopsy showed a Stage 0 rectal cancer—the earliest stage, when the tumor is confined to the inner layer of the rectum.

After surgery to remove the rest of the polyp, Emily underwent genetic testing that showed she has Lynch syndrome, a condition that runs in families and elevates the risk of developing colorectal and other cancers early in life. Subsequent testing revealed that her father, brother, and paternal grandmother also have the syndrome.

“We all need to have regular colonoscopies to ensure that any polyps we get don’t develop into cancer,” says Emily, who is now 29 and planning to start a family with her husband, Brandon. Once they have had children, she can opt for surgery to remove her ovaries to reduce her risk of ovarian cancer, also associated with Lynch syndrome.



SCREENING FOR COLORECTAL CANCER: WHAT YOU NEED TO KNOW

CRC “is probably the only cancer for which we have a screening test that not only catches the disease early but can potentially prevent it,” says Deborah Fisher, MD, a gastroenterologist and associate professor of medicine at Duke University School of Medicine in Durham, North Carolina.

She is talking about colonoscopy, considered the gold standard screening test for CRC. In addition to detecting CRC at an early stage, when about 90 percent of cases are curable, a colonoscopy also finds polyps—growths that could develop into cancer. Abnormalities found during a colonoscopy can usually be removed then and there.

Who should be screened for colorectal cancer?

All healthy adults ages 50 to 75 who do not have symptoms or a family history of CRC should be screened. If you have a family history, talk with your doctor about when to start screening—it might be earlier than age 50.

If you have symptoms—such as visible blood in your stool, unintended weight loss, diarrhea that lasts longer than a few days—see your doctor right away. You need diagnostic testing, not screening.

Do I have to have a colonoscopy?

No, there are several effective screening tests for CRC. For some you see a doctor; others you do at home. The bad news is that all tests have a “yuck” factor; and if a non-colonoscopy test finds anything abnormal, you’ll need a colonoscopy to check it out.

Can I wait until there is a blood test?

Researchers are working on a blood test for CRC, but it is unlikely that one will be on the market anytime soon. A blood test will need to be at least as good as existing tests, which—despite the yuck factor—work pretty well.

Which test is right for me?

The right test for you is the one you will actually get done. And remember, no CRC screening test is “one and done.” You need to be retested at recommended intervals, which vary depending on the test.

What else can I do to prevent CRC?

Eat your vegetables, maintain a healthy weight, get regular exercise, and don’t smoke. Consider eating more fish and less meat. In a recent study, people who ate fish at least once per month and meat less than once per month reduced their risk of CRC by about 40 percent.¹¹

If you take aspirin to help reduce your risk of heart attack or stroke, it will also reduce your risk of CRC, although you will still need a CRC screening test. Taking aspirin solely to reduce CRC risk is not recommended because aspirin heightens the risk of bleeding. Some studies suggest that high blood levels of vitamin D may reduce CRC risk, but the evidence is not clear enough to recommend taking vitamin D supplements to prevent CRC.

What are the pros and cons of CRC screening tests?

See the following chart.

TEST

TESTS DONE BY A DOCTOR

COLONOSCOPY

HOW OFTEN?

- Every 10 years if nothing abnormal is found
- Otherwise, every 3 to 8 years

“VIRTUAL COLONOSCOPY”

(also called CT colonography)

HOW OFTEN?

- Every 5 years

FLEXIBLE SIGMOIDOSCOPY

HOW OFTEN?

- Every 5 years if nothing abnormal is found

TESTS YOU DO AT HOME

FECAL OCCULT BLOOD TEST

(also called Guaiac [“gwy-ack”] test)

HOW OFTEN?

- Once per year

FECAL IMMUNOCHEMICAL TEST

HOW OFTEN?

- Once per year

STOOL DNA TEST

HOW OFTEN?

- Once every 3 years



PROS	CONS
<ul style="list-style-type: none"> Examines entire colon Most accurate test for finding both cancer and polyps Abnormal growths usually removed then and there 	<ul style="list-style-type: none"> Bowel preparation is needed to clean out the colon. The day before, you need to drink clear liquids only (no solid food), take a laxative, and stay close to the bathroom. "The prep is the hardest part but also the most important part," says Dr. Fisher. "The test is more accurate when your colon is really clean." Your doctor may suggest avoiding medications like aspirin and ibuprofen for several days before the test. The test must be performed by a specialist. It requires sedation. You will need a ride home, and you may need to take the day off work. It is more costly than other colorectal cancer screening tests. Check that your insurance covers it. There is a small risk of bleeding, infection, or torn bowel.
<ul style="list-style-type: none"> CT scan of the colon replaces regular colonoscopy No sedation—you can drive yourself home or to work afterward 	<ul style="list-style-type: none"> Full bowel prep is needed, as for a regular colonoscopy. The test may produce a false-positive result (i.e., you do not have cancer, but the test shows you do). Air pumped into the colon may cause discomfort. It may miss small polyps or cancers. Regular colonoscopy is needed if anything abnormal is found. Radiation exposure Costly Usually not covered by insurance
<ul style="list-style-type: none"> May not require full bowel prep Sedation usually not needed—you can drive yourself home or to work afterward Can be done in your primary care physician's office Less costly than a colonoscopy 	<ul style="list-style-type: none"> Some bowel prep is needed. It examines only about one-third of the colon. It may cause discomfort. Colonoscopy is needed if anything abnormal is found. It is not offered by many primary care physicians or gastroenterologists in the United States.
<ul style="list-style-type: none"> Finds cancer by looking for invisible blood in stool No bowel prep Done in the privacy of your bathroom, using a kit the doctor gives you or sends you by mail Inexpensive 	<ul style="list-style-type: none"> You use a brush or applicator to collect samples from several bowel movements, smear each sample onto a card or slide, seal the samples into the envelope provided, and mail the envelope. Your doctor may suggest not eating meat or citrus fruits and not taking vitamin C supplements or medications like aspirin or ibuprofen for several days before the test. It may produce a false-positive result. It may miss some cancers. It is not designed to find polyps. Colonoscopy is needed if anything abnormal is found.
<ul style="list-style-type: none"> Finds cancer by looking for invisible blood in stool No bowel prep Done in the privacy of your bathroom, using a kit the doctor gives you or sends you by mail No restrictions on diet or medications Few false positives Inexpensive 	<ul style="list-style-type: none"> The procedure is similar to that for a fecal occult blood test. It may miss some cancers. It is not designed to find polyps. Colonoscopy is needed if anything abnormal is found.
<ul style="list-style-type: none"> Finds cancer by looking for DNA changes and invisible blood in stool No bowel prep Done in the privacy of your bathroom, using a kit sent to you by mail No restrictions on diet or medications 	<ul style="list-style-type: none"> You attach a provided container to the toilet, have a bowel movement into the container, and ship the container to a lab. It may produce a false-positive result. It may miss some cancers. It is not designed to find polyps. Colonoscopy is needed if anything abnormal is found. Costly New—may not be covered by insurance





RESOURCES

CANCERCONNECT

cancerconnect.com

CancerConnect is the leading social network for colon cancer patients and their friends and family. This unique site combines with a social network a robust information platform consisting of current comprehensive information about colon cancer. It is populated with rich content to support the many ongoing needs of individuals battling cancer and encompasses communities of people with similar interests related to cancer.

THEGICONNECTION.COM

thegiconnection.com

The GI Connection Colon Cancer Community is the leading social media application for colon cancer patients and caregivers seeking information, inspiration, and support in the wake of a cancer diagnosis. With more than 50,000 members, the network offers patients and caregivers a thriving community to support their many ongoing needs from diagnosis to survivorship.

COLON CANCER ALLIANCE

ccalliance.org

Patient advocacy organization

Toll-free helpline: (877) 422-2030

COLORECTAL CANCER

cancer.org/cancer/colonandrectumcancer/detailedguide/index

Detailed guide from the American Cancer Society

COLORECTAL CANCER RISK ASSESSMENT TOOL

cancer.gov/colorectalcanccerrisk

Online tool that helps estimate the risk of developing CRC

GUT-CHECK

gutcheck.cancer.gov

CRC screening choices explained in plain English

SCREENFORCOLONCANCER.ORG

screenforcoloncancer.org

Supported by the American Society for Gastrointestinal Endoscopy

GENETIC TESTING FOR CANCER: WHAT YOU NEED TO KNOW

cancer.org/acs/groups/cid/documents/webcontent/002548-pdf.pdf

Information from the American Cancer Society about testing for inherited cancer risk

GENOMIC TESTS

- Multi-gene tests
Oncotype DX[®] Colon Cancer Assay
colon-cancer.oncotypedx.com/en-US/Patient.aspx
- FDA-approved test for KRAS mutations
Therascreen[®] KRAS RQ_Q PCR Kit
fda.gov/MedicalDevices/ProductsandMedicalProcedures/DeviceApprovalsandClearances/Recently-ApprovedDevices/ucm312055.htm
- Caris Molecular Intelligence
carislifesciences.com/oncology-molecular-intelligence
- FoundationOne
foundationone.com

CLINICAL TRIALS

- National Cancer Institute: cancer.gov/clinicaltrials/search
- CenterWatch: centerwatch.com/clinical-trials/listings
- National Institutes of Health: clinicaltrials.gov
- Coalition of Cancer Cooperative Groups: cancertrialshelp.org

References

- Bailey CE, Hu CY, You YN, et al. Increasing disparities in the age-related incidences of colon and rectal cancers in the United States, 1975-2010. *JAMA Surgery*. 2015;150(1):17-22. doi: 10.1001/jamasurg.2014.1756.
- Austin H, Henley SJ, King J, Richardson LC, Ehemann. Changes in colorectal cancer incidence rates in young and older adults in the United States: What does it tell us about screening. *Cancer Causes & Control*. 2014;25(2):191-201. doi: 10.1007/s10552-013-0321-y.
- Amado RG, Wolf M, Peeters M, et al. Wild-type KRAS is required for panitumumab efficacy in patients with metastatic colorectal cancer. *Journal of Clinical Oncology*. 2008;26(10):1626-34. doi: 10.1200/JCO.2007.14.7116.
- Douillard JY, Oliner KS, Siena S, et al. Panitumumab-FOLFOX4 treatment and RAS mutations in colorectal cancer. *New England Journal of Medicine*. 2013;369(11):1023-34. doi: 10.1056/NEJMoa1305275.
- Grothey A, Van Cutsem E, Sobrero A, et al. Regorafenib monotherapy for previously treated metastatic colorectal cancer (CORRECT): An international, multicentre, randomised, placebo-controlled, Phase 3 trial. *Lancet*. 2013;381(9863):303-12. doi: 10.1016/S0140-6736(12)61900-X.
- Van Cutsem E, Tabernero J, Lakomy R, et al. Addition of aflibercept to fluorouracil, leucovorin, and irinotecan improves survival in a Phase III randomized trial in patients with metastatic colorectal cancer previously treated with an oxaliplatin-based regimen. *Journal of Clinical Oncology*. 2012;30(28):3499-3506.
- Van Cutsem E, Ohtsu A, Falcone A, et al. Phase III RECURSE trial of TAS-102 vs. placebo, with best supportive care (BSC), in patients (pts) with metastatic colorectal cancer (mCRC) refractory to standard therapies. Paper presented at European Society for Medical Oncology Congress; September 26-30, 2014; Madrid, Spain. Abstract LBA 13.
- Fisher GA. A Phase III study of Xilonix in refractory colorectal cancer patients with weight loss. Paper presented at 2015 Gastrointestinal Cancers Symposium; January 21-23, 2015; San Francisco, CA. Abstract 685.
- Institute of Medicine Forum on Drug Discovery, Development, and Translation. Transforming Clinical Research in the United States: Challenges and Opportunities: Workshop Summary. Washington, DC: National Academies Press; 2010.
- Comis RL, Aldige CR, Stovall EL, Krebs LU, Risher PJ, Taylor HJ. A quantitative survey of public attitudes towards cancer clinical trials. Philadelphia, PA: Coalition of National Cancer Cooperative Groups; Alexandria, VA: Cancer Research Foundation of America; Washington, DC: Cancer Leadership Council; Pittsburgh, PA: Oncology Nursing Society; New York: Harris Interactive; 2000. Available at: <http://www.cancertrialshelp.org/CTHpdf/308-9.pdf>. Accessed April 21, 2015.
- Orlich MJ, Singh PN, Sabaté J, et al. Vegetarian dietary patterns and the risk of colorectal cancers. *JAMA Internal Medicine* [early online publication]. March 9, 2015. doi: 10.1001/jamainternmed.2015.59.