

December 16, 2014

Martha Kruhm, MS RAC
Head, Protocol and Information Office
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6130 Executive Boulevard
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Dear Ms. Kruhm:

Enclosed is E5202, Update #6, *A Randomized Phase III Study Comparing 5-FU, Leucovorin and Oxaliplatin versus 5-FU, Leucovorin, Oxaliplatin and Bevacizumab in Patients with Stage II Colon Cancer at High Risk for Recurrence to Determine Prospectively the Prognostic Value of Molecular Markers*.

This update contains administrative and editorial changes only. We are submitting this update to the NCI and activating it within ECOG-ACRIN simultaneously.

The following revisions to the E5202 protocol were made in this update:

	Section	Change
1.	Cover Page	Updated NCI Update Date
2.	Global	Updated names, addresses, numbers, and forms relating to the move from ECOG-ACRIN PCO to ECOG-ACRIN CBPF.

The following revisions to the E5202 Informed Consent were made in this update:

	Section	Change
3.	Cover Page	Updated NCI Update Date

If you have any questions regarding this update, please contact Madeline Spiers at spiers.madeline@jimmy.harvard.edu or (617) 632-3610.

Thank you.

Sincerely,

Pamela Cogliano
Protocol Development Manager

Enclosure

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Official Study Title for Internet Search on <http://www.ClinicalTrials.gov>:
A Randomized Phase III Study Comparing 5-FU, Leucovorin and Oxaliplatin versus 5-FU, Leucovorin, Oxaliplatin and Bevacizumab in Patients with Stage II Colon Cancer at High Risk for Recurrence to Determine Prospectively the Prognostic Value of Molecular Markers

Version Date: April 30, 2014
NCI Update Date: December 16

This is a clinical trial, which is a type of research study. Your doctor will explain this clinical trial to you. Clinical trials include only those people who choose to take part. Please take your time in making a decision about taking part. You may discuss it with your family and friends. You may also discuss it with your health care team. If you have any questions, you can ask your doctor for more information or explanation.

WHY HAVE I BEEN ASKED TO TAKE PART IN THIS RESEARCH STUDY?

You are being asked to take part in this study because you have had surgery to remove colon cancer and you may benefit from additional treatment. Since the cancer was found in the colon and extended through the wall of the colon, but not in the lymph nodes or other organs, it is considered Stage II colon cancer.

WHY IS THIS STUDY BEING DONE?

- To determine whether specific biological features (often called tumor markers or markers) seen in tests done on a tumor (found in the colon) can be used to predict recurrence of tumors in patients with stage II colon cancer.
- To compare the effects (good and bad) of a combination of chemotherapy drugs, when given with and without a new drug, bevacizumab, on patients with stage II colon cancer at high-risk for recurrence.

The chemotherapy drugs given in this study are 5-fluorouracil (5-FU), leucovorin and oxaliplatin. We want to see if adding bevacizumab to the other cancer-fighting agents is better for treating colon cancer patients, who may be at increased risk for recurrence based on the markers shown in their tumor. We also want to see if adding bevacizumab will help prevent the cancer from coming back.

Rev. 12/08

The US Food and Drug Administration (FDA) considers the use of bevacizumab to be investigational for treating Stage II colon cancer.

NOTE: Centers outside the US must insert the applicable country and government oversight agencies in place of the US and the FDA, where appropriate, throughout the protocol.

Rev. 8/09

Recent information from a large, randomized Phase III study of bevacizumab in colon cancer could affect your decision to participate in E5202.

The recently reported study is called NSABP C-08 and is commonly referred to as C-08. The results from C-08 showed that adding bevacizumab to FOLFOX chemotherapy (the same chemotherapy in E5202) did not decrease (nor did it increase) the number of patients who had their cancer come back at 3 years after surgery.

There are differences between C-08 and E5202 and these differences are important to know when thinking about how the results from C-08 might affect your decision to join E5202. The research study C-08 included patients with both stage II and stage III colon cancer, whereas E5202 only includes patients with stage II colon cancer. We already know that the risks of cancer recurrence are lower in people with stage II colon cancer. But we don't know if chemotherapy is helpful in stage II patients, and that is one of the questions being asked in E5202. In addition, E5202 requires that participants getting treatment have genetic changes in their cancer that may increase the chances of having their cancer come back. The participants in C-08 were not required to have those changes.

HOW MANY PEOPLE WILL TAKE PART IN THE STUDY?

About 3610 people will take part in this study.

WHAT WILL HAPPEN IF I TAKE PART IN THIS RESEARCH STUDY?

Before you begin this study....

You will need to have the following exams, tests or procedures. With the exception of the special laboratory tests performed on the tumor, all are part of regular cancer care and may be done even if you do not join the study. If you have had some of them recently, they may not need to be repeated.

- Biopsy of the tumor to evaluate two particular tumor markers, 18q LOH and microsatellite instability (MSI)
- Complete physical exam
- Blood and urine samples to evaluate your health status
- Pregnancy test, if you are female

During the study...

If the marker evaluation of your tumor shows that you may be at **low-risk** for tumor recurrence, then you will have regular follow-up office visits to monitor your health, but you will not receive any further treatment for the cancer, including chemotherapy.

Rev. 12/08

If, however, the marker evaluation shows that you may be at **high-risk** for tumor recurrence, then you will be randomized into one of two study groups, often called 'arms', arm A or arm B. Randomize means 'to place into a group by chance'. Neither you nor your doctor can choose the group you will be in. You will have an equal chance of being placed in one of the two arms.

You will receive treatment as described below.

- You will be seen by a doctor at the beginning of each cycle of treatment.
- You will have a complete physical exam and blood/urine samples will be obtained to evaluate your health status and to monitor treatment side effects throughout treatment.
- You will need to keep a diary of your aspirin use-if applicable
- If you are in Arm A, you will receive a standard two-day regimen of chemotherapy, often referred to as FOLFOX (fluorouracil/leucovorin/oxaliplatin), given on days 1 and 2, every two weeks for a total of twelve (12) two-week cycles. Medications are given before chemotherapy to prevent nausea and vomiting. All of the chemotherapy drugs will be given intravenously (through a vein). Oxaliplatin and leucovorin are given together over two hours, followed by 5-fluorouracil (5-FU) given as a quick infusion, followed by 5-FU given as a continuous infusion through a portable pump over the next 46 hours.
- If you are in Arm B, you will receive a standard two-day regimen of chemotherapy, referred to as FOLFOX (fluorouracil/leucovorin/oxaliplatin), given on days 1 and 2, every two weeks for a total of twelve (12) two-week cycles. You will also receive bevacizumab, on day 1 every two weeks. After the first twelve two-week cycles, you will receive bevacizumab alone for an additional twelve (12) two-week cycles, for a total time period of 24 two-week cycles [one year]. Medications are given before chemotherapy to prevent nausea and vomiting. All of the drugs will be given intravenously (through a vein). Bevacizumab is given over 90 minutes, before the oxaliplatin, leucovorin and 5-FU. Oxaliplatin and leucovorin are given together over two hours, followed by 5-fluorouracil (5-FU) given as a quick infusion, followed by 5-FU given as a continuous infusion through a portable pump over the next 46 hours.
- You will require the placement of a temporary tube into a vein in your chest or your arm during the course of your treatment. This tube will be attached to a small portable pump. The drug, 5-FU, will be given using this pump. The pump is small enough to allow it to be attached to your clothing, so it can be used without restricting most movements and activities. You will wear this pump for a 46-hour period.

Central Review

Samples of your tumor tissue will be forwarded to a designated laboratory and examined. This review will be used to determine whether you are assigned to the high-risk or the low-risk group.

Rev. 1/06, 4/06

Rev. 11/06

Rev. 4/06

WHEN I AM FINISHED WITH MY TREATMENT (HIGH-RISK GROUP) OR IF I AM IN THE OBSERVATION (LOW-RISK GROUP) I WILL HAVE THE FOLLOWING ROUTINE TESTS WHICH ARE PART OF STANDARD FOLLOW-UP CARE:

High-risk group (Arm A & B):

- Routine physical exam and blood tests every three months for 1½ years after completing FOLFOX or for 1 year after completing bevacizumab, then every six months for the next three years, then once a year for the next five years.

Low-risk group (Arm C):

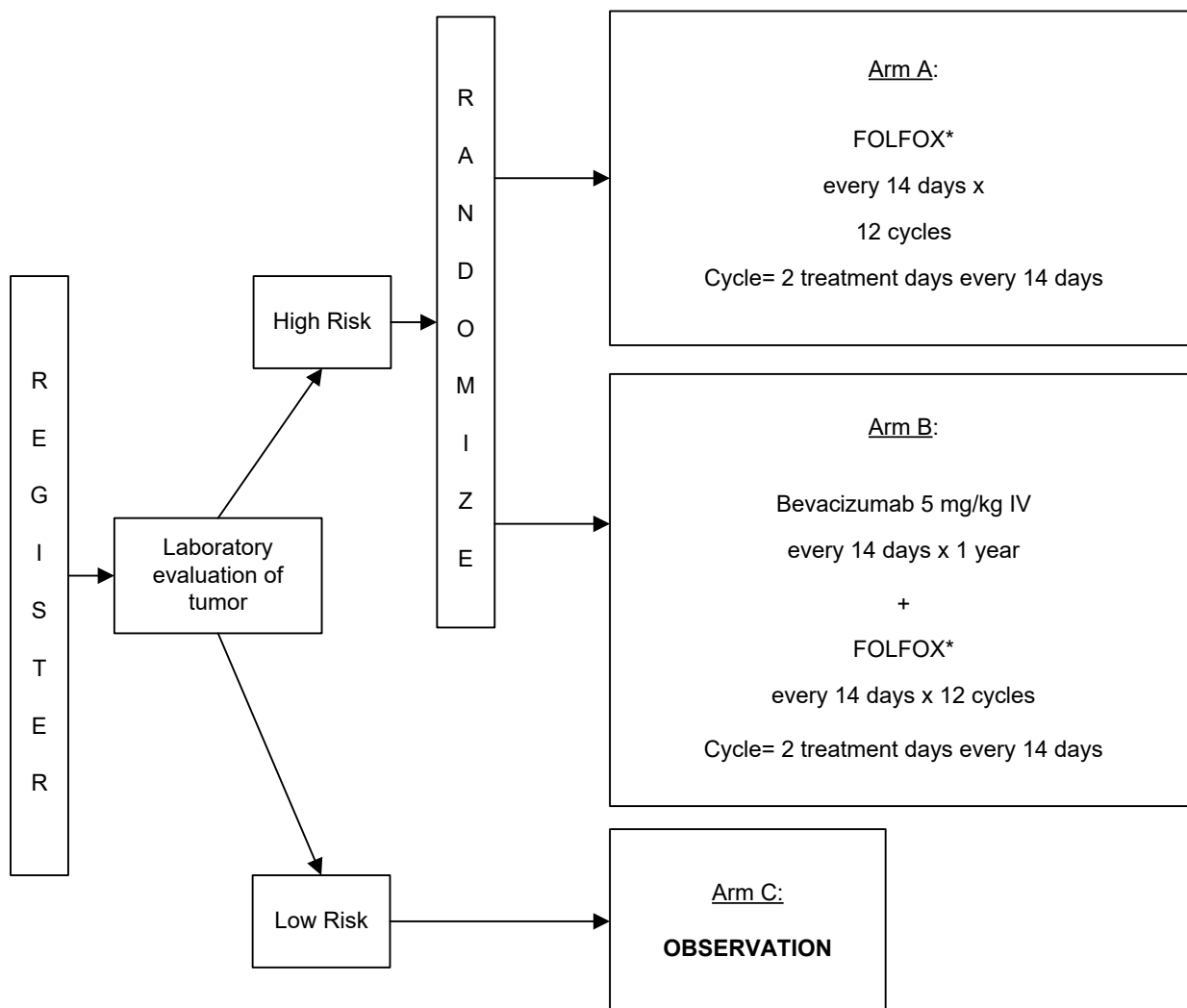
- Routine physical exam and blood tests every three months for two years, then every six months for the next three years, then once a year for the next five years.

THE FOLLOWING TABLE TELLS YOU WHAT TESTS, EXAMINATIONS AND TREATMENTS YOU WILL HAVE.

Rev. 7/07

After Primary Surgery (not later than 50 days after surgery)	<ul style="list-style-type: none"> • Submission of tumor tissue.
Within 14 days prior to randomization (Arms A & B)	<ul style="list-style-type: none"> • Pregnancy test for females who are able to become pregnant • Routine physical exam • Blood tests • Urine test
Arm A: Treatment Cycle (12 2-week cycles = 6 month)	<ul style="list-style-type: none"> • Day 1: oxaliplatin and leucovorin IV (into a vein) for two hours • Day 1: 5-FU IV (into a vein) injection, followed by 5-FU IV continuous infusion via a small portable pump for 46 hours (Days 1&2) • Treatment cycles are two weeks; treatment is for twelve 2-week cycles, totaling 24 weeks.
Arm B: Treatment Cycle (12 2-week cycles) for first 6 months	<ul style="list-style-type: none"> • Day 1: bevacizumab IV (into a vein) for 90 minutes • Day 1: oxaliplatin and leucovorin IV (into a vein) for two hours • Day 1: 5-FU IV (into a vein) injection, followed by 5-FU IV continuous infusion via a small portable pump for 46 hours (Days 1&2) • Treatment cycles are two weeks; treatment is for twelve 2-week cycles, totaling 24 weeks.
Arm B: Treatment Cycle (12 2-week cycles) for last 6 months	<ul style="list-style-type: none"> • Day 1: bevacizumab IV (into a vein) for 90 minutes • Treatment cycles are two weeks; treatment is for twelve 2-week cycles, totaling 24 weeks.

Rev. 7/14	Follow Up – Arm A:	<ul style="list-style-type: none"> • Routine physical exam and blood tests every three months for 1½ years after FOLFOX, every six months for the next three years and then annually until ten years from randomization. • Colonoscopy is recommended one year after surgery and then every five years thereafter.
Rev. 7/14	Follow Up – Arm B:	<ul style="list-style-type: none"> • Routine physical exam and blood tests every three months for one year after bevacizumab, every six months for the next three years and then annually until ten years from randomization. • Colonoscopy is recommended one year after surgery and then every five years thereafter.
Rev. 7/14	Follow-up – Arm C:	<ul style="list-style-type: none"> • Routine physical exam and blood tests every three months for two years, every six months for the next three years and then annually until ten years from randomization. • Colonoscopy is recommended one year after surgery and then every five years thereafter.



* FOLFOX regimen:
Oxaliplatin 85 mg/m² IV Day 1
Leucovorin 400 mg/m² IV Day 1
5-FU 400 mg/m² IV bolus Day 1
5-FU 2.4 gm/m² continuous IV infusion over 46 hours (Day 1 and Day 2)

HOW LONG WILL I BE IN THE STUDY?

Arm A patients will receive FOLFOX for 6 months and will be followed for 10 years from start of treatment. Arm B patients will receive FOLFOX plus bevacizumab for six months and then bevacizumab alone, for an additional six months for a total of one year of treatment. Arm B patients will also be followed for 10 years from start of treatment. How long you will be in the study will depend on how you do with the drugs and how the cancer acts. Should you decide to stop taking the study drugs, your doctor will still want to keep in touch with you. Arm C patients also will be followed for ten years.

CAN I STOP BEING IN THE STUDY?

Yes. You can decide to stop at any time. Tell the doctor if you are thinking about stopping or decide to stop. He or she will tell you how to stop safely.

It is important to tell the doctor if you are thinking about stopping so any risks from the drugs can be evaluated by your doctor. Another reason to tell your doctor that you are thinking about stopping is to discuss what follow-up care and testing could be most helpful for you.

The doctor may stop you from taking part in this study at any time if he/she believes it is in your best interest; if you do not follow the study rules; or if the study is stopped.

WHAT SIDE EFFECTS OR RISKS CAN I EXPECT FROM THE DRUGS GIVEN DURING TREATMENT?

Rev. 7/07

At the present time, we do not know if chemotherapy, for your stage of colon cancer, can help reduce the chances that your cancer might come back. However, many doctors do prescribe chemotherapy (such as oxaliplatin, leucovorin and 5-fluorouracil/5-FU) for Stage II colorectal cancers because it has been effective in colorectal cancers that have spread to the lymph nodes. We believe, however, there may be biological features in the tumor (called tumor markers or markers) that will help to identify patients who should receive chemotherapy. The tumor markers to be used in this research study were selected based on experiments that showed they might identify patients who have a greater chance of having their cancer come back. The cancer researchers who designed this trial are trying to determine if patients with these tumor markers have a better chance of being cured if they receive chemotherapy after surgery. Therefore, the decision to give you chemotherapy will be made after your tumor has been tested for the tumor markers. If those tumor markers suggest you may be at higher risk for the cancer coming back, you will get chemotherapy. However, if the tumor markers suggest you may be at a lower risk for the cancer coming back, you will not receive chemotherapy but you will be seen by your doctor with regularly scheduled visits.

One of the purposes of this research study is to learn if the tumor markers help doctors identify patients who are less likely to have the cancer come back if they receive chemotherapy. As we do not know if this is true, one of the risks of this study is that you might receive chemotherapy when you didn't need it.

You may have side effects while on this study. The bevacizumab, oxaliplatin, leucovorin and 5-FU may cause some, all or none of the side effects listed. Side effects vary from person to person. You should discuss these with your doctor. There may also be other side effects that we cannot predict. Other drugs will be given to make side effects less serious and less uncomfortable. Many side effects go away shortly after the treatment drugs are stopped, but in some cases, side effects can be serious, long-lasting, permanent or life-threatening. Death is rare, but possible.

During the study, your physician will check you closely to see if any of these side effects are occurring. Routine blood and urine tests will be done to see if the doses of the drugs you are receiving should be changed or delayed. You will not need to be hospitalized unless you have serious side effects. Risks and side effects related to the oxaliplatin, leucovorin, 5-FU and bevacizumab are listed below

Rev. 8/10 **5-Fluorouracil (5-FU)**

More Likely:

- Loss of appetite
- Soreness or painful ulcers of the mouth or throat
- Pain when swallowing
- Diarrhea (loose and frequent stools)
- Constipation
- Nausea (feeling sick to the stomach)
- Vomiting (throwing up)
- Temporary hair loss
- Decreases in the blood cells produced in the bone marrow, leading to decreased white blood cells, red blood cells and platelets

Less Likely:

- Swelling and pain of the hands and feet
- Thinning of the skin
- Fingernail changes
- Redness or increased skin coloring over the veins
- Skin rash
- Increased sensitivity to the sun

Rare:

- Irritation of the eyes with watery eyes and a scratchy feeling
- Unsteadiness in walking
- Dizziness
- Confusion
- Chest pain
- Changes in the heart rhythm

Leucovorin

More likely: This drug is a vitamin that is used to increase the ability of 5-FU to block TS protein. The side effects of 5-FU may be made worse, especially the side effects

on the small and large intestines.

Rare:

- Allergic reaction (rash, itching, difficulty breathing, low blood pressure)
- Seizures
- Fainting
- Fever

Oxaliplatin

Likely:

- Lack of enough red blood cells (anemia)
- Diarrhea
- Nausea or the urge to vomit
- Vomiting
- Fatigue or tiredness
- Increased blood level of a liver enzyme (ALT/SGPT)
- Increased blood level of a liver enzyme (AST/SGOT)
- Decreased number of a type of blood cell that help to clot blood (platelet)
- Inflammation (swelling and redness) or degeneration of the peripheral nerves (those nerves outside of brain and spinal cord) causing numbness, tingling, burning

Less Likely:

- Abnormal blood clotting and/or bleeding
- Fever associated with dangerously low levels of a type of white blood cell (neutrophils)
- Destruction of red blood cells
- Abnormally fast irregular heartbeat involving the upper chambers of the heart (atria)
- Abnormally fast regular heartbeat involving the upper chambers of the heart (atria)
- Period of very rapid and regular heartbeats that begins and ends suddenly
- Slow heartbeat; regular rhythm
- Fast heartbeat; regular rhythm
- Fast heartbeat usually originating in an area located above the ventricles
- Irregular heartbeat resulting from an abnormality in the one of the lower chambers of the heart (ventricle)

- Irregular heartbeat that involves the lower chambers of the heart (ventricles) that results in uncoordinated muscle movement of the ventricles making them tremble rather than contract properly; life-threatening, needs immediate attention
- Rapid heartbeat of one of the lower chambers (ventricle) of the heart; regular rhythm but potentially life-threatening, needs immediate attention
- Hearing loss
- Inflammation (swelling and redness) to the middle ear
- Inflammation (swelling and redness) of the conjunctiva (the outermost layer of the eye and the inner surface of the eyelids). Commonly called "pink eye".
- Dry eye
- A situation in which one has temporary blindness of one eye, due to a blockage (or decreased blood flow) in the blood vessels leading to that eye
- Temporary vision problems caused by the cold
- Problem with eyelid
- Swelling around the nerve responsible for sight
- Belly pain
- Fluid collection in the abdomen
- Inflammation (swelling and redness) of the large bowel (colon)
- Constipation
- Dry mouth
- Heartburn
- Difficulty swallowing
- Inflammation (swelling and redness) of the small and large bowel
- Inflammation (swelling and redness) of the esophagus (gullet or the tube that goes from mouth to stomach through which food passes)
- Excess passing of gas
- Inflammation (swelling and redness) of the stomach lining
- Bleeding in some organ(s) of the digestive tract
- Death of tissue somewhere in the digestive tract
- Sore (ulcer) somewhere in the digestive tract
- Partial or complete blockage of the small and/or large bowel. Ileus is a functional rather than actual blockage of the bowel.
- Irritation or sores in the lining of the mouth
- Inflammation (swelling and redness) of the pancreas
- Blockage of the small bowel
- Chills
- Swelling of the face

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- Swelling of the extremities (arms and/or legs)
 - Fever
 - Limp or difficulty walking
 - A condition in which both the liver and kidneys fail
 - Inflammation (swelling and redness) or damage to the tissue surrounding where a drug was injected
 - Chest pain not heart-related
 - Liver failure
 - Increase in size of the liver
 - A condition in which there is blockage of the veins of the liver; leads to liver damage
 - Abnormal reaction of the body to substances, called allergens, that are contacted through the skin, inhaled into the lungs, swallowed, or injected (allergic reaction)
 - Infection
 - Test that shows a problem in blood clotting
 - Increased blood level of a liver or bone enzyme (alkaline phosphatase)
 - Increased blood level of a liver pigment (bilirubin) often a sign of liver problems
 - Increased blood level of creatinine (a substance normally eliminated by the kidneys into the urine)
 - Increased blood level of a liver enzyme (GGT)
 - Increased INR (measure of the ability of the blood to clot properly) which increases the risk of bleeding
 - Decreased number of a type of white blood cell (lymphocyte)
 - Decreased number of a type of white blood cell (neutrophil/granulocyte)
 - Weight gain
 - Weight loss
 - Decrease in the total number of white blood cells (leukocytes)
 - More acid than normal in the blood
 - Loss of appetite
 - Dehydration (when your body does not have as much water and fluid as it should)
 - Increased blood sugar level
 - Increased blood level of uric acid, a waste material from food digestion
 - Decreased levels of a blood protein called albumin
 - Decreased blood level of calcium
 - Decreased blood sugar level
 - Decreased blood level of potassium

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- Decreased blood level of magnesium
 - Decreased blood level of sodium
 - Decreased blood level of phosphate
 - Joint pain
 - Back pain
 - Bone pain
 - Muscle pain
 - Difficulty or limitation in ability to open mouth
 - Loss of muscle coordination; awkward, uncoordinated walking; unsteadiness when walking
 - Sleepiness
 - Dizziness (or sensation of lightheadedness, unsteadiness, giddiness, spinning or rocking)
 - Taste changes
 - Speech problems
 - Restless, repetitive, or involuntary movements and rapid speech
 - Headache or head pain
 - Bleeding in the brain
 - Decreased blood flow to the brain which may lead to stroke
 - A malfunction of the nerves within the head and neck
 - Paralysis of facial muscles due to problems with the nerves that supply them
 - Weakness or paralysis (loss of muscle function) caused by damage to peripheral nerves (those nerves outside of brain and spinal cord)
 - Convulsion or seizure
 - Anxiety, feelings of dread or danger
 - Confusion
 - Feelings of sadness, worthlessness, thoughts of suicide or death (depression)
 - Difficulty sleeping or falling asleep
 - Blood in the urine
 - Bleeding in the kidney
 - Need to urinate often
 - Difficulty emptying the bladder
 - Presence of blood in a fallopian tube (tube between ovary to uterus [womb])
 - Bleeding in the ovary
 - Bleeding in the prostate

- Bleeding in the spermatic cord (a structure resembling a cord that suspends the testis within the scrotum and contains the vas deferens [the tube that carries sperm] and other vessels and nerves)
- Bleeding in the testis
- Bleeding in the uterus (womb)
- Bleeding in the vagina
- Stuffy or runny nose, sneezing
- Bleeding in the respiratory tract
- Sudden constriction of the muscles in the walls of the bronchioles (small airways of the lung)
- Cough
- Shortness of breath
- Hiccups
- Inflammation (swelling and redness) of the lungs
- Scarring of the lungs that can cause shortness of breath and interfere with breathing
- Problem of the sinuses
- Voice change
- Hair loss
- Dry skin
- Excess sweating
- Itching
- Skin rash with the presence of macules (flat discolored area) and papules (raised bump)
- Hives
- Sudden reddening of the face and/or neck
- Hot flashes
- High blood pressure
- Low blood pressure
- Inflammation (swelling and irritation) of a vein; blood clot
- Formation of a blood clot that breaks loose and is carried by the blood stream to plug another blood vessel
- Bleeding with a decreased number of blood cells that help to clot blood (platelets)

Rare but Serious:

- Formation of blood clots in small blood vessels around the body that leads to a low platelet (a type of blood cell that helps to clot blood) count
- Gas in the intestinal (bowel) wall

- Inflammation (swelling and redness) of the gallbladder possibly associated with gall stones
- Sudden or traumatic injury to the kidney
- Severe potentially life-threatening damage to the lungs which can lead to fluid in the lungs
- Swelling and redness of the skin on the palms of the hands and soles of the feet

Rev. 9/10 **Bevacizumab**

Likely:

- Diarrhea
- Nausea or the urge to vomit
- Vomiting
- Fatigue or tiredness
- Headache or head pain
- High blood pressure

Less Likely:

- Lack of enough red blood cells (anemia)
- Fast heartbeat usually originating in an area located above the ventricles
- Feeling of spinning or whirling
- Belly pain
- Inflammation (swelling and redness) of the large bowel (colon)
- Constipation
- Heartburn
- Bleeding in some organ(s) of the digestive tract
- Partial or complete blockage of the small and/or large bowel. Ileus is a functional rather than actual blockage of the bowel.
- Irritation or sores in the lining of the mouth
- Reaction that can occur during or following infusion of the drug. The reaction may include fever, chills, rash, low blood pressure, and difficulty breathing.
- Chest pain not heart-related
- Pain
- Allergic reaction by your body to the drug product that can occur immediately or may be delayed. The reaction may include hives, low blood pressure, wheezing, swelling of the throat, and difficulty breathing.
- Infection
- Infection (collection of pus) around the rectum

- Premature opening of a wound along surgical stitches after surgery
- Increased blood level of a liver enzyme (ALT/SGPT)
- Increased blood level of a liver or bone enzyme (alkaline phosphatase)
- Increased blood level of a liver enzyme (AST/SGOT)
- Increased blood level of a liver pigment (bilirubin) often a sign of liver problems
- Increased blood level of a heart muscle protein (troponin I) indicating damage to the heart muscle
- Decreased number of a type of white blood cell (neutrophil/granulocyte)
- Weight loss
- Decrease in the total number of white blood cells (leukocytes)
- Loss of appetite
- Joint pain
- Abnormal changes in the growth plate that may affect the growth of long bones in very young children. This side effect appeared to be reversible after the treatment was stopped but has not been assessed with long-term use of the bevacizumab drug.
- Muscle pain
- Dizziness (or sensation of lightheadedness, unsteadiness, or giddiness)
- Fainting
- Sudden decrease of kidney function
- Blood in the urine
- More protein leaking into the urine than usual, often a sign of kidney disease
- Bleeding in the vagina
- Cough
- Shortness of breath
- Nose bleed
- Hoarseness
- Stuffy nose
- Itching
- Skin rash
- Hives
- Formation of a blood clot that plugs the blood vessel; blood clots may break loose and travel to another place, such as the lung

Rare but Serious:

- Damage of or clots in small blood vessels in the kidney that can cause complications, some of which are serious including abnormal destruction of red blood cells (hemolysis) or platelets (that help to clot blood) and kidney failure

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- Collection of signs and symptoms that indicate sudden heart disease in which the heart does not get enough oxygen. Sudden symptoms such as chest pain, shortness of breath, or fainting could indicate heart disease and should be reported right away. Signs such as abnormal EKG and blood tests can confirm damage to the heart.
 - Heart failure: inability of the heart to adequately pump blood to supply oxygen to the body
 - Decrease in heart's ability to pump blood during the "active" phase of the heartbeat (systole)
 - Heart attack caused by a blockage or decreased blood supply to the heart
 - Irregular heartbeat resulting from an abnormality in the one of the lower chambers of the heart (ventricle)
 - Ventricular fibrillation: irregular heartbeat that involves the lower chambers of the heart (ventricles) that results in uncoordinated contraction of the heart; life threatening and potentially fatal, needing immediate attention
 - Gastrointestinal fistula: Abnormal hole between an organ of the digestive tract and another organ or tissue
 - Gastrointestinal perforation : A tear or hole in the stomach or gut that can lead to serious complications and may require surgery to repair
 - Sore (ulcer) somewhere in the digestive tract
 - Serious, life-threatening allergic reaction requiring immediate medical treatment by your doctor. The reaction may include extremely low blood pressure, swelling of the throat, difficulty breathing, and loss of consciousness.
 - Leakage from stomach due to breakdown of an anastomosis (surgical connection of two separate body structures)
 - Bleeding in the brain
 - Stroke caused by decreased blood flow to the brain
 - Abnormal changes in the brain that can cause a collection of symptoms including headache, confusion, seizures, and vision loss associated with MRI imaging findings (RPLS)
 - A condition in which the kidneys leak a large amount of protein into the urine that can cause complications including swelling and kidney failure
 - Kidney failure
 - Abnormal hole between part of the urinary system and another organ or tissue
 - Abnormal hole between the vagina and another organ or tissue
 - Abnormal hole between the lower breathing tube and the body cavity that surrounds the lungs
 - Bleeding from the lungs
 - Hole in the wall that separates the nostrils of the nose
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- Abnormal hole between the breathing tube (windpipe) and the tube that goes from mouth to stomach through which food passes (esophagus). This is life-threatening and potentially fatal.
- Blockage or narrowing of a blood vessel (artery) that can cause damage or loss of function including a heart attack or stroke

Reproductive risks: Patients in Arms A and B will receive drugs that may affect the way a woman's ovaries work and her ability to get pregnant. The drugs in this study can affect an unborn baby. Therefore, women should not become pregnant and men should not father a baby while on this study. (Men and women in Treatment Arm B should continue to take precautions for at least 3 months after their last dose of bevacizumab). Both male and female patients should ask about counseling and more information about preventing pregnancy. Female patients who think they might be pregnant, even though they practiced birth control, must notify the study doctor immediately. A pregnancy test may be performed. Male patients should also inform the study doctor immediately if their sexual partner(s) become pregnant while the patient is receiving treatment. Women should not breastfeed a baby while on this study, and, if they are in Treatment Arm B, for at least 3 months after their last dose of bevacizumab.

Doctors do not know for sure how bevacizumab may affect unborn children or children nursed by mothers who received bevacizumab. We do not know how long after stopping bevacizumab that you safely can become pregnant, father a child or nurse a child. A period of at least 3 months is recommended, although we do not know if this is actually best. It is best to discuss your concerns with your doctor.

For more information about risks and side effects, ask your doctor.

ARE THERE BENEFITS TO TAKING PART IN THE STUDY?

Taking part in this study may or may not make your health better. While doctors hope the drugs will be more useful against cancer, compared to the usual treatment, there is no proof of this yet. We do know that the information from this study will help doctors learn more about this combination of drugs as a treatment for cancer. This information could help cancer patients in the future.

If the results of study do correctly identify high and low risk patients for colon cancer recurrence, then another potential benefit is that only the high risk patients will receive chemotherapy whereas low risk patients will be spared the risks of receiving chemotherapy.

The possible benefits of taking part in the study are the same as receiving oxaliplatin, leucovorin, 5-FU and bevacizumab without being in the study. The benefits of research using tissue include learning more about what causes cancer and other diseases, how to prevent them, how to treat them and how to cure them.

WHAT OTHER OPTIONS ARE THERE?

Instead of being in this study, you have these options:

- Getting treatment or cancer care without being in this study
- Take part in another study
- Getting no treatment

All the drugs used in this study are available commercially in the United States but they have not been approved by the FDA for the stage of colon cancer (stage II) that patients in this study have. The FDA considers use of bevacizumab in this setting to be investigational.

Canadian sites must insert the following paragraph in place of the one above:

Bevacizumab and oxaliplatin are not commercially available in Canada. Health Canada considers the use of bevacizumab and oxaliplatin in this setting to be investigational.

Please talk with your doctor about your choices before you decide if you will take part in this study.

WILL MY MEDICAL INFORMATION BE KEPT PRIVATE?

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The ECOG-ACRIN Cancer Research Group is conducting this study. ECOG-ACRIN is a cancer research group that conducts studies for the National Cancer Institute. Your doctor is a member of ECOG-ACRIN or another group that is participating in this study. To help protect your privacy, ECOG-ACRIN has obtained a Confidentiality Certificate from the Department of Health and Human Services (DHHS).

With this Certificate, ECOG-ACRIN cannot be forced (for example, by court subpoena) to disclose information that may identify you in any federal, state or local civil, criminal, administrative, legislative or other proceeding. Disclosure will be necessary, however, upon request of DHHS for audit or program evaluation purposes.

You should know that a Confidentiality Certificate does not prevent you or a member of your family from voluntarily releasing information about you or your involvement in this research. If an insurer or employer learns about your participation and obtains your consent to receive research information, then ECOG-ACRIN may not use the Certificate of Confidentiality to withhold this information. This means that you and your family must also actively protect your privacy.

You should also understand that your doctor and ECOG-ACRIN may take steps, including reporting to authorities, to prevent you from seriously harming yourself or others.

Finally, the Certificate does not prevent the review of your research records under some circumstances by certain organizations for an internal program audit or evaluation. Organizations that may inspect and/or copy your research records for quality assurance and data analysis include groups such as:

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- ECOG-ACRIN Cancer Research Group
- National Cancer Institute (NCI)
- National Cancer Institute of Canada Clinical Trials Group (NCIC CTG), the sponsor of this trial in Canada
- Cancer Trials Support Unit (CTSU), a research group sponsored by the NCI to provide greater access to cancer trials
- Food and Drug Administration (FDA)
- Other regulatory agencies and/or their designated representatives
- Drug manufacturers and/or their representatives
- Central laboratories

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A description of this clinical trial will be available on <http://www.ClinicalTrials.gov> as required by U.S. Law. This Web site will not include information that can identify you. At most, the web site will include a summary of the results. You can search this web site at any time.

WHAT ARE THE COSTS OF TAKING PART IN THIS STUDY?

You and/or your health plan/insurance company will need to pay for some or all of the costs of treating your cancer in this study. Some health plans will not pay these costs for people taking part in studies. Check with your health plan or insurance company to find out what they will pay for. Taking part in this study may or may not cost your insurance company more than the cost of getting regular cancer treatment.

Genentech will provide you with the bevacizumab free-of-charge for this study through the Division of Cancer Treatment and Diagnosis at the National Cancer Institute. Genentech will also pay for the costs associated with evaluating the biological markers included as part of this research. Sanofi-Synthelabo will provide you with oxaliplatin free-of-charge for this study through the Division of Cancer Treatment and Diagnosis at the National Cancer Institute. However, you or your health plan will need to pay for the cost of supplies and personnel who give you the drugs. Every effort will be made to ensure adequate supplies of both bevacizumab and oxaliplatin, free of charge, for all patients. If oxaliplatin and/or bevacizumab are approved for the stage of colon cancer that you have (Stage II), you and/or your health plan may have to pay for the drugs needed to complete this study. Your doctor will discuss this with you, if this occurs. Fluorouracil (5-FU) and leucovorin will not be provided for free in this study.

Neither you nor your insurer will be charged for the tumor tissue testing (18q LOH, MSI) required by this trial nor any other tests performed on the tissue in the future.

You will not be paid for taking part in this study.

For more information on clinical trials and insurance coverage, you can visit the

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National Cancer Institute's Web site at <http://www.cancer.gov/clinicaltrials/learningabout/payingfor>. You can print a copy of the "Clinical Trials and Insurance Coverage" information from this Web site.

Another way to get the information is to call 1-800-4-CANCER (1-800-422-6237) and ask them to send you a free copy.

WHAT HAPPENS IF I AM INJURED BECAUSE I TOOK PART IN THIS STUDY?

It is important that you tell your study doctor, _____ *[investigator's name(s)]*, if you feel that you have been injured because of taking part in this study. You can tell the doctor in person or call him/her at _____ *[telephone number]*.

You will get medical treatment if you are injured as a result of taking part in this study. You and/or your health plan will be charged for this treatment. The study will not pay for medical treatment

WHAT ARE MY RIGHTS IF I TAKE PART IN THIS STUDY?

Taking part in this study is your choice. You may choose either to take part or not to take part in the study. If you decide to take part in this study, you may leave the study at any time. No matter what decision you make, there will be no penalty to you and you will not lose any of your regular benefits. Leaving the study will not affect your medical care. You can still get your medical care from our institution.

We will tell you about new information or changes in the study that may affect your health or your willingness to continue in the study.

In the case of injury resulting from this study, you do not lose any of your legal rights to seek payment by signing this form.

WHO CAN ANSWER MY QUESTIONS ABOUT THE STUDY?

You can talk to your study doctor about any questions or concerns you have about this study. Contact your study doctor _____ *[name(s)]* at _____ *[telephone number]*.

For questions about your rights while taking part in this study, call the _____ *[name of center]* Institutional Review Board (a group of people who review the research to protect your rights) at _____ *(telephone number)*.

*You may also call the Operations Office of the NCI Central Institutional Review Board (CIRB) at 888-657-3711 (from the continental US only).

Please note: The sections of the informed consent form that follow are about additional research studies being done with people who are taking part in the main study. You may take part in these additional studies if you want to. You can still be a

part of the main study even if you say 'no' to taking part in any of these additional studies.

You can say "yes" or "no" to each of the following studies. Please mark your choice for each study, found on the next page

Rev. 8/09 **ABOUT USING SPECIMENS FOR RESEARCH**

If you participate in the clinical trial, we would also like samples of your tissue and blood to be used for research studies. These samples are referred to as "specimens". These specimens and the health information collected during your participation in the clinical trial can be used to help doctors and scientists learn more about caring for and treating people with cancer and other diseases.

Below is some general information you should know before agreeing to allow the use of your specimens for research. After the general information there are descriptions of the research projects. Each project is described separately, including the types of specimens requested and how they are collected. Each description is followed by questions concerning your participation in the project. Your specimens will be used only for the projects in which you agree to participate.

You will not receive any payments for allowing your specimens to be used for these research studies, even if your specimens are used to help develop commercial products or tests someday. You or your insurance company will not be billed for the research studies performed using your specimens.

HOW WILL MY SPECIMENS BE USED BE FOR RESEARCH?

There are two types of projects:

- Laboratory Research projects: These research studies are already planned and the project details are written into the study plan. They are approved by ECOG-ACRIN and NCI, and have been reviewed by the researchers' Institutional Review Board (IRB). An IRB is a group of people who review research to protect patient rights.
- Future Research projects: Specimens are stored in central locations for use in future research. The type of projects they will be used for are not yet known. Future projects must be approved by ECOG-ACRIN and have been reviewed by the researchers' IRB.

Researchers may study the differences and similarities of the cells or parts of the cells in the specimens, such as normal cells, tumor cells, proteins, and genetic material. The level of drug in the specimens may be studied. Some projects may study characteristics that are passed on in families (inheritable). The study of inheritable traits is a type of genetic research. To better understand the results, the researcher may compare the test results to the information collected from your participation in the clinical trial (such as your age, side effects you experience, and your cancer's response to treatment).

Additional information on the importance of donating your specimens for research and how specimens are used for research can be found on the patient advocacy website (www.researchadvocacy.org) and on the NCI website at www.cancer.gov/clinicaltrials/.

WHERE WILL MY SPECIMENS BE STORED AND WHO HAS ACCESS TO THEM?

If you agree to allow your specimens to be used for the research projects, your specimens will be sent to research laboratories for testing. After these tests are completed, the researchers will send any left over specimens to a repository (bank) where, if you agree, they will be stored for use by other researchers. The stored specimens will be kept indefinitely or until they are used up.

Because your specimens are valuable, researchers must present their projects for review and approval to scientific reviewers appointed by the ECOG-ACRIN Cancer Research Group. Any research done on the specimens must also be reviewed by the researcher's IRB. Some projects may also require approval by the National Cancer Institute (NCI).

WILL PERSONAL INFORMATION BE ASSOCIATED WITH THE SPECIMENS?

The specimens sent to research laboratories and repositories will have some identifying information, such as initials and where the specimens were collected. To protect your identity, your specimens and any related information will receive a unique identification code. Researchers approved to use the specimens for future research will only receive the code that is attached to your specimen. Any information from your research records that is approved to go to a researcher will also receive a code.

Any research or information that is published, presented at scientific meetings or made public in any other way will use only coded information.

WHAT ARE THE RISKS?

There can be a risk to you if your samples or information are improperly shared or used. The chance of this happening is very small. We have many protections in place to lower this risk. See the section, "How will the information related to your specimens be protected?"

There can be a risk in knowing genetic information. While we believe that the risks to you and your family are very low, we are not able to know all of the risks from taking part in genetic research studies. Your privacy will be protected to the fullest extent possible.

Certain health concerns that affect you and your blood relatives might be found as inherited traits are studied. Even though your genes are unique, you share some of the same genes with your blood relatives. While very rare, information could be

misused by employers, insurance companies, and others. For example, life insurance companies may charge a higher rate based on this information.

There is a national effort to share genetic testing results and related information among researchers. If this type of testing is done with your specimens in the future, coded data would probably be sent to a central database kept by the NCI. The NCI would determine which researchers may look in this database.

Some states have laws to protect against genetic discrimination [*list appropriate state information if your state has such laws*]. A new federal law called GINA, or the Genetic Information Non-Discrimination Act should help lower the risk from unfair health insurance or employment policies. The law does not include other types of misuse by life insurance or long term care insurance. To learn more about the GINA Law, please check the Internet or ask the study staff.

Rev. 7/14 **HOW WILL INFORMATION RELATED TO YOUR SPECIMENS BE PROTECTED?**

We have many ways to protect the information related to your specimens:

1. Your specimens and information receive a unique code. Researchers only receive coded specimens and information, and will not be able to see the key that links the code to you. Only approved people in ECOG-ACRIN can match you to the code on your specimens and related information.
2. Strict security safeguards are in place to reduce the chance of misuse or unplanned release of information. Steps we take include password protected access to databases and keeping freezers that contain specimens in a locked area.
3. Before specimens are given to researchers, studies are reviewed for the quality of the science and for patient protection. To make sure the research follows the rules of ECOG-ACRIN and state or federal laws, records from research studies can be reviewed by ECOG-ACRIN, by the sponsor, and by government agencies.
4. If research results are published, your name or other personal information will not be given.
5. ECOG-ACRIN also has a Certificate of Confidentiality from the U.S. Department of Health and Human Services. What this means is that ECOG-ACRIN cannot be forced to disclose your identity to any third party. It is possible that for some criminal proceedings, the Certificate of Confidentiality could be over-ridden.

Benefits

The research that may be done with your specimens will probably not benefit you directly. It may help researchers learn more about what causes cancer and other diseases, how to prevent them, and how to select the most appropriate treatment for future patients who have these diseases.

Changing your mind about letting us use your specimens

If at any time you decide you no longer want your specimens used for research, please give your doctor or study nurse a signed note stating your decision. They will contact ECOG-ACRIN and tell us about your decision.

If your specimens were already sent from the repository and are being used for a project when you withdraw your consent, your specimens and accompanying data will still be used for that approved project. Once you choose to end your participation, no further specimens or related information will be sent to researchers from the repository for any new research projects.

Specimens will NOT be returned to you. Depending on the type of specimen, it will be marked as not for research use or destroyed.

Voluntary Participation

The choice to participate in the optional laboratory research projects or to allow your specimens to be stored for future research is completely up to you. **No matter what you decide to do, your decision will not affect your medical care.** You can participate in the treatment part of the study without participating in these research projects.

Please read the research study descriptions below, review the questions carefully and circle “Yes” or “No”. If you circle “Yes”, you are indicating you understand:

- Coded information collected from your medical records may be given to researchers to perform these studies.
- The research results from your specimens will not be given to you or your doctor, they will not be placed in your medical record and they will not affect your medical care.
- Your specimens may be used in genetic research.
- The risks associated with allowing your specimens to be used in research, including the possible risks associated with genetic research.
- You will not receive any payment for the use of your specimens for these projects. You or your insurance will not be billed for any of these research studies.
- That at any time, you can end your participation in the projects and any remaining specimens or information will not be used for new research.

If you do not agree with any of the statements above, indicate “No” to ALL the questions below.

If you have any questions, please talk to your doctor or nurse, or call the institution’s research review board at *[IRB’s phone number]*.

Pharmacogenetic Laboratory Studies

When a patient receives a treatment for cancer, how effective the treatment may be depends on how the drugs act in both normal and cancer tissue. People differ in how their bodies break down and absorb drugs. Side effects are often different between patients. Different cancers also may respond differently to the same drug. It is

important to understand the differences between people and cancers so that patients can be treated with the most effective treatment with the fewest number of side effects.

Pharmacogenetics is the study of genetic differences (which may be inheritable) that effect response to drugs. Samples for these types of studies are only collected once or twice.

The purpose of the laboratory studies described below is to investigate how oxaliplatin affects your cancer and to understand some of the side effects caused by the treatment. About 5000 patients with colorectal cancers and who are being treated with oxaliplatin are being asked to participate in these studies. The results of these tests will not be given to you or your doctor. They will not be placed in your medical chart and they will not affect your care. You or your insurance company will not be billed for these tests. They are for research purposes only.

PHARMACOGENETIC STUDIES

The studies will look at differences in certain proteins and genes (DNA) that are known to be affected by or involved in processing oxaliplatin. Also, some studies will be a general search to look for other markers or genes that may predict response or toxicity to oxaliplatin. If you agree to participate in these studies, one tube of blood (about 1 tablespoon) will be collected (usually before you start treatment, but may be collected anytime). The samples of your tumor tissue, if available, will also be used in these studies. An additional biopsy is not necessary.

I agree to participate in the protein and DNA studies that are being done as part of this clinical trial.

Yes No

USING SPECIMENS FOR FUTURE RESEARCH

Leftover specimens from the central review to determine your “risk status” will be stored for future research.

We would like to collect additional tissue if your cancer returns for banking for future research. This tissue will be collected as part of your routine medical care.

If you participate in the laboratory research studies associated with this protocol, this means any specimens left over from the laboratory studies will be stored.

Although most future research studies will focus on cancer, some research projects may also include other diseases, such as heart disease, diabetes or Alzheimer’s disease.

As indicated above, the specimens will only be given to researchers approved by scientific reviewers appointed by the ECOG-ACRIN Cancer Research Group. Any research done on the specimens must also be reviewed by the researcher’s

Institutional Review Board.

Please review the points listed in the “Voluntary Participation” and the risks associated with allowing your specimens to be used for research (including genetic research) outlined in the section above. Then read the questions below carefully and circle “Yes” or “No”.

I agree to allow for additional specimens for research.

Yes No

My specimens may be kept for use in research to learn about, prevent, treat, or cure cancer. This may also include research on inherited traits.

Yes No

My specimens may be kept for research about other health problems (for example: causes of diabetes, Alzheimer's disease, or heart disease). This may also include research on inherited traits.

Yes No

PERMISSION TO CONTACT YOU IN THE FUTURE

We request your permission to contact you in the future about taking part in more research studies. If you agree and we decide to contact you in the future, we will first contact your doctor or some one at your hospital. They will tell you why we would like to contact you and, if you agree, they will send us your contact information. We will not attempt any direct contact without obtaining this second permission from you.

Someone from this institution may contact me in the future to ask me to take part in more research.

Yes No

WHERE CAN I GET MORE INFORMATION?

You may call the National Cancer Institute's Cancer Information Service at:

1-800-4-CANCER (1-800-422-6237) or TTY: 1-800-332-8615

You may also visit the NCI Web site at <http://cancer.gov/>

For NCI's clinical trials information, go to: <http://cancer.gov/clinicaltrials/>

For NCI's general information about cancer, go to
<http://cancer.gov/cancerinfo/>

You will get a copy of this form. If you want more information about this study, ask your doctor.

SIGNATURE

I have been given a copy of all _____ *[insert total of number of pages]* pages of this form. I have read it or it has been read to me. I understand the information and have had my questions answered. I agree to take part in this study.

Participant _____

Date _____