Bulletin from Cancer Control Alberta and AHS Laboratory Services

Date: March 17, 2014
To: Oncologists and AHS Laboratory Services
From: The AHS Provincial Cancer Care / Laboratory Medicine Advisory Committee
Re: Oncotype*Dx*™ Testing for Breast Cancer is Instituted Across the Province

PLEASE POST OR DISTRIBUTE AS WIDELY AS APPROPRIATE

Key Messages:

- AHS now funds Oncotype*Dx*™, a breast cancer biomarker test that predicts whether adjuvant chemotherapy is likely to be of benefit for a particular breast cancer patient.
- The test needs to be used in the broader context of breast cancer patient assessment and management, and can only be ordered by an authorized Medical Oncologist
- Only certain patients will benefit from the test, for example the breast cancer must be hormone receptor positive and the patient be lymph node negative.
- The test is extremely expensive, and a robust evaluation process is being performed concurrently by the Provincial Biomarker Working Group led by Dr. Gilbert Bigras.
- The requesting Oncologist will receive a report directly from GenomicHealth™ as well as a pathology report which contains an interpretation of the results by a Pathologist who is an expert in breast biomarkers.
- The process for how to obtain this test is outlined in the attached Oncotype Dx™ Testing and Reporting - Laboratory standard operating procedure. This will also be posted on the Anatomical Pathology Website portal.

Why this is important:

- Some women can be predicted to not benefit from adjuvant chemotherapy, and this information can spare them the potential toxicity of chemotherapy; others can be predicted to benefit from it, and they can be encouraged to complete the chemotherapy.

Action Required:

- Be aware of, and use the attached standard operating procedure for this biomarker test.

Inquiries and feedback may be directed as follows:

	Edmonton	Calgary
For ***clinical questions*** on the appropriate use of Oncotype*Dx*™ testing as funded by Alberta Health Services	Dr. Karen King 780-432-8343	Dr. Sasha Lupichuk 403-521-3093
For ***laboratory questions*** on tissue handling or the use of the Oncotype*Dx*™ test	Dr. Gilbert Bigras 780-432-8445 Or if not available 780-432-8454	Dr. Hua Yang 403-944-4056 Or if not available 403-944-4057

This bulletin has been reviewed and approved by:
Dr. James Wesenberg, AHS Provincial Medical / Scientific Director, Laboratory Services
Dr. Neil Hagen, Executive Director, Provincial Tumor Programs, Cancer Control Alberta

The AHS Provincial Cancer Care / Laboratory Medicine Advisory Committee wishes to acknowledge the support and leadership of the individuals and groups who contributed to this initiative, including amongst others, Dr. Judith Hugh, the Breast Pathology Special Interest Group and the Provincial Breast Tumor Team.

Oncotype Dx™ Testing and Reporting - Laboratory

Applicability This document applies to all personnel of AHS Laboratory Services, the Lamont Health Centre and laboratories administered by Covenant Health.

Purpose This document provides instruction on how to order and report Oncotype Dx™ (ODx) tests in Alberta

Responsibility This document outlines a coordinated process for Oncologists, Pathologists, Laboratory Staff and designated support staff to ensure consistency and efficiency across the province.

Process

Step	Responsible Person and Action	Detail
1.	Original Pathologist at the time of sign-out: • Chooses a block that would be optimal for Biomarkers (ER, PR, HER2) or Oncotype Dx testing (see Details) and • Records this in the synoptic as a Biomarker block. • May pre-emptively submit block to Biomarker Lab	Optimal block for ODx testing is: A. Neutral buffered Formalin fixed B. From the resection specimen C. Maximizes the area of highest grade invasive carcinoma (foci <0.1cm are not acceptable) D. Minimizes non-invasive epithelium (e.g. in situ, hyperplastic and normal). E. Minimizes fresh biopsy changes (e.g. inflammation and vascular proliferation) Note: Hemorrhage, necrosis, and fat contain little RNA and will not impact the test.
2.	Oncologist or designate completes: • Request form (Appendix A) submits it to the laboratory that performed the original Biomarker testing (see "Details").	<u>In Calgary</u>: Consult Desk, Dept. of Pathology, Peter Lougheed Center <u>In Edmonton</u>: Edmonton Zone IHC Lab (EZIHC), Dept of Lab Med, Cross Cancer Institute
3.	Anatomical Pathology Laboratory: • Confirms ordering Oncologist is on approved list* Retrieves block from pre-emptive files or contacts the original laboratory and requests ODx designated block	**IF:** the requesting physician is not on the approved list **THEN**: the request is sent to the Provincial Head of the Alberta Breast Cancer Program** and the requesting physician is notified by the laboratory
4.	Original Laboratory: sends the pre-selected ODx block to the requesting Biomarker Laboratory, indicating this for ODx.	**IF:** No ODx block has been designated **THEN:** the original sign-out pathologist is asked to choose a block **OR:** all slides and blocks are sent to the requesting Biomarker Lab.

5.	Anatomical Pathology Laboratory: assembles case for review by biomarker pathologist on duty for the day.	• pulls all previous biomarker slides (H&E, ER, PR, HER2) for review. This may be from a core and/or excision specimen. Cuts 20 unstained slides, 2 used for H&E's
6.	Biomarker pathologist: • reviews previous biomarker results (must be ER+ and HER2 neg) and notes presence of ER- component if applicable. • confirms suitability of ODx block activates ODx testing protocol on the selected block.	• slide 8 is stained for Ki67 and 1 H&E is kept locally • slide 9 & 1 H&E is sent to the other provincial biomarker lab for Ki67 testing • slide 10 sent to EZIHC for Ki67 assay development • Case is entered into a prospective ODx database submits 15 unstained slides to Genomic Health with appropriate forms (Appendix C-E)
7.	Genomic Health: • returns ODx result to Biomarker Laboratory returns ODx results to requesting Oncologist	
8.	Biomarker pathologist (ideally same pathologist as Steps 6, but if not available, the "on duty"): • Compares previous BM, Ki67 and ODx result • Dictates Supplementary Report (Appendix F) Authorizes Supplementary Report	• Supplementary Report to HR (Edmonton) or Surgical (Calgary). • Pathologist notes on concordance/discordance to be entered on database. • Supplementary Report authorized and transferred to Netcare. Full Genomic Health report is filed in the Biomarker Laboratory.

Procedure Notes

A list of Approved Medical Oncologists will be supplied to the two Biomarker Laboratories by the Provincial Breast Cancer Program. This list will be reviewed and updated annually.
*****For the current Program Lead see:***
http://www.albertahealthservices.ca/cancerguidelines.asp

Breast cancer is a heterogeneous disease with at least two endocrine sensitive (estrogen receptor positive – ER+) subtypes. Although the majority of ER+ patients have a low relapse risk and benefit largely from endocrine therapy alone approximately 15% of these patients will recur within 5 years and may benefit from the addition of chemotherapy. Gene expression profiling tests such as the ODx (Genomic Health Inc., Redwood City, CA, USA) provide prognostic information that reduces the use of adjuvant chemotherapy, restricting it to only those patients who are most likely to benefit. ODx assesses the mRNA expression of 5 housekeeping and 16 key genes (including ER, progesterone receptor, HER2 and Ki67) using reverse transcriptase polymerase chain reaction on formalin fixed paraffin embedded material and provides a Recurrence Score (RS) and Risk Category for recurrence (low RS< 18; intermediate 18-30; or high RS≥ 31). There is controversy in the literature as to whether the RS score adds materially to information that can be provided by an immunohistochemical panel of ER, PR, HER2 and Ki67 (IHC4). Currently, ODx is being funded to inform adjuvant chemotherapy treatment decisions in patients with fully resected ER+ and/or PR+, lymph node-negative, HER2-negative early breast cancer patients. This funding will be re-examined after comparison with emerging alternative testing strategies in 2-3 years. Therefore this document establishes a provincial testing policy to capture all ODx testing in the province to standardize testing and to facilitate future comparison and validation of any alternative test.

Related Documents

Appendix A. Oncotype Dx™ Request Form – Oncologist
Appendix B: Protocol for Pathology Material Submission to Genomic Health
Appendix C: Oncotype Dx™ Requisition Form (sample) 2 pages
Appendix D: Customs Invoice
Appendix E: Supplementary Report
Appendix F: Process Flow-Chart

Appendix A: Oncotype Dx™ Request Form – Oncologist

BREAST Oncotype Dx™ REQUEST (Oncologist)

Note: Only Oncologists authorized by the Provincial Breast Cancer Program can request this test.

☐ Original Biomarker Testing Laboratory in Calgary:

Send to:
Consult Desk, Department of Pathology,
Peter Lougheed Center
3500 26 Avenue NE
Calgary, AB T2N 2T9
Phone: 403-943-5642 Fax: 403-291-2931

☐ Original Biomarker Testing Laboratory in Edmonton:

Send to:
Edmonton Zone IHC Lab
Dept of Lab Med, Cross Cancer Inst.,
Rm: 1484, 11560 University Avenue
Edmonton, AB T6G 1Z2
Phone. 780-432-8587 Fax. 780-432-8455

ORDERING PHYSICIAN (PLEASE PRINT): _____ **DATE:** _____

FAX NUMBER: _____ **TELEPHONE NUMBER:** _____

PATIENT NAME: _____

PHN: _____**DOB (DD/MM/YYYY):** _____

**Oncotype Dx is funded for patients fulfilling the following criteria: ER and/or PR positive, HER2negative, Node Negative*

REQUESTING ONCOLOGIST TO COMPLETE THE FOLLOWING *(prior to form submission)*:

1. ***Based upon current available clinicopathologic information (pre-Oncotype Dx result) how would you categorize this patient's risk of recurrence?***
   - ☐ ***Low***
   - ☐ ***Intermediate***
   - ☐ ***High***

2. ***Would you currently recommend adjuvant chemotherapy to your patient (pre-Oncotype Dx result)?***
   - ☐ ***Yes***
   - ☐ ***No***
   - ☐ ***Unsure***

_____ **DATE:** _____
Oncologist Signature

Appendix B: Protocol for Pathology Material Submission to Genomic Health

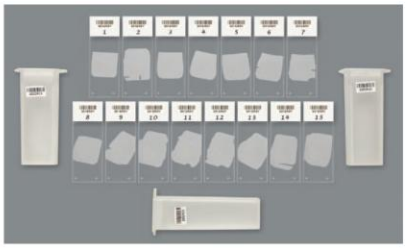
UNSTAINED SLIDES

NOTE: Follow your laboratory's standard practice guidelines for the processing of FPE tissue.

To reduce cross-contamination:

- Use a new section of the microtome blade (or a new blade) between cases.
- Clean the water bath between cases (e.g., using a clean Kimwipe).
- Wear clean gloves during the cutting and mounting process.

1. Prepare ***fifteen*** 5 µm serial unstained slides with one 5 µm serial section on each slide.
   A. Use charged glass slides (standard 1" x 3" or 25mm x 75mm size).
   B. Ensure the sections on each slide are oriented similarly.
   C. Allow the slides to air dry. Do not place the slides on a hot plate.
   D. Do not place the cover slips on the unstained slides.
2. Label the slides as follows:
   A. Apply one S barcode label, obtained from the inner top lid of the Onco*type* DX Specimen Kit, to each slide (See photo, right).



   B. Hand number the serially sectioned unstained slides (1-15) to indicate the order in which they were cut.
3. Once the slides are dry, insert them into slide carriers and place one S barcode label from the Onco*type* DX Specimen Kit on the outside of each slide carrier. Place the slide carriers in the Onco*type* DX Specimen Kit for shipping.
4. Seal the large secondary containment bag and close the box using the tab.

SHIPPING INSTRUCTIONS

MATERIALS AND EQUIPMENT:

1. Onco*type* DX Requisition Form
2. Copy of Pathology Report
3. Onco*type* DX Specimen Kit containing the patient specimen
4. FedEx® US Airbill pre-printed with Genomic Health shipping information
5. FedEx® Clinical Pak, Large — a plastic "over wrap" used to ship the specimen to Genomic Health
6. FedEx® adhesive airbill pouch for the FedEx® Airbill

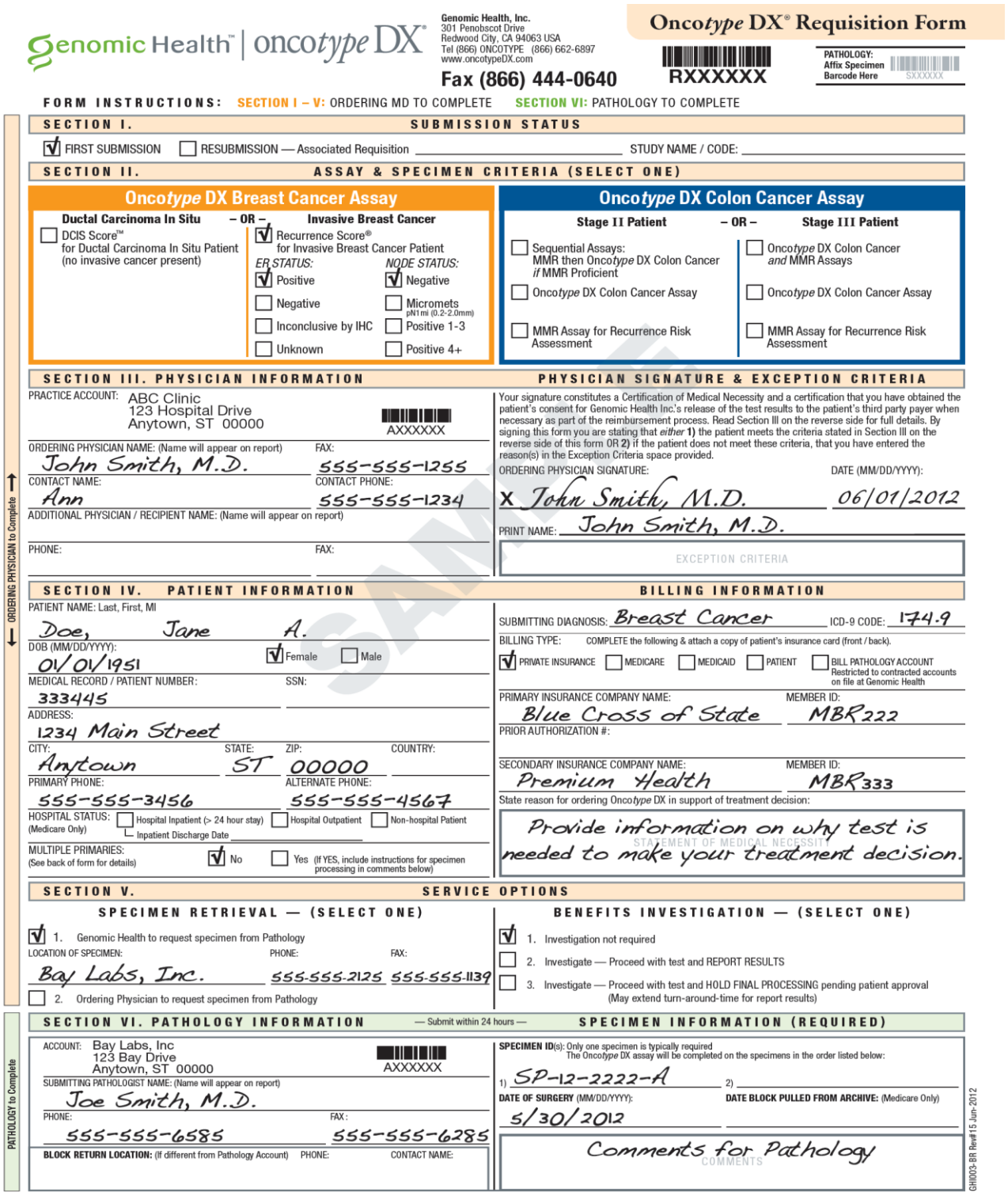
NOTE: To order additional kits, e-mail Genomic Health Customer Service at customerservice@genomichealth.com or call the number listed below.

REQUISITION FORM AND SUPPORTING MATERIALS:

1. Complete one Onco*type* DX Specimen Kit and Requisition Form for each patient and each primary tumor (if applicable). Extra S barcode labels should be left in the Onco*type* DX Specimen Kit and should NOT be used for another patient or primary tumor.
2. Before shipping, make a copy of the Onco*type* DX Requisition Form and retain it for your records.
3. Place the Onco*type* DX Requisition Form, a copy of the pathology report, and relevant patient insurance materials in the Onco*type* DX Specimen Kit, between the box and the large secondary containment bag.

QUESTIONS? PLEASE CALL 866-ONCOTYPE (866-662-6897)
301 Penobscot Drive | Redwood City CA 94063 USA | www.oncotypeDX.com

Appendix C: Oncotype Dx™ Requisition Form (sample) 2 pages



Genomic Health™ | oncotype DX®

Genomic Health, Inc.
301 Penobscot Drive
Redwood City, CA 94063 USA
Tel (866) ONCOTYPE (866) 662-6897
www.oncotypeDX.com
Fax (866) 444-0640

Oncotype DX® Requisition Form

RXXXXXX

PATHOLOGY: Affix Specimen Barcode Here SXXXXXX

FORM INSTRUCTIONS: SECTION I – V: ORDERING MD TO COMPLETE SECTION VI: PATHOLOGY TO COMPLETE

SECTION I. SUBMISSION STATUS

☑ FIRST SUBMISSION ☐ RESUBMISSION — Associated Requisition _____ STUDY NAME / CODE: _____

SECTION II. ASSAY & SPECIMEN CRITERIA (SELECT ONE)

Oncotype DX Breast Cancer Assay

Ductal Carcinoma In Situ – OR – Invasive Breast Cancer

☐ DCIS Score™ for Ductal Carcinoma In Situ Patient (no invasive cancer present)

☑ Recurrence Score® for Invasive Breast Cancer Patient

ER STATUS: ☑ Positive ☐ Negative ☐ Inconclusive by IHC ☐ Unknown

NODE STATUS: ☑ Negative ☐ Micromets pN1 mi (0.2-2.0mm) ☐ Positive 1-3 ☐ Positive 4+

Oncotype DX Colon Cancer Assay

Stage II Patient – OR – Stage III Patient

☐ Sequential Assays: MMR then Oncotype DX Colon Cancer *if* MMR Proficient

☐ Oncotype DX Colon Cancer Assay

☐ MMR Assay for Recurrence Risk Assessment

☐ Oncotype DX Colon Cancer *and* MMR Assays

☐ Oncotype DX Colon Cancer Assay

☐ MMR Assay for Recurrence Risk Assessment

SECTION III. PHYSICIAN INFORMATION

PRACTICE ACCOUNT: ABC Clinic, 123 Hospital Drive, Anytown, ST 00000 AXXXXXX

ORDERING PHYSICIAN NAME: (Name will appear on report) John Smith, M.D. FAX: 555-555-1255

CONTACT NAME: Ann CONTACT PHONE: 555-555-1234

ADDITIONAL PHYSICIAN / RECIPIENT NAME: (Name will appear on report)

PHONE: FAX:

PHYSICIAN SIGNATURE & EXCEPTION CRITERIA

Your signature constitutes a Certification of Medical Necessity and a certification that you have obtained the patient's consent for Genomic Health Inc.'s release of the test results to the patient's third party payer when necessary as part of the reimbursement process. Read Section III on the reverse side for full details. By signing this form you are stating that *either* **1)** the patient meets the criteria stated in Section III on the reverse side of this form OR **2)** if the patient does not meet these criteria, that you have entered the reason(s) in the Exception Criteria space provided.

ORDERING PHYSICIAN SIGNATURE: X John Smith, M.D. DATE (MM/DD/YYYY): 06/01/2012

PRINT NAME: John Smith, M.D.

EXCEPTION CRITERIA

SECTION IV. PATIENT INFORMATION

PATIENT NAME: Last, First, MI: Doe, Jane A.

DOB (MM/DD/YYYY): 01/01/1951 ☑ Female ☐ Male

MEDICAL RECORD / PATIENT NUMBER: 333445 SSN:

ADDRESS: 1234 Main Street

CITY: Anytown STATE: ST ZIP: 00000 COUNTRY:

PRIMARY PHONE: 555-555-3456 ALTERNATE PHONE: 555-555-4567

HOSPITAL STATUS: (Medicare Only) ☐ Hospital Inpatient (> 24 hour stay) ☐ Hospital Outpatient ☐ Non-hospital Patient
└ Inpatient Discharge Date _____

MULTIPLE PRIMARIES: (See back of form for details) ☑ No ☐ Yes (If YES, include instructions for specimen processing in comments below)

BILLING INFORMATION

SUBMITTING DIAGNOSIS: Breast Cancer ICD-9 CODE: 174.9

BILLING TYPE: COMPLETE the following & attach a copy of patient's insurance card (front / back).

☑ PRIVATE INSURANCE ☐ MEDICARE ☐ MEDICAID ☐ PATIENT ☐ BILL PATHOLOGY ACCOUNT Restricted to contracted accounts on file at Genomic Health

PRIMARY INSURANCE COMPANY NAME: Blue Cross of State MEMBER ID: MBR222

PRIOR AUTHORIZATION #:

SECONDARY INSURANCE COMPANY NAME: Premium Health MEMBER ID: MBR333

State reason for ordering Oncotype DX in support of treatment decision:

STATEMENT OF MEDICAL NECESSITY: Provide information on why test is needed to make your treatment decision.

SECTION V. SERVICE OPTIONS

SPECIMEN RETRIEVAL — (SELECT ONE)

☑ 1. Genomic Health to request specimen from Pathology

LOCATION OF SPECIMEN: Bay Labs, Inc. PHONE: 555-555-2125 FAX: 555-555-1139

☐ 2. Ordering Physician to request specimen from Pathology

BENEFITS INVESTIGATION — (SELECT ONE)

☑ 1. Investigation not required

☐ 2. Investigate — Proceed with test and REPORT RESULTS

☐ 3. Investigate — Proceed with test and HOLD FINAL PROCESSING pending patient approval (May extend turn-around-time for report results)

SECTION VI. PATHOLOGY INFORMATION — Submit within 24 hours —

ACCOUNT: Bay Labs, Inc, 123 Bay Drive, Anytown, ST 00000 AXXXXXX

SUBMITTING PATHOLOGIST NAME: (Name will appear on report) Joe Smith, M.D.

PHONE: 555-555-6585 FAX: 555-555-6285

BLOCK RETURN LOCATION: (If different from Pathology Account) PHONE: CONTACT NAME:

SPECIMEN INFORMATION (REQUIRED)

SPECIMEN ID(s): Only one specimen is typically required. The Oncotype DX assay will be completed on the specimens in the order listed below:

1) SP-12-2222-A 2) _____

DATE OF SURGERY (MM/DD/YYYY): 5/30/2012 DATE BLOCK PULLED FROM ARCHIVE: (Medicare Only) _____

COMMENTS: Comments for Pathology

ORDERING PHYSICIAN to Complete

PATHOLOGY to Complete

GHI003-BR Rev#15 Jun-2012

SAMPLE

REQUISITION FORM INSTRUCTIONS

A. Complete all sections of the Requisition Form. Missing information may result in delays in test results.

B. After signing, fax the completed Requisition Form to 866-444-0640 or, if submitting a specimen, include the form with the specimen collection kit.

C. Online ordering is available at www.online.genomichealth.com. For assistance in setting up an Online Portal Account for online ordering, please contact Customer Service at customerservice@genomichealth.com or 866-ONCOTYPE (866-662-6897).

D. Assay results will be delivered to the ordering physician and additional recipients according to the physicians' preferences on file at Genomic Health, Inc. (GHI). To establish or change report delivery preferences, please contact Customer Service at customerservice@genomichealth.com or by calling 866-ONCOTYPE (866-662-6897).

SECTION I. SUBMISSION STATUS

A. Select the submission type.

B. If this requisition is a resubmission, include the associated requisition number.

SECTION II. ASSAY & SPECIMEN CRITERIA

ONCOTYPE® DX BREAST CANCER ASSAY

A. Select ONE assay from the available options to be ordered.

> **NOTE:** For Ductal Carcinoma In Situ patients, result reports will include ER and PR scores. For Invasive Breast Cancer patients, result reports will include ER, PR, and HER2 scores.

B. For Invasive Breast Cancer patients, enter the ER and Node Status.

ER Status:
A specimen submitted for Oncotype DX Breast Cancer Assay testing must be estrogen receptor positive (ER+) by either the IHC method used by a referring laboratory or the quantitative RT-PCR method used by GHI. If GHI determines that the submitted specimen is not ER+ by either method, a result will not be reported and the patient / payer will not be billed. The specimen is assumed to be ER+ if no selection is made.

Node Status:
Enter the node status for the patient in the designated area. The node status is required to determine the extent of the clinical experience information to be included in the report for your patient. If the node status is not provided, a report with clinical experience for both node negative and node positive specimens will be sent. Additionally, the node status may be required for payor coverage determinations. If the node status is not specified, GHI may use the pathology report, if provided, to determine the node status for reimbursement purposes.

C. See Section III for assay criteria.

ONCOTYPE DX COLON CANCER ASSAY

A. Select ONE assay from the available options to be ordered.

> **NOTE:** For Stage II patients, if "Sequential Assays" is selected, the Oncotype DX Colon Cancer Assay will be run only if the specimen is Mismatch Repair Proficient (MMR-P). MMR-P specimens have a positive immunohistochemistry score for both MLH1 and MSH2.

B. See Section III for assay criteria.

SECTION III. PHYSICIAN INFORMATION / SIGNATURE & ASSAY CRITERIA

PHYSICIAN INFORMATION

A. ADDITIONAL PHYSICIAN / RECIPIENT INFORMATION (OPTIONAL). If another physician is responsible for the care of this patient and has requested a copy of the report, enter the applicable information in the spaces provided under this section.

SIGNATURE

A. Sign and date the Requisition Form and print your name. The signature must be of an ordering physician (treating physician or pathologist) or his/her representative.

> **NOTE:** *Stamped signatures are NOT acceptable.*

B. ATTESTATION: The signature constitutes a certification of the following: (1) with respect to tests reimbursed by Medicare, Medicaid or other third party payers, the test is medically necessary and the results will be used in the management of the patient; (2) If the ordering physician is not the treating physician (or his/her authorized representative), the ordering physician confirms that the treating physician has ordered the assay for this purpose; (3) the treating physician has obtained the patient's consent for GHI to send the patient's test results to the patient's third party payer in connection with an appeal of a reimbursement denial or other reimbursement matter, if GHI has made prior attempts to obtain reimbursement without the release of such test results; (4) the patient meets the criteria defined in the breast assay or colon assay section below unless otherwise indicated in the Exception Criteria field.

If GHI determines that the specimen does not fit the criteria stated in the applicable assay criteria section below, the patient's test report will indicate, where appropriate, that the clinical interpretation of the assay result is unknown or adjusted. In all cases, it is the treating physician's responsibility to determine whether and how the assay result should be used in determining a treatment plan for that patient.

GHI will run the assay and report a result unless it determines that the specimen does not have adequate cancer tissue or it determines that the Requisition Form provides insufficient information to perform and report a result.

In some cases additional assessment methods, including confirmatory testing of HER2 status, may be used to verify that the specimen meets the criteria for the Oncotype DX assay.

ONCOTYPE DX BREAST CANCER ASSAY CRITERIA

A. Ductal Carcinoma In Situ patients
If the Requisition Form attestation has been signed and no exception criteria have been entered, you attest that the specimen is from a newly diagnosed female patient with DCIS (Stage 0: Tis, N0, M0).

B. Invasive Breast Cancer patients
If the Requisition Form attestation has been signed, no exception criteria have been entered, and the completed specimen criteria fields do not indicate otherwise, you attest that the specimen is from a newly diagnosed female patient with Stage I, II, or III (T3, N1) ER positive breast cancer.

ONCOTYPE DX COLON CANCER ASSAY CRITERIA

A. If the Requisition Form attestation has been signed and no exception criteria have been entered, you attest that the specimen is from a newly diagnosed Stage II or III colon cancer patient with adenocarcinoma or mucinous carcinoma.

SECTION IV. PATIENT INFORMATION / BILLING INFORMATION

PATIENT INFORMATION

A. **Hospitalization Status** is required if the patient's insurance is MEDICARE. If inpatient status is selected, enter the date of discharge from the hospital.

B. **Multiple Primaries:** For patients with multiple primary tumors, select YES. Indicate the specimen(s) to be processed in Section VI, Pathology & Specimen Information. List the most representative specimen (i.e. the highest grade and largest tumor) on line one. The specimen on line one will be processed first.

> **NOTE:** If multiple tests are processed, there will be a charge for each test. Contact Customer Service to discuss insurance coverage information.

BILLING INFORMATION

A. Indicate the party responsible for payment.

B. If **Private Insurance / Medicare / Medicaid** is selected:
1. Include a copy of the front and back of both the primary and secondary insurance cards.
2. All **Medicare** patients will have an eligibility check and may be contacted during the process.

C. If **Patient** is selected, a representative will contact the ordering physician's office to collect payment information.

D. Before selecting **Bill Pathology Account**, verify with GHI that you have a contracted account on file.

E. Complete the Primary and Secondary Insurance Information fields.

F. GHI will use the statement of medical necessity you provide to expedite insurance appeals.

SECTION V. SERVICE OPTIONS

SPECIMEN RETRIEVAL

A. If indicated, GHI will request the retrieval of the appropriate specimen for the ordered assay on your behalf.

> **NOTE:** If the specimen retrieval section is not completed and the specimen is not submitted with the Requisition Form, GHI will request the specimen on your behalf. GHI will contact your office to determine the location of the patient's specimen.

BENEFITS INVESTIGATION

A. If option 2 or 3 is selected, GHI will contact your patient's insurance company to verify coverage and coverage amounts.

> **NOTE:** A Benefits Investigation will not be performed for the MMR Assay.

SECTION VI. PATHOLOGY & SPECIMEN INFORMATION

A. List the most representative specimen (i.e. the highest grade and largest tumor) on line one.

B. While the GHI laboratory can accept tumor blocks and unstained slides, blocks are preferred.

C. Include a copy of the pathology report with the Specimen Kit submission box. The pathology report may be used for reimbursement and/or administrative purposes.

> **NOTE:** If more than one tumor is being submitted for the patient, each tumor must be labeled with a unique Specimen Barcode (S-Barcode). GHI is not responsible for selecting the order in which specimens will be run. GHI will use the specimens in the order listed to complete the test.

SPECIMEN INSTRUCTIONS

A. For specimen criteria and specimen preparation instructions, visit www.oncotypeDX.com or call 866-ONCOTYPE (866-662-6897).

B. Please send either:
1. One fixed paraffin embedded tumor block (neutral buffered formalin is the preferred fixative. Alternative fixatives are not recommended.)
2. Fifteen 5µm serial unstained slides, labeled to indicate the order in which they were cut.

C. All specimens must be labeled with S-Barcode labels from the Specimen Collection and Transportation Kit for the patient.

D. Affix a coinciding S-Barcode to the top right corner of the Requisition Form.

E. If you have any questions, please contact Customer Service at 866-ONCOTYPE (866-662-6897).

> **NOTE:** Assay report is based upon GHI's analysis of the submitted specimen and information provided on the Requisition Form. Additional materials or information that may have been submitted with the specimen are not considered in analyzing the specimen or preparing the report.

DOMESTIC SHIPPING INSTRUCTIONS

A. Materials and equipment
1. Oncotype DX Specimen Kit containing the patient specimen, pathology report and Oncotype DX Requisition Form.
2. FedEx® Clinical Pak, Large plastic over wrap used to ship the specimen to Genomic Health.
3. FedEx® US Airbill pre-printed with Genomic Health shipping information.
4. FedEx® adhesive airbill pouch for the FedEx® Airbill.

B. Place the Oncotype DX Specimen Kit into the FedEx® Clinical Pak.

C. Complete the FedEx® US Airbill.

D. Seal the Clinical Pak by removing the plastic adhesive protector from the white strip and secure.

E. Place the package in the designated FedEx® pickup location at your site.

F. If your site does not have standard FedEx® pickup, call 800-GO FEDEX (800-463-3339) to arrange for pick up.

> **NOTE:**
> - To order additional kits, e-mail Customer Service at customerservice@genomichealth.com or call 866-ONCOTYPE (866-662-6897).
> - Before shipping, make a copy of the Requisition Form and retain it for your records.

FOR ADDITIONAL ASSISTANCE:

- **GO TO WWW.ONCOTYPEDX.COM** OR
- **CALL 866-ONCOTYPE (866-662-6897)**

Appendix D: Customs Invoice

The customs invoice should be submitted on the letterhead of the submitting physician or institution, if possible. The approximate format is:

DATE:

SHIPPER: Institution/Clinic
Physician
Street Address 1
Street Address 2
City/County/Postal Code
Country

CONSIGNEE: GENOMIC HEALTH, INC.
Customer Service
301 Penobscot Drive
Redwood City, CA 94063
USA

PACKAGES: **1**

CONTENTS: **Diagnostic Specimen, Not Restricted, Packed In Compliance with IATA Packaging Instruction 650**

Non-infectious human tumor tissue: Fixed, paraffin-embedded tumor tissue.

For Laboratory Testing Only.

Human material was neither inoculated with nor exposed to infectious agents.

Obtained directly from humans, not recombinant, not cultured.

NO COMMERCIAL VALUE – For Customs Purposes Only $1 USD.

Signature and Job Title

Print Name Daytime Phone Number

Appendix E: Supplementary Report

The Oncotype Dx report constitutes additional information to the biomarker report (HR – Edmonton) or Surgical Accession (Calgary) that while it does not alter the intent of the original report includes clarification of clinicopathological data and additional report elements. As such, a Supplementary Report is to be generated (see "Revision of Previously Released Laboratory Reports Policy" Version 1.1 Effective Date: 17 December 2012).

The Supplementary Report will include the following elements:

1. the results of Oncotype Dx
2. commentary from the Biomarker Pathologists as to whether the Oncotype Dx results are:
    - concordant with the original impression (including grade, ER, PR, HER2)
    - discordant with the original impression (including grade, ER, PR, HER2).
3. If the Oncotype Dx results are deemed to be discordant, the biomarker pathologist will indicate whether this most likely represents:
    - a refinement of the existing studies due to tumour heterogeneity (Oncotype Dx most likely correct) or
    - an artifact (inclusion of inflammatory elements, DCIS, etc.) e.g. Oncotype Dx most likely incorrect

This is a professional interpretation of a machine derived measure and is key to the clinical relevance of the additional pathologic data from Oncotype Dx.

Appendix F: Process Flow-Chart