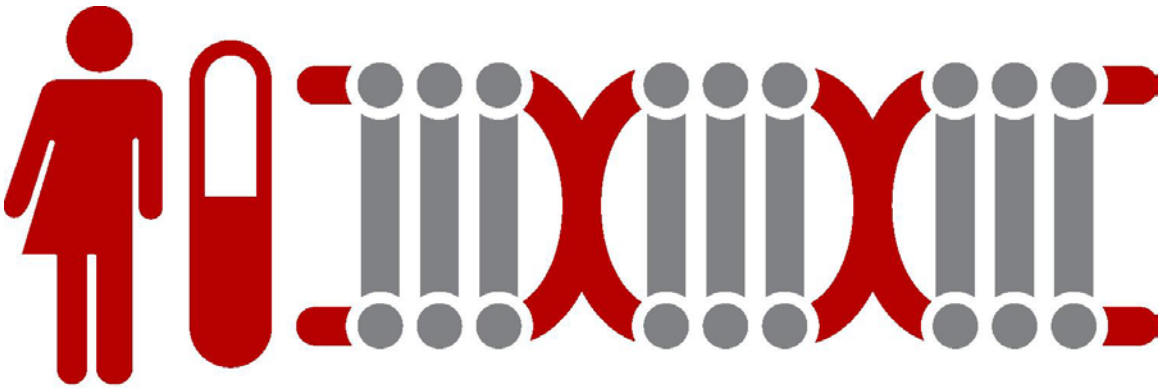

UWCCC Precison Medicine Molecular Tumor Board

Carbone Cancer Center
UNIVERSITY OF WISCONSIN
SCHOOL OF MEDICINE AND PUBLIC HEALTH

Collaborative Genomics Core
UNIVERSITY OF WISCONSIN–MADISON

The UW Carbone Cancer Center Precision Medicine Molecular Tumor Board

In partnership with the UW Collaborative Genomics Core, the UW Carbone Cancer Center (UWCCC) has developed a Precision Medicine Molecular Tumor Board (PMMTB). PMMTB services are available to all UW oncologists as well as oncologists within the UWCCC Wisconsin Oncology Network. Below is information that we hope is helpful as you consider utilizing this new service.

---

1. ***PMMTB Meetings*** are held the first and third Thursdays of each month in 7170 WIMR, starting at 4:30PM. If you would like to be included in the PMMTB, please submit request to **mtb@uwcarbone.wisc.edu.** Attendance through GoToMeeting is also available. Requests for meeting invitations are available through:

   UW Cytogenetic Services
   Phone: 608-262-0403 or 800-862-1013
   Email: cytogenetics@mail.slh.wisc.edu

2. ***Scheduling a case presentation at the PMMTB*** can be accomplished in two ways:

   Method #1:

   a. The online portal for Wisconsin State Laboratory of Hygiene (WSLH) can be used to request/order a PMMTB consult and to view, print and save copies of recommendations from presented cases.
   b. The online portal website address is: is **https://www.med.wisc.edu/uwcgc** (Please see **appendix A** for the OutReach for Cytogenetics User Guide). OutReach can only be accessed by entering a valid user code and password. The Web Portal Authorization Request Application can be found in **appendix B**. Please fax the completed form to 608-265-7818.
   c. Cases must be submitted at least 7 days prior to the meeting date. Once you submit a case, you will be assigned a meeting date and invited to attend.
   d. Fill out and email the Case Submission form. Clinical information needed from submitting clinician for cases to be considered for presentation at PMMTB:
      - Genomic reports (acceptable from a variety of sources; eg UWHC Cancer Gene Mutation Panel, Foundation One or other)
      - Patient's name
      - MRN
      - Age
      - Gender
      - Diagnosis (including stage)
      - Current and prior therapies
      - Measurable disease?
      - Other clinically relevant information (eg. affecting clinical trial eligibility or treatment)

- Information on tumor sample obtained for molecular testing (i.e. when was sample taken and at what tumor site)
- Specific questions from submitting physician
- Is there a timeline by which it would be helpful to present this case?
- Would you like the recommendation faxed or mailed to you?

e. Clinicians are strongly encouraged to attend the meeting to present their case.

f. Clinicians, pathologists and laboratory personnel are required to remove PHI prior to presenting cases. The UW policy on de-identification of PHI can be found in **appendix C** and includes a list on pages 2 and 3 of identifiers which are required to be removed prior to case presentation.

g. Treatment recommendations will be discussed at the PMMTB meeting. Recommendations will be either faxed and/or mailed to the submitting physician. A final recommendation letter will be uploaded into Health Link and the online portal at **https://www.slh.wisc.edu/elabs/Cytogenetics/**.

Method #2:

a. Submit case to **mtb@uwcarbone.wisc.edu** by emailing your patient's genomic report and case submission form. You can also fax the information to (608) 262-4285, but please send a notification of the fax to **mtb@uwcarbone.wisc.edu**.

b. Include in your submission, the patient's genomic report (acceptable from a variety of sources; eg UWHC Cancer Gene Mutation Panel, Foundation One or other) and the Case Submission form that includes the following information:

- Patient's name
- MRN
- Age
- Gender
- Diagnosis (including stage)
- Current and prior therapies
- Measurable disease?
- Other clinically relevant information (i.e. affecting clinical trial eligibility or treatment)
- Information on tumor sample obtained for molecular testing (i.e. when was sample taken and at what tumor site)
- Specific questions from submitting physician
- Is there a timeline by which it would be helpful to present this case?
- Would you like the recommendation faxed or mailed to you?

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f. Treatment recommendations will be discussed at the PMMTB meeting. Recommendations will be either faxed and/or mailed to the submitting physician. A final recommendation letter will be uploaded into Health Link and the online portal at **https://www.slh.wisc.edu/elabs/Cytogenetics/**.

3. ***The PMMTB meeting is a new part of the CME series and is a complement to the Wisconsin State Laboratory of Hygiene Collaborative Genomics Case (CGC) conference***

   a. To receive CME credit for this educational activity it is **REQUIRED** that you complete the online survey (link is provided after the activity). This survey is sent to the same address as the activity invitation and serves as your sign-in sheet and session evaluation. **Surveys must be completed by the Sunday following the session at 11:59 PM (CST).**
   b. Global Objective: Upon completion of this activity, participants will have the ability to recognize both common and rare genetic abnormalities associated with developmental delay, infertility, prenatal ultrasound findings, and oncology specimens. The MTB activity focuses on genetics and genomics in oncology.
   c. Policy on Disclosure: It is the policy of the University of Wisconsin School of Medicine and Public Health that the faculty, authors, planners and other persons who may influence the content of this CME activity disclose all relevant financial relationships with commercial interests* in order to allow CME staff to identify and resolve any potential conflicts of interest. Faculty must also disclose any planned discussions of unlabeled/unapproved uses of drugs or devices during their presentation(s).

4. ***PMMTB Clinical Practice Guidelines*** were approved in September, 2015 by UW Health. The guidelines can be found in **appendix D** and are also posted on uConnect under Oncology at: **https://uconnect.wisc.edu/clinical/cckm-tools/cpg/guidelines/oncology/**.

5. ***The UWCCC Precision Medicine Molecular Tumor Board Registry protocol*** is currently in development and once IRB approved, all patients referred to the PMMTB will be presented and consented for study participation.

Thank you for considering the PMMTB. Please contact Marissa Schuh at **mrschuh@uwcarbone.wisc.edu** or Dona Alberti at **dba@uwcarbone.wisc.edu** with questions.

PMMTB Chairs

Clinical Co-Chairs: Mark Burkard, Dusty Deming, Josh Lang, Natalie Callander, Fotios A. Asimakopoulos
Research Co-Chairs: Jill Kolesar, Anne Traynor
Laboratory Science Co-Chairs: Bill Rehrauer, Jennifer Laffin
Pathology Co-Chairs: Kristina Matkowskyj, Darya Buehler

APPENDIX A

Cytogenetics Outreach User Guide

UWCCC Precison Medicine
Molecular Tumor Board

Outreach User Guide

I. The online portal, **Outreach (Psyche),** for Wisconsin State Laboratory of Hygiene (WSLH) can be used to request/order a PMMTB consult and to view, print and save copies of recommendations from presented cases. The program has been tested to be compatible using Internet Explorer (or some versions of Firefox).

A. The Outreach website address is **https://www.med.wisc.edu/uwcgc**

1. Then click on the **Online Portal Access** tab located on the left-hand side of the screen.
2. If you have a valid Outreach user ID and password, click on the **Log onto Outreach (Psyche)** link and that will bring up the log-in screen.
    a. If you do not have a valid user ID or password, click on the **Web Portal Authorization Request for WSLH Partners and Clients** link. This will bring up a form that you will need to fill out and fax to UW Cytogenetic Services and Molecular Genetics to obtain a valid user ID and password. Once you obtain your user ID and password, then you can click on the **Log onto Outreach (Psyche)** link.

B. Outreach can only be accessed by entering a valid user ID and password. Enter your user name and password, and then click **Log In**. Three consecutive login attempts with an incorrect password will disable the user account. Once an account has been disabled, it must be reset by the Outreach System manager at WSLH.

C. Each user will need to read and accept the HIPAA authorization before first using the site and once per year thereafter.

II. The program opens to the **Results Retrieval** window (to order tests, click on the **Orders** button in the lower right and see section **III** below)

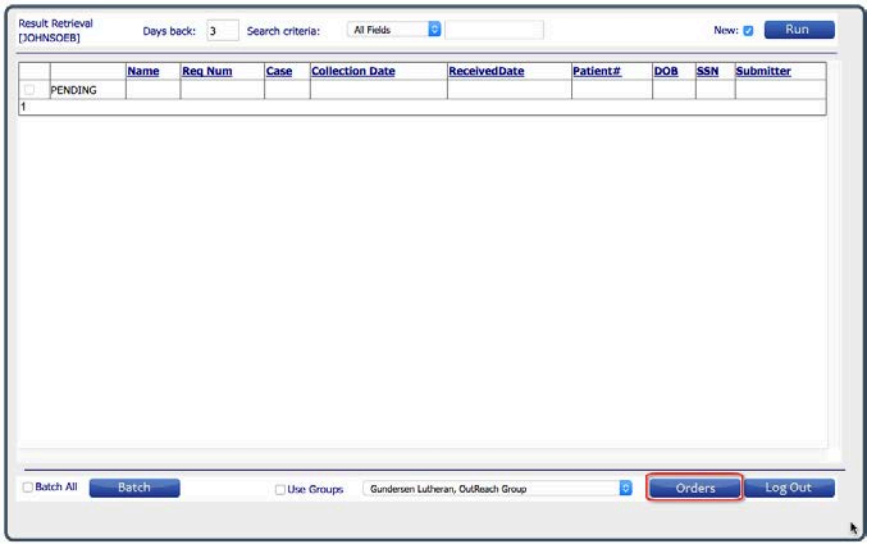

Figure 1 Results Retrieval

A. To display a list of cases with results, click on the **Run** button. This will load all cases that were signed out within the past 7 days as well as pending cases (cases that have been accessioned by the cytogenetics lab, but that are not complete).

1. The **Days back** can be changed to look for cases signed out in a shorter or longer time frame, then click **Run** again.
2. The case list is sorted alphabetically by patient, to sort by a different field click on the column heading.

3. To further narrow the list of results, additional search criteria may be used; select a field to search and then enter the specific criteria.

B. To view a report:

1. To see a single report, click on **View Report**. The pdf of the case report will be displayed. The report may be printed from this window or saved to an electronic file (the file will need to be renamed when being saved).
2. To see multiple reports, click in the box in front of View Report for each patient and then click **Batch**. All of the reports will be displayed in a single file. The reports may be printed from this window, but if saved all reports will be compiled into a single file.
3. To return to the Results list, click on **Results** in the upper left corner.

III. The **Orders** window will be displayed when the user clicks **Orders** in the lower right.

A. To order testing on a patient, click on **New Order** in the lower left corner (see figure 2).

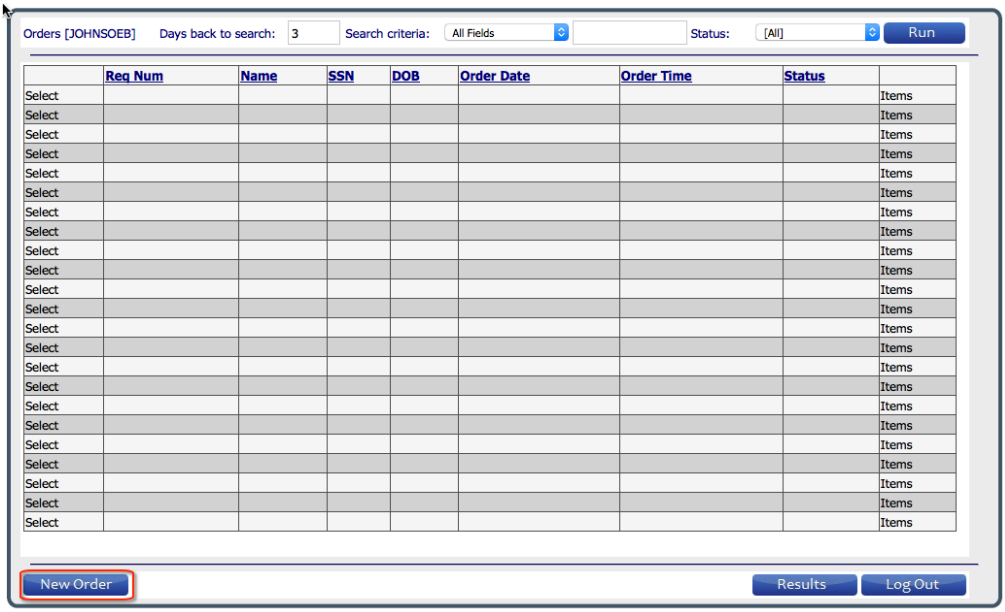

Figure 2 Orders window

1. The submitting clinician is selected by clicking **Set Submitter** (see figure 3). An alphabetical list of physicians associated with the ordering location is displayed. To search, enter part or all of the clinician's name into the Search Criteria field, and click **Run**. Click on **Select** to the left of the clinician's entry. Mode should be "Pathology"

a. **Note**: the selected clinician will be used as the default Submitter for additional orders placed unless Set Submitter is used to select a new clinician.

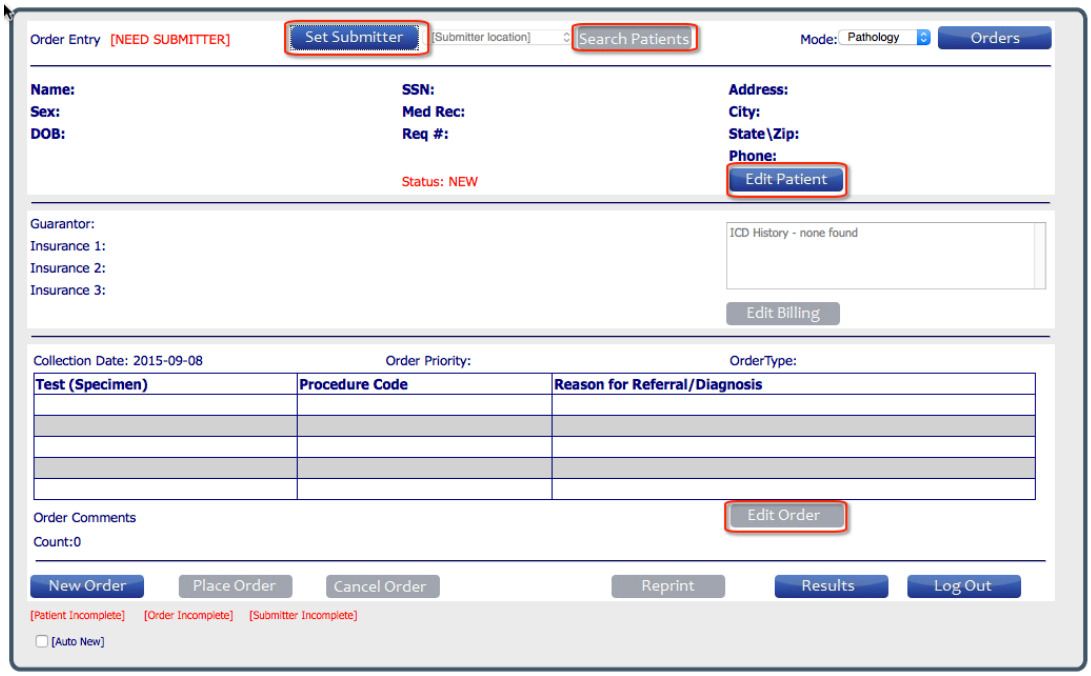

Figure 3 Order entry window 1

2. If testing on the patient has been ordered in the past, click on **Search Patients** to find the patient entry and then click **Select**, or click **Edit Patient** to create a new entry (also used to modify/update information in a patient's entry). (see figure 3)
   a. Patient name must be entered as Last, First
   b. Patient DOB must be entered as YYYY-MM-DD or use the calendar feature
3. To order tests for the patient, click on **Edit Order** (figure 3), the second order entry window opens (see figure 4).
   a. Fields with * must be filled
   b. Select the Order Type (Molecular Tumor Board Request)
   c. Collection date defaults to current date, but can be modified.
   d. Select test to be ordered from the pull down list (UWCCC Molecular Tumor Board). The Procedure code will load automatically.

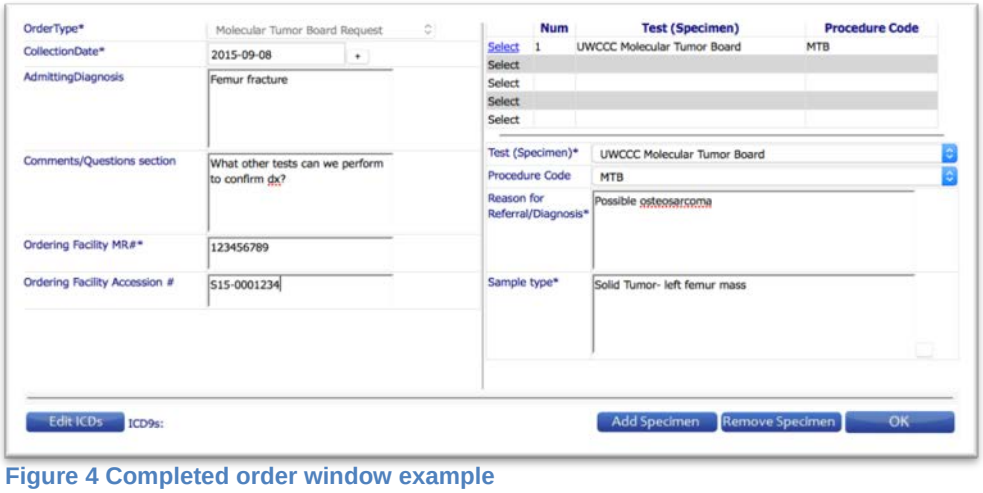

Figure 4 Completed order window example

e. Sample type may be selected from list (click on the small button immediately to the right of the field) or free texted.
f. To order multiple tests, fill in all fields for the first test, and then click **Add Specimen**. Fill in all fields (may use "same" for Reason for Referral).
g. If **Questions** is displayed on the lower left, click on Questions and select the appropriate response; the order cannot be placed until the question is answered.
h. Click on **OK** to save all entries and return to the Order Entry window.

4. Click on **Place Order** (see figure 3 – lower left), this will open a dialog window to print the requisition form to send in with the specimen. The Status will change from New to Open.
5. After the specimen has been received and accessioned by the cytogenetics lab the status will change from Open to Accessioned. Orders may be edited or cancelled through Outreach only until they have been accessioned by the cytogenetics lab.

B. To display a list of cases that were ordered within the past 7 days, click on the Run button (see figure 2). The **Days back** can be changed to look for cases ordered in a shorter or longer time frame, then click **Run** again.
1. The case list is sorted alphabetically by patient, to sort by a different field click on the column heading.
2. To further narrow the list of results, additional search criteria may be used; select a field to search and then enter the specific criteria.
3. To return to the **Results Retrieval** window, click on **Results**.

For questions or concerns regarding the Online Portal Access, please contact:

UW Cytogenetic Services and Molecular Genetics
465 Henry Mall, Room 419 Madison, WI 53706
cytogenetics@mail.slh.wisc.edu
(608) 262-0402 or (800) 862-1013
Secure Fax: (608) 265-7818

APPENDIX B

Web Portal Authorization Request Application

Wisconsin State Laboratory of Hygiene
UNIVERSITY OF WISCONSIN–MADISON

Web Portal Authorization Request for WSLH Partners and Clients

Use Policy:
Access to the laboratory online ordering and results presentation portal for UW Cytogenetic Services and Molecular Genetics, Outreach, will be managed by the Wisconsin State Laboratory of Hygiene UW Cytogenetic Services and Molecular Genetics.

Access for healthcare providers may be restricted to results/specimen status or a limited test menu when the affiliated healthcare organization has a centralized send out laboratory for management of test orders. Authorization verification and healthcare organization affiliation will be reviewed annually.

Users placing orders via Outreach are responsible for the cost of testing.
Access for healthcare organizations may include test ordering and results/specimen status.
Orders made using an institutional billing account must have prior authorization with the health organization to use that account.
Users entering private insurance billing information are required to also provide an advanced beneficiary notice (ABN).

Request for: ☐ New Account ☐ Deletion ☐ Change
(check one)

User Information:

Last Name: _____ First Name: _____ MI. _____

Employee of: _____ Position Title: _____

Work Phone: _____ Email address: _____

System Access: Please indicate access needed.

☐ OutReach Cytogenetics (WindoPath) web portal account

- ☐ Provider Access (direct test order capabilities may be limited per affiliated healthcare organization)
- ☐ Healthcare organization Access

User Security and Use Policy Agreement – User's signature can be obtained after the initial start date. When I am given an account on a WSLH web portal I will create a password that I will not reveal to anyone. I understand that I may only access information for which I have been authorized. I understand that I must keep patient data confidential and comply with all HIPAA regulations. I understand that I am responsible for the cost of testing I order. I have read, understand and will abide by the use policy.

User's Signature: _____ Date: _____

WSLH Responsible Supervisor Name: _____

WSLH Responsible Supervisor Signature: _____ Date: _____

My signature certifies that this Partner/Client has requested access appropriate for their responsibilities. Please scan and submit this completed form to the Service Desk via FootPrints.

Please fax this form to UW Cytogenetic Services and Molecular Genetics at (608) 265-7818.
Questions? Please call (608)-262-0402.

APPENDIX C

University of Wisconsin – Madison Policy and Procedure

De-identification of Protected Health Information

Under the HIPPA Privacy Rule

University of Wisconsin-Madison
Policy and Procedure

Policy Number:	5.1
Policy Title:	De-identification of Protected Health Information Under the HIPAA Privacy Rule
Effective Date:	April 3, 2003
Last Revision Date:	July 13, 2014

I. Policy

Health information that is de-identified, i.e., does not identify a patient and with respect to which there is no reasonable basis to believe that the information can be used to identify a patient, does not constitute protected health information and therefore is not subject to the requirements for the use and disclosure of protected health information in the Privacy Rule. This document describes how protected health information may be de-identified under the Privacy Rule of HIPAA.

II. Definitions

A. Business Associate: A person or entity not affiliated with UW-Madison that performs or assists in performing, for or on behalf of any unit in the UW-Madison Health Care Component, business support functions/services that involve the use of Protected Health Information.

B. Protected Health Information ("PHI"): Health information or health care payment information, including demographic information, which identifies the patient or can be used to identify the patient. PHI does not include student records held by educational institutions or employment records held by employers.

C. University of Wisconsin-Madison Health Care Component ("UW HCC"): Those units of the University of Wisconsin-Madison that have been designated by the University as part of its health care component under HIPAA. See Privacy Policy # 1.1 "Designation of UW-Madison Health Care Component" for a listing of these units.

III. Procedures

A. Use or Disclosure of PHI for Creating a De-identified Data Set

1. A UW HCC unit may use PHI to create de-identified information, whether or not the de-identified information is to be used by the

UW HCC unit or disclosed to another entity or individual, without patient authorization.

2. A UW HCC unit may disclose PHI to a business associate in order to create de-identified information, whether or not the de-identified information is to be used by the UW HCC unit or disclosed to another entity or individual, without patient authorization. Additional requirements apply before disclosing PHI to a business associate. (See Privacy Policy # 6.1 "Managing Arrangements of Business Associates with the University of Wisconsin-Madison").

B. Procedures for De-identification of PHI

A UW HCC unit may determine that health information is de-identified only if the requirements set forth in sections 1 or 2 below are met.

1. The following identifiers of the patient or of relatives, employers, or household members of the patient, are removed:

   a. Name
   b. Geographic subdivisions smaller than a state (i.e., county, town or city, street address, and zip code) (note: in some cases, the initial three digits of a zip code may be used)
   c. All elements of dates (except year) for dates directly related to an individual (including birth date, admission date, discharge date, date of death, all ages over 89 and dates indicative of age over 89) (note: ages and elements may be aggregated into a single category of age 90 or older)
   d. Phone numbers
   e. Fax numbers
   f. E-mail addresses
   g. Social security number
   h. Medical record number
   i. Health plan beneficiary number
   j. Account numbers

k. Certificate/license numbers
l. Vehicle identifiers and serial numbers
m. Device identifiers and serial numbers
n. URLs
o. Internet protocol (IP) address numbers
p. Biometric identifiers (e.g., fingerprints)
q. Full face photographic and any comparable images
r. Any other unique identifying number, characteristic, or code
s. Any other information about which the UW HCC unit has actual knowledge that it could be used alone or in combination with other information to identify the individual

2. A person with appropriate expertise in statistics and other relevant scientific principles and methods does both of the following:

a. Determines that the risk is very small that the information could be used, alone or in combination with other reasonably available information, by an anticipated recipient to identify a patient who is the subject of the information.

b. Documents the methods and results of the analysis that justify such determination.

C. Re-Identification

1. The UW HCC unit may assign a code or other means of record identification to allow information de-identified to be re-identified by that UW HCC unit provided that both of the following are true:

a. The code or other means of record identification is not derived from or related to information about the patient and

is not otherwise capable of being translated so as to identify the patient.

b. The UW HCC unit does not use or disclose the code or other means of record identification for any other purpose (other than re-identification) and does not disclose the mechanism for re-identification.

2. Disclosure of a code or other means of record identification, designed to enable coded or otherwise de-identified information to be re-identified, constitutes disclosure of PHI.

3. If de-identified information is re-identified, such re-identified information is PHI and the UW HCC unit may use or disclose such re-identified information only as permitted for PHI under the Privacy Rule.

IV. Documentation Requirements

None.

V. Forms

None

VI. References

- 45 CFR 164.502(d) (HIPAA Privacy Rule)
- 45 CFR 164.514(a)-(c) (HIPAA Privacy Rule)

VII. Related Policies

Policy Number 6.1 "Managing Arrangements of Business Associates with the University of Wisconsin-Madison"

VIII. For Further Information

For further information concerning this policy, please contact the UW-Madison HIPAA Privacy Officer or the appropriate unit HIPAA Privacy Coordinator or sub-Coordinator. Contact information is available within the "Contact Us" tab at hipaa.wisc.edu.

Reviewed By
Chancellor
Chancellor's Task Force on HIPAA Privacy
UW-Madison HIPAA Privacy Officer
UW-Madison Office of Legal Affairs

Approved By
Interim HIPAA Privacy and Security Operations Committee

APPENDIX D

UW Health Molecular Tumor Genetic Testing-

Adult Ambulatory Clinical Practice Guideline

Molecular Tumor Genetic Testing – Adult – Ambulatory Clinical Practice Guideline

Note: Active Table of Contents -- Click to follow link

Table of Contents

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Phone Number: (608) 890-6403
Email Address: lspencer2@uwhealth.org

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Joshua Lang, MD- Hematology/Oncology
Mark Albertini, MD- Hematology/Oncology
Anne Traynor, MD- Hematology/Oncology
Anwaar Saeed, MD- Hematology/Oncology
William Rehrauer, Ph.D. - Clinical Laboratories
Jennifer Laffin, Ph.D. - Wisconsin State Laboratory of Hygiene
Jill Kolesar, PharmD- School of Pharmacy
Kris Hahn, PharmD- Center for Clinical Knowledge Management (CCKM)

Review Individuals/Bodies:
Molecular Tumor Board (09/17/2015)

Committee Approvals/Dates:
Clinical Knowledge Management (CKM) Council (09/24/2015)

Release Date: September 2015

Next Review Date: September 2017

Executive Summary

Guideline Overview

This guideline contains recommendations for the indications for genetic testing of oncology tumors, and is heavily influenced by recommendations released by the National Comprehensive Cancer Network (NCCN) as well as local expert opinion.

Key Practice Recommendations

1. It is recommended that patients with cancer gene mutation panel testing are referred to the UWCCC/WON Molecular Tumor Board. *(UW Health Low quality evidence, weak recommendation)*
2. Patients with colorectal cancer *(UW Health Moderate quality evidence, weak recommendation)*, non-small cell lung cancer *(NCCN Category 2A)*, thyroid *(UW Health Low quality evidence, weak recommendation)*, or melanoma *(UW Health Low quality evidence, weak recommendation)* should be tested upon initial diagnosis of advanced disease using a cancer gene mutation panel.
3. Genomic testing using a cancer gene mutation panel may be considered in all other patients with solid tumors who lack sufficient treatment options. *(UW Health Low quality evidence, weak recommendation)*

Companion Documents

1. UW Health Lab Test Directory
2. cBioPortal Website

Pertinent UW Health Policies & Procedures

1. UWHC Policy 7.98- Entering Test Results Into UW Health Link (EPIC)

Patient Resources

1. My Cancer Genome

Scope

Disease/Condition(s): Cancer

Clinical Specialty: Medical Oncology, Laboratory

Intended Users: Oncologists, Referring Oncologists (i.e., WON providers)

CPG objective(s):

To outline evidence-based recommendations for molecular tumor diagnostic testing in patients with cancer which will support treatment decision-making using somatic test results.

Target Population:

Adult patients 18 years or older with cancer (solid tumors).

Major Outcomes Considered:

1. Molecular genetic testing

Guideline Metrics:

1. Percentage of patients with panel testing who are referred to the UWCCC/WON Molecular Tumor Board.
2. Number of patients with advanced colorectal cancer, non-small cell lung cancer, thyroid, or melanoma tested upon initial diagnosis using a cancer gene mutation panel.

Methodology

Methods Used to Collect/Select the Evidence:

Electronic database searches (i.e., PUBMED) were conducted by the Center for Clinical Knowledge Management and workgroup members to collect evidence for review. Expert opinion, clinical experience, and regard for patient safety/experience were also considered during discussions of the evidence.

Methods Used to Formulate the Recommendations:

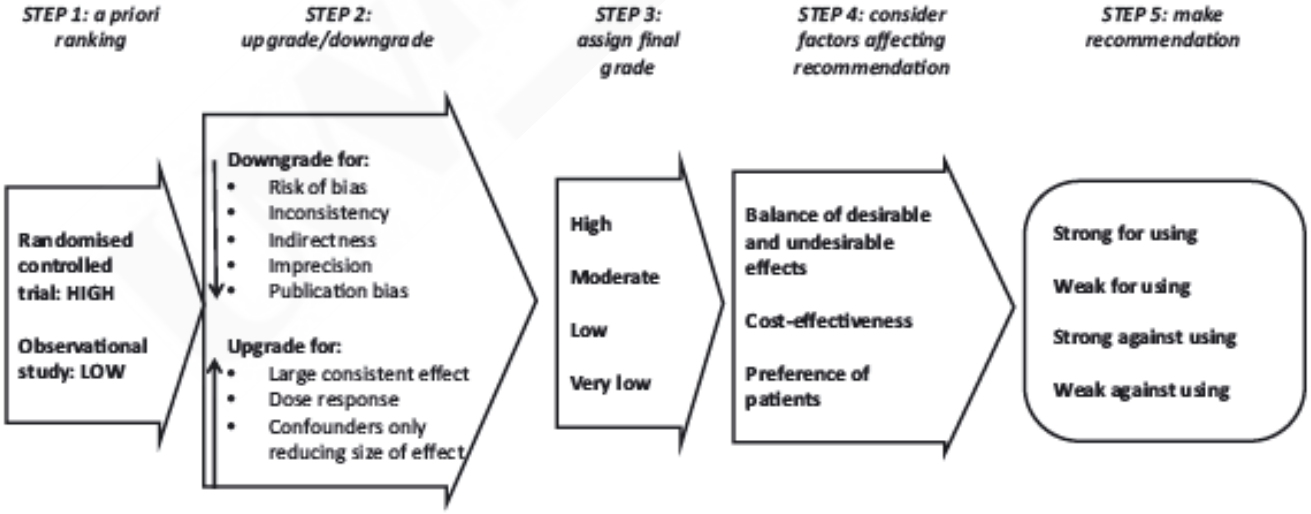
The interdisciplinary workgroup members agreed to adopt recommendations developed by external organizations, and arrived at a consensus through discussion of the literature evidence and expert/institutional experiences.

Methods Used to Assess the Quality and Strength of the Evidence/Recommendations:

Recommendations developed by external organizations, such as the National Cancer Center Network (NCCN), maintained the evidence grades assigned within the original document and were adopted for use at UW Health.

Internally developed recommendations during the workgroup meetings were evaluated using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) algorithm (**Figure 1**) to establish evidence grades for each individual piece of literature and/or recommendation.

Figure 1. GRADE Algorithm



Rating Scheme for the Strength of the Evidence/Recommendations:

See Appendix A for the various rating schemes used within this document.

Introduction

Advances in technology have enabled routine molecular testing of tumors, which may provide guidance in treatment decisions for some of the most common and deadly malignancies. This guideline provides recommendations for genetic testing in common cancer types and education on the UWCCC/WON Molecular Tumor Board.

Recommendations

Molecular Tumor Board Review

It is recommended that patients with cancer gene mutation panel testing are referred to the UWCCC/WON (University of Wisconsin-Madison Carbone Cancer Center/Wisconsin Oncology Network) Molecular Tumor Board. *(UW Health Low quality evidence, weak recommendation)* Regional affiliates or outreach facilities may consider submitting cases to the UWCCC/WON Molecular Tumor Board based upon a discussion of the risks and benefits with their patients. *(UW Health Very low quality evidence, weak recommendation)*

Test Type

Cancer gene mutation panel test results must be available prior to case presentation at the UWCCC/WON Molecular Tumor Board. *(UW Health Very low quality evidence, strong recommendation)* Benefits to ordering a panel over sequential individual tests include increasing efficiency (e.g., cost effective) and improving patient care (e.g., avoiding lengthy turnaround time for sequential test results and exhaustion of tissue which requires the patient to undergo an additional biopsy). When using a multi-gene panel clinically actionable mutations which drive treatment decisions are more likely to be identified with the first test ordered. In addition, markers with promising utility may be identified which may direct additional lines of therapy or clinical trial participation; clinical trials are routinely recommended as standard management for many patients with cancer. *(NCCN Evidence Category 2A)*

Individual tests or additional genomic testing may be completed when the genetic mutation of interest is not captured within the panel. Genetic mutations may be captured by another type of testing that is standard of care (e.g. HER2 amplification and EML4-ALK translocation detected by FISH) or based upon the characteristics specific to the case (e.g., SNP array comparative genomic hybridization or whole exome sequencing).

Ordering providers should be cognizant of the cancer gene mutation panel specifications and are encouraged to reference the UW Health Lab Test Directory or regional affiliates or outreach facilities should contact the Wisconsin State Laboratory of Hygiene via the following website for additional details.

When to Test

Patients with colorectal cancer *(UW Health Moderate quality evidence, weak recommendation)*, non-small cell lung cancer *(NCCN Category 2A)*, thyroid *(UW Health Low quality evidence, weak recommendation)*, or melanoma *(UW Health Low quality evidence, weak recommendation)* should

be tested upon initial diagnosis of advanced disease using a cancer gene mutation panel. Genomic testing using a cancer gene mutation panel may be considered in all other patients with solid tumors who lack sufficient treatment options. *(UW Health Low quality evidence, weak recommendation)*

Rationale for Comprehensive Profiling in Common Cancer Types

Determining each patient's mutation status allows clinicians to make better therapy selection decisions, including eligibility for clinical trials. The following recommendations for genetic testing by cancer type are not exhaustive, but function to provide guidance related to the mutations in common cancer types. This listing will be continuously updated to reflect evolving evidence in this field.

Breast Cancer

Along with estrogen receptor (ER) and progesterone receptor (PR), the determination of human epidermal growth factor 2 (HER2) tumor statuses is recommended for all newly diagnosed invasive breast cancers and for first recurrences of breast cancer whenever possible.[1,2] *(NCCN Evidence Category 2A)*

Due to the growing list of emerging targeted agents for genetic alterations within breast cancer, broad molecular profiling is recommended. The additional mutations listed in the table below have shown promising utility in guiding therapy selection.[3-9] *(UW Health Low quality evidence, weak recommendation)*

Table 1. Genetic Mutations in Breast Cancer

HER2 (ERBB2)	AR	PIK3CA
ER (ESR1)	CDH1	PTEN
PR (PGR)	FGFR1	TP53
AKT1	FGFR2	

Colorectal Cancer

All patients with metastatic colorectal cancer should have their tumor tissue genotyped for RAS mutations (KRAS and NRAS).[1,10] *(NCCN Evidence Category 2A)* Testing may be performed on the primary colorectal cancers and/or the metastasis.[10] *(NCCN Evidence Category 2A)* If KRAS non-mutated, consider testing for BRAF mutation.[1] *(NCCN Evidence Category 2A)*

Due to the growing list of emerging targeted agents for genetic alterations within colorectal cancer, broad molecular profiling is recommended. The additional mutations listed in the table below have shown promising utility in guiding therapy selection.[3,11,12] *(UW Health Low quality evidence, weak recommendation)*

Table 2. Genetic Mutations in Colorectal Cancer

KRAS	AKT1
NRAS	PIK3CA
BRAF	PTEN
	SMAD4

Lung Cancer

All patients with recurrent or metastatic non-small cell lung cancer (NSCLC) should be tested for ALK gene rearrangements and EGFR mutations.[1,13] *(NCCN Evidence Category 1)* EGFR and ALK testing in early stage disease (stage I, II, or III) is encouraged.[14] Testing in early stage disease allows for the availability of molecular information if recurrence should occur.[15] KRAS mutations in lung adenocarcinomas are mutually exclusive with EGFR and ALK. It is not recommended that KRAS mutation be used as a sole determinant of EGFR tyrosine kinase inhibitor therapy selection.[15]

Due to the growing list of emerging targeted agents for genetic alterations within NSCLC, broad molecular profiling is recommended.[13] Some of the genetic alterations with the strongest evidence are BRAF V600E mutation, MET amplification, and ROS1 rearrangements.[13] *(NCCN Evidence Category 2A)* In addition, other disease-relevant genes providing information on available targeted agents include HER2 mutations and RET rearrangements.[13] (*NCCN Evidence Category 2B)* The additional mutations listed in the table below have shown promising utility in guiding therapy selection.[16-22] *(UW Health Low quality evidence, weak recommendation)*

Table 3. Genetic Mutations in NSCLC

ALK	CCND1	ERBB2 (HER2)	NTRK1
EGFR	CCND2	FGFR1	PIK3CA
KRAS	CCND3	MEK1	PTEN
AKT1	CDK4	MET	RET
BRAF	DDR2	NRAS	ROS1

Melanoma

All patients with recurrent or advanced melanoma should be tested for BRAF mutation status.[23,24] *(UW Health High quality evidence, strong recommendation)* Targeted therapy significantly improves overall survival in previously untreated patients with metastatic melanoma with BRAF V600E or V600K mutations. Melanomas that arise on mucosal, acral, or chronic sun damaged skin should be assessed for KIT mutations.[25] *(UW Health Low quality evidence, weak recommendation)* All patients with recurrent or advanced melanoma being considered for routine treatment or clinical trials should receive mutational analysis.[23] *(NCCN Evidence Category 2A)* Due to the growing list of emerging targeted agents for genetic alterations within melanoma, broad molecular profiling is recommended. The additional mutations listed in the table below have shown promising utility in guiding therapy selection.[26-29] *(UW Health Low quality evidence, weak recommendation)*

Table 4. Genetic Mutations in Melanoma

BRAF	GNAQ
KIT	MEK1 (MAP2K1)
CTNNB1	NF1
GNA11	NRAS

Thyroid Cancer

Molecular diagnostic testing can be done to assist in management decisions on cytologically indeterminate thyroid nodules.[32] *(NCCN Category 2B)* Both point mutations (BRAF and N/K/H-RAS) and rearrangements (RET/PTC and PAX8/PPARγ) are commonly associated with thyroid cancer.[32,33]

Due to the growing list of emerging targeted agents for genetic alterations within thyroid cancer, broad molecular profiling is recommended. The mutations and rearrangements listed in the table below have shown promising utility in guiding therapy selection.[34] *(UW Health Low quality evidence, weak recommendation)*

Table 5. Genetic Mutations in Thyroid Cancer

BRAF	PTEN
HRAS	P53
KRAS	RET/PTC
NRAS	PAX8/PPARγ
PI3KCA	

Tumors of the Central Nervous System

Gliomas are the most common tumors of the central nervous system (CNS). Astrocytomas, oligodendrogliomas, and mixed oligoastrocytomas are the major histologic types of human gliomas; histologic differentiation among these tumors can be difficult. It has been shown that specific genetic alterations, such as deletions of the short arm of chromosome 1(1p) and long arm of chromosome 19 (19q), methylation of the MGMT (O[6]-methylguanine-DNA methyltransferase) promoter and certain mutations in the IDH1 and IDH2 (nicotinamide adenine dinucleotide phosphate (NADP)-dependent isocitrate dehydrogenases 1 and 2) genes are highly associated with specific morphologic types of gliomas.[33-35] In addition, specific genetic alterations seem to predict prognosis (survival), as well as response to specific chemotherapeutic and radiotherapeutic regimens, irrespective of tumor morphology.[35-37] *(UW Health Low quality evidence, weak recommendation)*

Table 6. Genetic Mutations in CNS Tumors

1p 19q deletions
MGMT promoter methylation
IDH1/IDH2 mutations

UW Health Implementation

Potential Benefits:

Following these guidelines should lead to standardized tumor genotyping by providers. The results from appropriate molecular testing can aid in the selection of optimal treatment regimens, which may result in improved cancer patient outcomes.

Potential Harms:

None identified.

Implementation Plan/Tools

1. Guideline will be housed on U-Connect in a dedicated folder for CPGs and linked on a webpage associated with the lab portal.
2. Release of the guideline will be advertised in the Clinical Knowledge Management Corner within the Best Practice newsletter.
3. Education and communication will be provided at Oncology DOWGs and Chemotherapy Council.
4. Reference link will be added the Cancer Gene Mutation Panel EAP [HCCANPNL].

Disclaimer

CPGs are described to assist clinicians by providing a framework for the evaluation and treatment of patients. This Clinical Practice Guideline outlines the preferred approach for most patients. It is not intended to replace a clinician's judgment or to establish a protocol for all patients. It is understood that some patients will not fit the clinical condition contemplated by a guideline and that a guideline will rarely establish the only appropriate approach to a problem.

Appendix A. Rating Schemes for the Strength of Evidence/Recommendations

Grading of Recommendations Assessment, Development and Evaluation (GRADE)

GRADE Ranking of Evidence

High	We are confident that the effect in the study reflects the actual effect.
Moderate	We are quite confident that the effect in the study is close to the true effect, but it is also possible it is substantially different.
Low	The true effect may differ significantly from the estimate.
Very Low	The true effect is likely to be substantially different from the estimated effect.

GRADE Ratings for Recommendations

Strong for using/Strong against using	The net benefit of the treatment is clear, patient values and circumstances are unlikely to affect the decision.
Weak for using/ Weak against using	The evidence is weak or the balance of positive and negative effects is vague.

National Comprehensive Cancer Network (NCCN)

NCCN Categories of Evidence and Consensus

Category	
1	Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate.
2A	Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate.
2B	Based upon lower-level evidence, there is NCCN consensus that the intervention is appropriate.
3	Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate.

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