Virtual Tumor Boards:
Key Concepts and Future Directions in Molecular Testing and Care Delivery

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This project is sponsored by Genentech.
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Webinar Instructions

Your Participation

- Please submit your text questions and comments using the Questions panel

Note: Today’s presentation is being recorded and will be provided at a future date.
Project Background and Goal

Cancer programs can form valuable relationships with research centers to access experts who can translate molecular and genomic science into individual patient treatment recommendations.

- Compare various tumor board models, partnership benefits, and effective practices
- Identify areas for potential multidisciplinary interactions and collaboration to improve patient care
Project Overview

- Seattle Cancer Care Alliance
- University of California Davis
- Sanford Health
- St. Joseph Hospital of Orange, The Center for Cancer Prevention and Treatment

http://accc-cancer.org/resources/virtual-tumor-boards.asp
# Webinars

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| Using Virtual Molecular Tumor Boards to Access the Experts          | Annie Chapman, MPH, Seattle Cancer Care Alliance  
Eric Duncavage, MD, Washington University in St. Louis  
Mark S. Soberman, MD, MBA, FACS, Frederick Regional Health System |
| Virtual Molecular Tumor Board: Breast Cancer Case Studies            | Arvind Chaudhry, MD, PhD, Summit Cancer Centers  
V.K. Gadi, MD, PhD, Seattle Cancer Care Alliance |
| Overview of Genomic Profiling                                       | Jeffrey Gregg, MD  
University of California, Davis Medical Center |
| Precision Medicine and Personalized Cancer Therapy in Lung Cancer    | Jeffrey Gregg, MD  
University of California, Davis Medical Center |

http://accc-cancer.org/resources/virtual-tumor-boards.asp
## Webinars (cont...)

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<td>An Ongoing Journey to Advance Molecular Testing in Lung Cancer</td>
<td>John Maurice, MD Enza Esposito-Nguyen, RN, MSN, ANP-BC Lavinia Dobrea, RN, MS, OCN&lt;br&gt;St. Joseph Hospital of Orange, The Center for Cancer Prevention and Treatment</td>
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<td>The Role of Genetics Professionals in a Community Cancer Program</td>
<td>Megan Landsverk, PhD, FACMG Patricia Crotwell, PhD, FACMG&lt;br&gt;Sanford Cancer Center</td>
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<td>Clinical Genetics vs. Tumor Genomic Profiling: Relevance in Cancer Care</td>
<td>Olufunmilayo I. Olopade, MD, FACP&lt;br&gt;The University of Chicago Medicine</td>
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| The New Age of Molecular Testing and Targeted Therapies for Lung Cancer | Melissa L. Johnson, MD  
Sarah Cannon Research Institute, Tennessee Oncology                                                                 |
| Engaging Multidisciplinary Clinicians in Genomic Tumor Boards        | Steven Powell, MD  
Sanford Cancer Center                                                                 |
| Real-World Considerations When Implementing a Genomic Tumor Board Program | Sharon Hunt, MBA  
Sanford Cancer Center                                                                 |

http://accc-cancer.org/resources/virtual-tumor-boards.asp
Upcoming Article: Virtual Molecular Tumor Boards

- Evolving roles
- Ongoing molecular testing issues
- Developing a program
  - Clinical champions
  - Identifying and preparing patient cases
  - Scheduling
  - Genomics expertise
  - Technology
  - Participation and engagement
Today’s Speakers

**Eric Duncavage, MD**
Associate Professor of Pathology & Immunology
Washington University School of Medicine
Barnes-Jewish Hospital

**Annette S. Kim, MD, PhD**
Associate Professor of Pathology
Harvard Medical School
Associate Pathologist
Brigham And Women's Hospital

accc-cancer.org
Outline

• Brief overview of NGS (Dr. Duncavage)

• Lung Cancer (Dr. Kim)
  • Standard of care (brief)
  • Not standard of care (brief)
  • Current BWH practice of molecular testing
  • Future of molecular testing
  • BWH Tumor Boards

• Breast Cancer (Dr. Kim)
  • Standard of care
  • Not standard of care
  • Current BWH practice of molecular testing
  • Future of molecular testing
  • BWH Tumor Boards

• How to bring the fore-front of molecular testing to the community (Dr. Duncavage)
Sequencing Based Diagnostics

• Next Generation Sequencing (NGS) or Massively Parallel Sequencing encompasses class of new sequencing technologies that for inexpensive sequencing of large regions

• NGS can be used in ‘cancer panels’ to identify clinically important genes mutated in common cancer types.

• NGS may also be used to detect chromosomal rearrangements, gains, and losses
Next Generation Sequencing Methods

• All NGS methods rely on large scale parallelization so that millions of sequencing reactions take place simultaneously.
• Sequence parallelization decreases cost and greatly increases throughput.

Johnsen, Blood, 2013
Cost of Sequencing

Currently $1,000 to sequence genome
Price will be $250 within 12 months

Source: genome.gov/sequencingcosts
Types of NGS Panels

- Whole Genome: $3 \times 10^9$ bp
- Exome: $5 \times 10^7$ bp
- Clinical Cancer Panel: $5 \times 10^5$ bp

* Not to scale
NGS Can More Than DNA Mutations

- NGS can identify chromosomal alterations and could potentially replace routine cytogenetics.
- RNA sequencing can be used to detect gene fusions and gene expression

Example Copy Number Calling with Panel Based NGS

Example Detection of ALK Fusions using RNA Seq

Rosenbaum et al
Lung
Standard of Care

  • Required testing: EGFR, ALK, ROS1 (new)
    • EGFR = Molecular
    • ALK/ROS1: FISH or IHC (or molecular if intronic breakpoint regions sufficiently covered)
  • Possible Testing (new):
    • ERBB2, BRAF, MET, RET, KRAS (all panel)
    • Just KRAS if only single gene assays are available and EGFR mutated
  • Who to test? (new recommendations)
    • All stage 3B/4 with adenocarcinoma component
    • Non-Adenocarcinoma NSCLC, <50 yo
    • Non-Adeno NSCLC, any age non-smoker
NOT Standard of Care

• Other recurrent variants in lung cancer - most of the genes on our Oncopanel

Lung squamous cell
Nature. 2012 Sep 27;489(7417):519-25

• We have clinical Oncopanel that specifically is reimbursed for EGFR, KRAS, BRAF hotspot variants

• We have a research oncopanel (DFCI grant)
Current use of Molecular Testing

• ddPCR (tumor testing, new diagnosis)
  • EGFR p.L858R (43% of EGFR mutations in lung cancer)
  • EGFR exon 19 deletion (48% of EGFR mutations)

• ddPCR (liquid biopsy, progression or new diagnosis)
  • EGFR p.L858R/EGFR exon 19 deletion (to determine if ctDNA is present)
  • EGFR p.T790M (to assess for secondary resistance)

• Oncopanel (NGS 447-gene panel)
What is in a name?

Liquid Biopsies (cfDNA)

• Requirements:
  • Samples: How do you preserve the cfDNA?
    • Peripheral blood in EDTA tube
    • Must be spun within 4 hours to separate the cfDNA in the plasma from the white blood cells (esp. PMNs) that can degrade the DNA
  OR
    • Specialized tubes designed to preserve cfDNA (or cfRNA), e.g., Streck tubes
  • Methodology: Is your assay sufficiently sensitive?
    • ddPCR methods can detect as low as 3 droplets as definitively positive, with the denominator as high as you can go (>300, but often much higher)
    • Digital sequencing can identify down to 0.25% VAF with 99.6% PPV for SNVs
  • Interpretation: How do you know you are testing the tumor (i.e., you have ctDNA rather than just cfDNA)?
    • Must have sufficient clinical sensitivity- this is why we test for EGFR p.L858R/exon 19 deletions to assure us that we are looking at tumor-derived DNA
Liquid Biopsies (cfDNA)

- Digital Droplet PCR
Clinical scenarios for liquid biopsies

• Background:
  • Tumors with larger volume and increased Ki67 (proliferation)
  • High stage disease (3B-4)
  • Tumor shedding of ctDNA: squamous > adenocarcinoma

• Current Clinical Applications
  • At progression (ideally with known tumor variant(s))
  • At diagnosis and tissue not sufficient or not attainable

• Future Clinical Applications
  • At diagnosis in lieu of a tissue biopsy even in early stage dz
  • For serial monitoring of minimal residual dz
Current use of Molecular Testing

- ddPCR (tumor testing, new diagnosis)
- ddPCR (liquid biopsy in patients with a diagnosis)

- Oncopanel (NGS 447-gene panel)
  - Assess for other SNVs (e.g., EGFR, KRAS, BRAF and others)
  - Assess for amplification (e.g., MET, ERBB2, FGFR1)
  - Assess for translocations (e.g., ALK, ROS1, RET)
    - All common break regions for ALK, ROS1 (except for ROS1 intron 31), and RET
  - **NEW** Assess for a mismatch repair deficient signature (for immunotherapy purposes)
    - Based upon small indels in homopolymer regions as a percentage of all MB covered by the assay
  - Tissue Type: FFPE, Fresh tissue, cytology smears (we use cut-off of >500 cells) – even better than cores since there are no fixation issues
Current use of Molecular Testing

<table>
<thead>
<tr>
<th>Chr position</th>
<th>Gene</th>
<th>DNA</th>
<th>AA</th>
<th>AF</th>
<th>Cov</th>
<th>Canonical</th>
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<tr>
<td>IGV1</td>
<td>RIT1</td>
<td>c.274G&gt;T</td>
<td>p.A92S</td>
<td>8</td>
<td>235</td>
<td>Missense</td>
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<tr>
<td>IGV10</td>
<td>KAT6B</td>
<td>c.709T&gt;C</td>
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<td>KRAS</td>
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<td>p.G12A</td>
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<td>Missense</td>
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Mutational Burden:

Tumor Mutational Burden/Megabase: 12.167
This is higher than 73% of all Non-Small Cell Lung Cancer cancers sequenced by this version of OncoPanel.
This is higher than 87% of all Profile cases sequenced by this version of OncoPanel.

Mutational Signatures:

MMR-Status: Proficient (MMR-P / MSS)
Future of Molecular Testing

• Use of RNA to detect fusions is becoming routine

• Expanded use of liquid biopsies with NGS
  • At diagnosis
  • For minimal residual disease tracking

• Immunotherapy
  • We already routinely do PDL1 staining for all advanced stage NSCLC
  • Pembrolizumab approved for multiple tumor types:
    • Melanoma, NSCLC, HNSCC, cHL, urothelial cancer
    • Any tumor with MSI-H or MMR defects (method not specified)
Tumor Boards

- Monthly “Precision Medicine Tumor Board”
  - Tumor focus varies from month to month
  - 3-5 cases that illustrate the impact of NGS panel testing on patient care

- Biweekly Thoracic Oncology Program Meeting
  - 2-3 active cases reviewed with clinical, pathology, radiology teams
  - Moderator calls on individuals for optimal interactions and educational benefit
  - 20-30 minute didactic on a chosen topic

- DFCI faculty have outlying hospital appointments/practices

- Molecular Tumor Boards currently focused on cases within the BWH/DFCI/BCH community
Breast
Standard of Care

- CAP Biomarkers guidelines
  - New Focused update of guidelines in progress
- ER/PR by IHC
- HER2 IHC, reflex to FISH if equivocal

HER2 IHC-FISH Correlation

- 0: >95% negative
- 1+: What about these 30-40% of cases? These may be truly biologically equivocal, or may be due to suboptimal IHC.
- 2+: >95% positive
- 3+: Images courtesy of Dr. Deborah Dillon
HER2 FISH

<table>
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<th>Result</th>
<th>Criteria</th>
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<tr>
<td>Negative (not amplified)</td>
<td>HER2/CEP17 ratio &lt; 2.0 AND average HER2 copy number &lt; 4.0 signals/cell</td>
</tr>
<tr>
<td>Equivocal*</td>
<td>HER2/CEP17 ratio &lt; 2.0 AND average HER2 copy number ≥ 4.0 but &lt; 6.0 signals/cell†</td>
</tr>
<tr>
<td>Positive (amplified)</td>
<td>HER2/CEP17 ratio ≥ 2.0† (regardless of average HER2 copy number) or Average HER2 copy number ≥ 6.0 signals/cell† (regardless of ratio)</td>
</tr>
</tbody>
</table>

Images courtesy of Dr. Deborah Dillon
CAP Breast Cancer Biomarker Guidelines
HER2 FISH Caveats

Technically positive, but due to loss of CEP17, not significant amplification of HER2

Technically negative, even though HER2 increased by copy number but not by ratio due to polysomy or centromere amplification


Images courtesy of Dr. Deborah Dillon
Other Molecular Testing Options

1. Alternative probes for FISH

   - Makes the oncologist/patient feel better about not using chemo when the result comes back low risk...
   - Makes the oncologist/patient feel better about using chemo when the result comes back high risk...

   • MAJORITY OF CASES ARE INTERMEDIATE RISK!

2. Multigene expression assays
   - Makes the oncologist/patient feel better about not using chemo when the result comes back low risk...
   - Makes the oncologist/patient feel better about using chemo when the result comes back high risk...

   • MAJORITY OF CASES ARE INTERMEDIATE RISK!
NOT SOC: Other Molecular Testing

Luminal A-type with recurrent PIK3CA mutations (45%)

Most GATA3 and CDH1 mutations are in the luminal A and B groups.

Basal-like with TP53 mutations (80%)

HER2 overexpressed in 80%

TP53, PIK3CA, ERBB2, MYC, FGFR1, GATA3, CCND1 = 58% of driver mutations

Also NOT SOC

• Androgen Receptor IHC
• ESR1 mutations – only in mets of patients treated with aromatase inhibitors
• ERBB2 mutations- in not amplified cases
  • Better response to neratinib
• Of ER neg AND HER2 pos and/or GCDFP15 pos cases, >50% are AR positive by IHC (>10%)
• Of ER-/PR- mBC, 12% AR positive
• 19% achieve clinical benefit from AR targeting (bicalutamide)

Lehmann-Che et al, Breast Ca Res 2013 15:R37
Images courtesy of Dr. Deborah Dillon
ESR1 Mutations

- Rare in primary tumors
- Present in 15-20% of patients with metastatic ER+ disease who received endocrine therapy
- Mutations are clustered in the ligand-binding domain of the ER and lead to constitutive ER activity and acquired endocrine resistance

Alluri PG (Chinnaiyan). Breast Cancer Research 2014, 16:494
ERBB2 (HER2) Mutations

- Prevalence 2.4% in mBC, most in tumors without HER2 amplification, and somewhat more common in relapsed ILC
- Kinase domain mutations are activating in preclinical models (alternate way to activate HER2)
- Appear to be LESS sensitive to trastuzumab and apatinib, but SENSITIVE to neratinib (15% response rate - MSKCC data)

MSKCC. SABCS 2015
Current Use of Molecular Testing

• Still for research purposes
• All cases of metastatic disease go through our Oncopanel (do mets preferentially to primary tissue if tissues/resources are limited)

• Considerations of molecular testing:
  • Tissue has to get to testing site in a timely manner or the results will be too late (current TAT of our Oncopanel is <3 weeks)
  • *Community pathology site MUST RETAIN tissue*
    • Often pathology sites do not retain blocks beyond the minimal requirement
    • Minimum of 1 good block of primary tumor and 1 good block of each metastatic tumor
Future of Molecular Testing

- Liquid Biopsy (cell free DNA (cfDNA), circulating tumor DNA (ctDNA))
- Sequential testing to look for changes as you treat
- Immunotherapy
  - Expression of PDL1 by IHC (not yet by copy number assessment)
  - Tumor infiltrating lymphocytes (TILs)
Tumor Boards

• Monthly “Precision Medicine Tumor Board”
  • Tumor focus varies from month to month
  • 3-5 cases that illustrate the impact of NGS panel testing on patient care

• Weekly Breast Tumor Board (BWH/DFCI)
  • Covers all aspects (histology, FISH, molecular, clinical) - not dedicated molecular
  • SOC markers as well as availability of clinical trials
  • Includes other BWH affiliates

• Eastern Maine Medical Center Tumor Boards
  • BWH/DFCI faculty present there as well
  • Real-time networked Tumor Board with 8-10 outlying hospitals
  • Face-to-face interactions help develop relationships
Making Treatment Decisions

• How do community physicians access new diagnostic technologies such as sequencing based diagnostics?
• How do we integrate complicated molecular testing in to patient care?
• How can the community physician get help interpreting data?
Ordering Molecular Testing

• In-house molecular testing
  • Ideal, but now always available
• Reference lab model (Mayo, Quest, ARUP, etc)
  • Return results with interpretation
  • May not integrate external clinical or pathological findings
• Technical only molecular services (PierianDx Gateway, others)
  • Sequencing performed at large center and results interpreted at local center
• ‘Expert Diagnostic’ model (PrecipoDx)
  • Cases tested at company and signed out by experts at local academic centers
How to Choose the Right Molecular Assay

• Does the panel have the correct genes for the cancer type?
  • Pan-cancer panels vs. disease-specific panels

• Number of Genes
  • More genes on the panel is not necessarily better

• Mutation Spectrum Identified
  • Does the assay detect larger insertions/deletions?
  • Will it detect chromosomal rearrangements

• Turn around time
  • Generally 2-3 weeks

• Reimbursement
  • Will insurance cover the assay?
How to Make Clinical Sense of Molecular Testing Data—Tumor Boards

• Tumor boards are a great venue to discuss molecular findings

• Many institutions have organ-system based tumor boards where molecular data is discussed along with other clinical findings

• Molecular only tumor boards are generally focused on interesting molecular findings or the application of new techniques
Finding Help

• Call your local pathologist

• Community oncologists can connect to larger centers through **virtual tumor boards**
  • Experts from a larger center provide opinions in real time
  • Offered by several academic centers as well as private companies

• Pathology Consults
  • Patient materials including the results of molecular testing can be sent to an academic for review and interpretation

• Patient Consults
  • Patient may be seen at a center with more expertise in the desired area
Acknowledgements

Neal Lindeman
Lynette Sholl
Deborah Dillon
Laura Macconaill
Elizabeth Garcia
Submit Questions

- Please submit your text questions and comments using the Questions panel

LEARN MORE
View archived webinars

http://accc-cancer.org/resources/virtual-tumor-boards.asp
Precision Medicine: Strategies for Improving Cancer Team Communication

In 2016, ACCC conducted four focus groups at ACCC member programs on the state of their breast and non-small cell lung cancer molecular testing programs.

An easy-to-use assessment tool designed to help programs identify potential gaps in patient identification, diagnosis, test selection, tissue preparation, and test results.

[accc-cancer.org/MolecularTestingCommunication](accc-cancer.org/MolecularTestingCommunication)