Point of Care Molecular Testing

Streamlining Cancer Care from the Anatomic Pathologist’s Office

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Medical Oncology

Dr. Brandon S. Sheffield
Anatomic Pathology
Disclosures, Dr. B Sheffield

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Speaker was provided monetary remuneration by Thermo Fisher Scientific for this presentation.
Objectives

1. Foster an appreciation for the role of ancillary biomarker testing in the treatment of cancer patients.

2. Appreciate how delays in test results can adversely affect cancer care.

3. Identify areas within your own lab or network that impede biomarker results.

4. Explore how existing and novel techniques can help support oncology practice within your centre.
Current state

1. Cancer is diagnosed by an anatomic pathologist

2. Cancer-related testing is requested by a medical oncologist

3. Biomarker testing is performed in a separate molecular facility
Cancer diagnosis

Oncology consult

Biomarker request

Pathologist review

Block retrieval

Material transferred to molecular lab

Microscopy

Histopathology review

Block accessioned at reference centre

Send block out to referral centre

Nucleic acid extraction

Library preparation

Gene sequencing

Report generation

Report drafted and signed

Returned to ordering oncologist

Signed by original pathologist

Transcribed into EMR

Report received at originating institution

Report faxed back to originating institution
Net effect

- Delayed biomarker testing
- Inefficient use of pathologist/oncologist time
- Missed treatment opportunities
- Inappropriate treatment decision
Diagnosis
Oncology Consult
Following Diagnosis
Biomarker Report
Completion
Treatment
Diagnosis
Oncology Consult
Following Diagnosis
Biomarker Report
Completion
Treatment

Median turnaround time: 64 days

Biomarkers available at oncology consult: 17%
Consequences of Inefficient Biomarker Testing

The mortality rate of untreated advanced NSCLC is 4% per week\(^1\)

Median life expectancy for stage IV NSCLC is 16 weeks\(^2\)


Updated Molecular Testing Guideline for the Selection of Lung Cancer Patients for Treatment With Targeted Tyrosine Kinase Inhibitors

3.1. **Expert consensus opinion:** EGFR and ALK results should be available within two weeks (10 working days) of receiving the specimen in the testing laboratory.

3.2. **Expert consensus opinion:** Laboratories with average turnaround times beyond two weeks need to make available a more rapid test—either in house or through a reference laboratory—in instances of clinical urgency.

3.3. **Expert consensus opinion:** Laboratory departments should establish processes to ensure that specimens that have a final histopathological diagnosis are sent to outside molecular pathology laboratories within 3 working days of receiving requests and to intramural molecular pathology laboratories within 24 hours.
FIGURE 2.9 Age-standardized mortality rates (ASMR) for selected cancers, females, Canada, 1984–2019
DIAGNOSIS

BREAST (RIGHT, 7 O’CLOCK), NEEDLE BIOPSY:
- INVASIVE DUCTAL CARCINOMA.
- Preliminary grade: 2 (tubules 3, nuclei 2, mitoses 1).
- Biomarkers:
  ER: POSITIVE (3+ staining in 100% of tumor nuclei; Allred 8).
  PR: POSITIVE (3+ staining in 100% of tumor nuclei; Allred 8).
  HER2: negative (IHC 1+).
DIAGNOSIS

BREAST (LEFT, LESION A), NEEDLE BIOPSY:
- INVASIVE DUCTAL CARCINOMA.
1. Preliminary grade: 3 (tubules 3, mitoses 3, nuclei 3).
2. Biomarkers:
   ER: negative (no staining present, no internal control present; Allred 0).
   PR: negative (no staining present, no internal control present; Allred 0).
   HER2: negative (IHC 0).
   Ki67: HIGH (nearly 100% tumor cell labelling).

COMMENT: The tumor shows a triple negative (ER-/PR-/HER2-) immunophenotype. No internal control is present for ER and PR stains, repeat testing on a subsequent specimen is recommended. Clinical correlation is required in determining the need for BRCA1/2 testing.
Point of care
For anatomic pathologists

One facility.
One pathologist.
One report.
Canadian testing recommendations
Immunohistochemistry as a Practical Tool in Molecular Pathology

PD-L1

BRAF V600E

panTRK

ALK

ROS
Canadian testing recommendations
Canadian testing recommendations
Canadian testing recommendations
Point of care
For anatomic pathologists

Order
Interpret

Report

One facility. One pathologist. One report.
Median Turnaround Time:
64 days
4 days

Biomarkers Available at Oncology Consult:
17%
94%
Cancer diagnosis with biomarkers → Oncology consult
E. LYMPH NODE (STATION 7), BIOPSY:
   - POSITIVE FOR METASTATIC NON-SMALL CELL LUNG CARCINOMA.
   - Favour adenocarcinoma (TTF1+, p40-).

LUNG BIOMARKERS:

EGFR: POSITIVE (L858R).
   - Cellularity: moderate
   - Estimated tumor content: 50%

PD-L1: low-level expression (tumor proportion score 1-49%).
   - Estimated tumor proportion score: 5%

ALK: negative.

BRAF V600E: negative.

ROS: negative.

INTERPRETATION: The sample demonstrates an activating mutation in the EGFR gene leading to the p. Leu858Arg protein change. The alteration is amenable to treatment with EGFR tyrosine kinase inhibitor therapy, if clinically indicated.
DIAGNOSIS

A. COLON (RECTOSIGMOID), ANTERIOR RESECTION:
   - INVASIVE ADENOCARCINOMA.
   1. Moderately differentiated (low-grade).
   2. Completely excised.
      - Proximal, distal, and radial margins clear.
      - Please see comment.
   3. Carcinoma invades through the mucularis propria, into pericolonic fat.
   4. Fifteen lymph nodes are identified.
      - Three tumor deposits are identified.
         - No definite nodal tissue is associated with the deposits.
         - Largest deposit measures 3.5 cm (see comment).
         - pN1c
         - No metastasis is identified within the 15 nodes (0/15).
   5. The tumor shows intact (wild-type) expression of MMR proteins.
   6. No mutation is identified in KRAS, NRAS, or BRAF (see below).
DIAGNOSIS

LYMPH NODE (7), BIOPSY:
- POSITIVE FOR METASTATIC MELANOMA.

COMMENT: The specimen contains malignant epithelioid-appearing cells. Pigment is present, and this is favoured to represent anthracosis. By immunohistochemistry, the lesional cells show strong and diffuse immunoreactivity for SOX10. There is no immunoreactivity identified for TTF1 or p40. The features support a diagnosis of metastatic melanoma. An activating BRAF mutation has been identified (see below).
But what about the rest?

KRAS, MET, ERBB2, RET, NRG1 ...
The benefits of NGS in your institution

- Comprehensive and actionable results, communicated clearly from one source
- Results in one report within days, not weeks
- Can be customized to the materials present at your centre: EBUS, surgical, etc.
- Cost saving for healthcare system, hospital, and patient
**Point of care**
Next-generation sequencing (NGS)

One facility. One pathologist. One report.
### Relevant Non-Small Cell Lung Cancer Findings

<table>
<thead>
<tr>
<th>Gene</th>
<th>Finding</th>
<th>Gene</th>
<th>Finding</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALK</td>
<td>Not detected</td>
<td>NTRK1</td>
<td>Not detected</td>
</tr>
<tr>
<td>BRAF</td>
<td>Not detected</td>
<td>NTRK2</td>
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</tr>
<tr>
<td>EGFR</td>
<td>Not detected</td>
<td>NTRK3</td>
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<tr>
<td>ERBB2</td>
<td>Not detected</td>
<td>RET</td>
<td>Not detected</td>
</tr>
<tr>
<td>KRAS</td>
<td>Not detected</td>
<td>ROS1</td>
<td>Not detected</td>
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<tr>
<td>MET</td>
<td><strong>MET exon 14 skipping</strong>, <strong>MET positive</strong></td>
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### Variant Details

#### DNA Sequence Variants

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<tr>
<th>Gene</th>
<th>Amino Acid Change</th>
<th>Coding</th>
<th>Variant ID</th>
<th>Locus</th>
<th>Allele Frequency</th>
<th>Transcript</th>
<th>Variant Effect</th>
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</thead>
<tbody>
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<td>PIK3CA</td>
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</table>

#### Gene Fusions (RNA)

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<th>Variant ID</th>
<th>Locus</th>
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<tr>
<td>MET-MET</td>
<td>MET-MET.M13M15.1</td>
<td>chr7:116411708 - chr7:116414935</td>
</tr>
</tbody>
</table>
What’s good for patients also saves money

Reduced oncology visits

Reduced number of times a pathologist assesses any given case

Elimination of:
- Extra accessioning
- Additional reporting / transcription
- Shipping

Conclusions

1. Anatomic pathologists play a critical role in cancer care – diagnostics

2. The role of the pathologist in treatment determination is under appreciated

3. Introducing point of care testing to the pathology lab, including IHC, and NGS can have a deep and meaningful impact on patient care

4. The role of the pathologist is evolving:
The pathologist is more than simply a diagnostician, but a medical expert charged with the task of integrating all available laboratory data to support patients through their journey
Point of Care Molecular Testing
Clinician Perspective

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Head of Cancer research
William Osler Health System

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Disclosures

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Overview

1. Review the evolving uses of molecular testing in treating patients with cancer, using lung cancer as the example

2. Clinical impact of point of care molecular testing

3. Evolving role of close pathology and molecular oncology collaboration
Molecular profiling is standard of care for patients with advanced NSCLC

Up to 60% of lung adenocarcinoma have a known oncogenic driver mutation
ASCO & NCCN recommendations for molecular oncogenic driven NSCLC

**EGFR**
- osimertinib (preferred) or
- erlotinib or
- afatinib or
- gefitinib or
- dacomtinib

**ALK**
- alectinib (preferred) or
  - brigatinib or
  - ceritinib or
  - crizotinib

**ROS-1**
- crizotinib or
- ceritinib

**BRAF**
- dabrafenib and trametinib

**Progression – switch therapy**

**T790M+**
- osimertinib

- Local therapy, continuation of therapy, or cytotoxic systemic therapy

Canadian guidelines on biomarker testing in NSCLC

50% of patients never get more than one line of therapy
Molecular profiling is standard of care for patients with advanced NSCLC

At time of diagnosis
NGS can be more sensitive than other tests

| 60M, never smoker, adenocarcinoma NSCLC | EGFR negative, ALK negative, PD-L1 1-49% |

**EGFR Mutational Analysis:** No mutation detected, wild-type EGFR allele
RESULTS:

Single nucleotide variants:
EGFR ENSP00000275493.2:p.Gly719Cys (ENST00000275493.2:c.2155G>T)

Insertions/deletions:
No reportable INDELs with known clinical significance were detected.

Copy number variants:
No reportable CNVs with known clinical significance were detected.

INTERPRETATION:
POSITIVE for variant(s) in EGFR.
Molecular profiling in NSCLC is evolving

Reevaluate throughout cancer journey
“Resistance mutations”
“Discovery of new mutations”
Mechanisms of acquired resistance to 1st/2nd gen EGFR TKIs

The most common acquired resistance mechanisms are:

1. Target gene modification (EGFR)
2. Alternative pathway activation (HER2, MET, BRAF, PIK3CA)
3. Histological or phenotypic transformation (EMT or SCLC)

- EGFR alteration (T790M) 60%
- HER2 amplification, 2-13%
- MET amplification, 5%
- SCLC transformation, 5%
- EMT, 2%
- PIK3CA, 1-2%
- BRAF, 1%
- Unknown, 15%
Targeting T790M resistance mutation with osimertinib in T790M+ NSCLC improved outcomes compared to chemotherapy.

Progression Free Survival (Months)

<table>
<thead>
<tr>
<th></th>
<th>Progression Free Survival (Months)</th>
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<tbody>
<tr>
<td>Osimertinib</td>
<td>10.1</td>
</tr>
<tr>
<td>Platinum-pemetrexed</td>
<td>4.4</td>
</tr>
</tbody>
</table>

Hazard ratio for disease progression or death, 0.30 (95% CI, 0.23–0.41) \( P<0.001 \)


Population: intent-to-treat

PFS defined as time from randomization until date of objective disease progression or death. Progression included deaths in absence of RECIST progression. Tick Marks indicate censored data; CI, confidence interval; mPFS, median progression free survival.
ASCO and NCCN recommendations for molecular oncogenic-driven NSCLC


---

- **EGFR**
  - T790M+
    - osimertinib
  - EGFR mutation
    - osimertinib (preferred)
      - erlotinib
      - afatinib
      - gefitinib
      - dacomitinib

- **ALK**
  - ALK rearrangement
    - alectinib (preferred)
      - brigatinib
      - ceritinib
      - crizotinib
  - T790M+ mutation
    - osimertinib

- **ROS-1**
  - ROS-1 rearrangement
    - crizotinib
    - ceritinib

- **BRAF**
  - BRAF mutation
    - dabrafenib and trametinib

---

**Progression – switch therapy**

- **EGFR**
  - T790M+ mutation
    - osimertinib

- **ALK**
  - ALK rearrangement
    - alectinib (preferred)
      - brigatinib
      - ceritinib
      - crizotinib

- **ROS-1**
  - ROS-1 rearrangement
    - crizotinib
    - ceritinib

- **BRAF**
  - BRAF mutation
    - dabrafenib and trametinib

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Local therapy, continuation of therapy or cytotoxic systemic therapy

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Multiple ALK inhibitors for treatment of ALK+ NSCLC

How do you select the right drug for the patient?

Patient with metastatic ALK+ NSCLC → Crizotinib → Second-line ALK TKI therapy → Third-line (+ beyond) ALK TKI therapy

Approved agents
- Ceritinib\(^a\)
- Alectinib\(^a\)
- Brigatinib\(^b\)

Investigational agents
- Lorlatinib
- Ensartinib

\(^{a}\)Approved in Canada, the European Union, and the United States; \(^{b}\)Approved in Canada and the United States.

ALK, anaplastic lymphoma kinase; NSCLC, non-small cell lung cancer; TKI, tyrosine kinase inhibitor.
Secondary mutations can arise in the ALK tyrosine kinase domain.
### Variations in sensitivities to ALK-resistance mutations

<table>
<thead>
<tr>
<th>EML4-ALK mutation</th>
<th>Crizotinib</th>
<th>Ceritinib</th>
<th>Alectinib</th>
<th>Brigatinib</th>
<th>Lorlatinib</th>
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<tbody>
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<tr>
<td>D1203N + E1210K</td>
<td>I</td>
<td>I</td>
<td>I</td>
<td>S</td>
<td>S</td>
</tr>
</tbody>
</table>

**L1198F/C1156Y is lorlatinib resistant but crizotinib sensitive ALK mutation**

I, intermediate (IC\textsubscript{50} > 50 < 200 nmol/L); R, resistant (IC\textsubscript{50} ≥ 200 nmol/L); S, sensitive (IC\textsubscript{50} ≤ 50 nmol/L)

*Should we be rebiopsing patients for resistance mutations?*

35M with ROS1+ NSCLC on crizotinib
ROS1, NSCLC, and evolving role of NGS?

1st-LINE SYSTEMIC THERAPY

2nd-LINE SYSTEMIC THERAPY

ROS1 Rearrangement

Crizotinib

Future?

ROS1 Rearrangement

Entrectinib
Lorlatinib
Repotrectinib

Rebiopsy or Liquid biopsy
G2302R

Repotrectinib
Balancing limited tissue with the growing number of mutations to be tested

**Recommended for routine assessment**

- **EGFR**<sup>[1]</sup>: 13%
- **ALK**<sup>[1]</sup>: 5%
- **ROS1**<sup>[1]</sup>: 2%

**Recommended for further characterization as all have corresponding drugs in development**

- **KRAS**<sup>[1]</sup>: [V, A, L, U...]
- **MET**<sup>+</sup><sup>[1]</sup>: <[V, A, L...]
- **BRAF**<sup>[1]</sup>: 1% - 5%
- **RET**<sup>+</sup><sup>[1]</sup>: <1%
- **ERRB2**<sup>[1]</sup>: 4%

*Next generation sequencing preferred for detection, according to CAP/IASLC/AMP<sup>5</sup>*


“A new responsibility for pathologists ... is to manage small specimens strategically so there is sufficient tissue preserved for molecular studies.”<sup>3</sup>
Role of plasma based NGS advancing access to broad molecular testing

- 30% of patients have inadequate tumour tissue for molecular analysis at diagnosis
- Repeat biopsies are not feasible ~20% of patients with advanced NSCLC
- ~25% repeat biopsies fail to yield sufficient material for genomic analysis

Blood-based NGS has the potential to overcome some of the limitations associated with tissue collection and testing, which may enable clinicians to offer more effective personalised therapies.
Potential clinical applications of liquid biopsy and circulating DNA

Liquid biopsy is a **non-invasive**, easily repeatable sampling approach that collects peripheral blood containing cfDNA for analysis.¹

ctDNA is an established surrogate marker for monitoring disease burden and anticancer therapy response and has many other **possible clinical applications**.²,³

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Optimal state – point of care molecular testing

Cancer diagnosis with biomarkers

Oncology consult
In-house biomarker testing prevented missed opportunity for treatment

- Diagnosed w/ squamous cell NSCLC but was a non-smoker
- EGFR testing <24 hours of seeing Oncologist
- EGFR L858R + mutation found
- In 3 business days from seeing oncologist, patient was on targeted treatment

At this timepoint, with sending testing out, patient would have still been waiting for biomarker results
Timely biomarker results allows for appropriate treatment

**55F with ALK + NSCLC**

Started on targeted therapy instead of radiation to the whole brain +/- surgery

17 months after starting targeted therapy, complete response to brain lesion

**No radiation or surgery was done**
Point of care molecular testing

One facility. One pathologist. One report.
One report for diagnostic and molecular results optimizes treatment selection

1. 72F Asian, life-time non smoker

2. Malignant pleural effusion, pulmonary metastases

3. Adenocarcinoma:
   - Driver mutations: EGFR/ALK/ROS1 negative
   - Biomarkers: PDL1 >50%

Patient would get immunotherapy based on this information
Point of care NGS is needed to offer most effective therapy for patients

50% of patients do NOT get to a subsequent therapy

Baseline

3 months later
Case – impact of piecemeal broad molecular testing results

1. 46F, life-time nonsmoker history presents with persistent cough -> hemoptysis

2. Imaging shows large lung mass, mediastinal lymphadenopathy, bone metastases, and 1.1 cm brain metastasis; non squamous NSCLC

3. EGFR-/ALK-/PD-L1 > 50%

Treatment:

- Platinum doublet x 2 cycles
- Switched to pembrolizumab x 3 months, progression with new malignant pericardial effusion, new bone lesions, and increasing mediastinal adenopathy.
- Referred to Osler for clinical trials
- On presentation: in wheelchair, ECOG 2, on oxygen
- Plan: liquid NGS biopsy, repeat EBUS bx for inclusion into clinical trial
Molecular report

<table>
<thead>
<tr>
<th>Tumor Type: Lung Non-Small Cell Lung Carcinoma (NOS)</th>
</tr>
</thead>
</table>

Genomic Alterations Identified†

- RET KIF5B-RET fusion
- CDK4 amplification – equivocal‡
- TP53 E285K

On selpercatinib
One report of diagnostics and biomarkers

Move away from addendums

**DIAGNOSIS**

A. LIVER, EUS BIOPSY:
   - POSITIVE FOR METASTATIC NON-SMALL CELL CARCINOMA.

B. LYMPH NODE (7), EUS BIOPSY:
   - POSITIVE FOR METASTATIC NON-SMALL CELL CARCINOMA.
   - Favour pulmonary adenocarcinoma.

**LUNG BIOMARKERS:**

**EGFR:**
   - POSITIVE (exon 20 insertion)
     - Cellularity: low
     - Estimated tumor content: 10%
     - Please see comment.

**PD-L1:**
   - low-level expression (tumor proportion score 1-49%).
     - Estimated tumor proportion score: Please see comment.

**ALK:**
   - negative.

**BRAF V600E:**
   - negative.

**ROS:**
   - negative.

**COMMENT:** The tumor shows an activating EGFR exon 20 insertion. This type of activating mutation may show an attenuated response to EGFR inhibitors compared to more classical activating mutations.
**Interpretation by oncologists needs to be considered**

### Genomic Alterations Identified

<table>
<thead>
<tr>
<th>Gene</th>
<th>Alteration</th>
</tr>
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<tr>
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<tr>
<td>TP53</td>
<td>R273H</td>
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<tr>
<td>MET</td>
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### Variants of Unknown Significance Identified

<table>
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<th>Alteration</th>
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<tbody>
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<td>ERBB2</td>
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<td>CDK4</td>
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## Relevant Non-Small Cell Lung Cancer Findings

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<tr>
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</tr>
<tr>
<td>MET</td>
<td><em>MET exon 14 skipping, MET positive</em></td>
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</tr>
</tbody>
</table>
How do you treat this EGFR mutation?

1. **EGFR c.2369C>T**
2. **EGFR g. 7:55249071C>T**
3. **EGFR T790M mutation**
   Compatible with language of clinical trials for targeted therapies
Driver mutations/alterations and evolving targets with multiple promising agents

<table>
<thead>
<tr>
<th>Driver Mutations/Alterations</th>
<th>EGFR</th>
<th>EGFR T790 M</th>
<th>ALK</th>
<th>ROS1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Osimertinib/Afatinib/Gefitinib</td>
<td>Osimertinib</td>
<td>Alectinib, Lorlatinib, Certinib, Brigatinib, Ensartinib, Crizotinib</td>
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</tr>
<tr>
<td>Crizotinib, Lorlatinib, Repotrectinib, Entrectinib</td>
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<tr>
<td>Dabrafenib/Trametinib</td>
<td>Larotrectinib, Entrectinib</td>
<td>Selpercatinib, Pralsetinib</td>
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<tr>
<td>Capmatinib, Tepotinib, Crizotinib</td>
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</tbody>
</table>

Up and coming targeted therapies for the following drivers

- KRAS G12C
- HER2 mutations/amplifications
- Exon 20 insertion
- NRG1
- NRG1
Timely molecular testing in oncology is critical for treatment decisions
Providing the diagnosis without complete molecular information can lead to delays in treatment or patients receiving suboptimal treatment or no treatment at all.

1. In house testing is an option to improves turn around time for cancer programs.

2. Introducing **point of care** testing to the pathology lab, including IHC, and NGS can have a deep and meaningful impact on patient care.

3. The relationship of the medical oncologist and pathologist is evolving, and increased collaboration is required to optimize outcomes of patients.

4. The collaboration starts in the lab!
Thank you

Please visit our exhibit for more information or to speak with a representative