Positive Quality Intervention: Selpercatinib (Retevmo®) Genomic Testing Management

**Description:** This PQI is developed to provide guidance to genomic testing with respect to selpercatinib.

**Background:** RET-altered cancers include both RET fusions and RET mutations. Both alterations involve activating RET signaling pathways that promote unwanted cell proliferation in cancers. NCCN guidelines for NSCLC include a Category 2A recommendation for RET testing as part of broad molecular profiling in routine clinical practice. In multiple guidelines, RET testing is considered as part of a larger initial panel or secondary single analyte test following negative results for other genetic variants such as EGFR, ALK, and ROS1. Molecular testing within RET-mutated medullary thyroid cancer (MTC) is applicable as approximately 50% of patients with sporadic MTC have somatic RET mutations. In American Thyroid Association, NCCN, and ESMO guidelines, RET testing should be considered within the MTC space. Next generation sequencing (NGS) analyzes DNA and/or RNA when detecting RET. This method requires a small amount of tissue for multiplex testing for many common and rare cancer-related biomarkers. Tissue testing is often considered as RET alteration may not be found in the blood through liquid biopsy and up to 30% of RET alterations can be missed if only ctDNA is tested. There are multiple testing methods for RET that will help determine patient eligibility for selpercatinib, noting that indicated tumor types are associated with specific alterations (Review Supplemental Information section for approved indications).

<table>
<thead>
<tr>
<th>RET alteration to test</th>
<th>Associated tumor type(s)</th>
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<tbody>
<tr>
<td>RET-fusion</td>
<td>NSCLC, Thyroid</td>
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<tr>
<td>RET-mutation</td>
<td>MTC</td>
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</tbody>
</table>

*FDA-approved companion diagnostic tests for RET-fusion and RET-mutation alterations in plasma or other solid tumors other than NSCLC and MTC are not currently available

**PQI Process:**

- Consider the following preferred testing methods when planning for RET genomic testing:
  - Perform NGS when applicable
    - Account for 2-4 weeks for test completion
    - Both DNA and RNA-based NGS testing methods are appropriate and care team should discuss the general advantages and disadvantages of both
      - RNA-based NGS is able to reveal unbiased fusion information and there are no intron coverage issues
  - Reverse Transcription-PCR
    - Quick and relatively inexpensive; test completion with 1-2 days
    - PCR testing is designed predominantly for fusions and RET fusion frequency is underestimated
  - FISH
    - High rate of false positive/false negative
    - Should only be considered in rare circumstances (eg., if NGS/RT-PCR are not available)

**Patient-Centered Activities:**

- Provide education to patients regarding genetic testing and what to expect
- Provide testing schedule to patient
- Refer to [Selpercatinib (Retevmo®) Management PQI](#) and [Oral Chemotherapy Education (OCE) Sheet](#)
- Patient Assistance: [NCODA Financial Assistance Tool](#)

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Supplementary Information:
Selpercatinib is a kinase inhibitor indicated for the treatment of
- Adult patients with metastatic RET fusion-positive non-small cell lung cancer (NSCLC)*
- Adult and pediatric patients 12 years of age and older with advanced or metastatic RET-mutant medullary thyroid cancer (MTC) who require systemic therapy*
- Adult and pediatric patients 12 years of age and older with advanced or metastatic RET fusion-positive thyroid cancer who require systemic therapy and who are radioactive iodine-refractory (if radioactive iodine is appropriate)*

*Approved under accelerated approval based on overall response rate and duration of response3

References:
3. RETEVMO® [package insert]. Lilly USA, LLC, Indianapolis, IN.