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Positive Quality Intervention: Pharmacist's role in the interpretation and application of Next-Generation Sequencing (NGS)

Description: The purpose of this PQI is to provide recommendations for how to interpret and apply NGS results to patient care and demonstrate why the pharmacist is an important part of the precision medicine team.

Background: Genomic testing is essential for patients with advanced or metastatic solid tumors and many hematologic malignancies. By utilizing massive parallel sequencing, numerous cancer-related genes can be simultaneously analyzed for genomic abnormalities, creating a comprehensive molecular profile of a patient's malignancy. Next-generation sequencing (NGS) is now considered the standard of care for patients with advanced or metastatic tumors. The presence or absence of specific molecular alterations or genomic features helps determine if a patient meets FDA-approved criteria for targeted therapies in both first-line and subsequent treatment settings. This molecular profile also guides clinical trial eligibility and contributes to a more precise characterization of the disease. NGS results are integral to the entire treatment team's decision-making process. Pathologists rely on this information to refine diagnoses, genetic counselors use it to assess disease risk and recommend further testing, pharmacists apply it to suggest therapeutic strategies, and physicians incorporate it into their clinical decisions and discussions with patients. Pharmacists, in particular, focus on the therapeutic implications of NGS results, especially when selecting appropriate therapies and identifying opportunities for genome-guided clinical trials that match patients with suitable trials. Interpreting and applying NGS results is a complex process that involves multiple steps and considerations. These factors must be carefully weighed in therapeutic decision-making and other aspects of clinical care. This PQI will provide guidance on how to interpret and apply NGS results to inform patient care, with a particular emphasis on the role of the pharmacist.

PQI Process:

- Consider the Patient, Clinical Questions, and Treatment Goals
  - Understand the patient and their goals: Evaluate their cancer type, stage, prior therapies, comorbidities, and treatment goals to tailor the NGS analysis to their unique situation.
  - Establish clinical objectives for NGS testing:
    - Identify FDA-approved targeted therapies for the cancer type.
    - Determine eligibility for clinical trials (both current and for future lines of treatment).
    - Characterize their disease for diagnosis, classification, and/or prognosis.
  - Review any prior NGS or molecular testing results: Ensure comprehensive evaluation and provide a basis for comparison.
- Understand the NGS Test Specifications
  - Gene coverage: Verify that the test covers relevant genes and note which potentially important genes are not covered.
  - Test composition: Determine if the test analyzes DNA + RNA (better for detecting gene fusions) or DNA only (where fusion detection may be limited).
  - Review the NGS report including the appendix: Understand the specific test methodology, including any limitations mentioned.
  - Test type: Confirm whether the test uses tumor tissue or ctDNA from blood ("liquid biopsy") and its implications for result interpretation.
- Evaluate and Interpret NGS Results
  - Interpret specific genomic alterations[1]: Assess the known or predicted impact of the reported alterations on protein expression/function and review clinical data on the efficacy of targeted

therapies for these genomic alterations.
    - Clinical correlation: Ensure the results align with the patient's clinical history (e.g., diagnosis, prior treatments, and current treatments).
    - Diagnostic and prognostic information: Identify genetic alterations that provide relevant diagnostic or prognostic insights.
    - Therapeutic implications:
        - FDA-approved therapies: Identify if any detected alterations are associated with FDA-approved therapies in the diagnosed cancer type and where they fit into the treatment algorithm (first-line, second-line, etc.).
        - Clinical trial eligibility: Assess eligibility for both local and national clinical trials based on the patient's disease state and ability to travel.
        - Tumor-agnostic therapies: Evaluate potential therapies for biomarkers such as TMB, MSI, and specific gene fusions, which may provide a tumor-agnostic indication.
- Germline Alterations: Recognize alterations that are suspicious for clinically significant germline mutations (e.g., *TP53*, *BRCA1/2*, MMR genes) that can affect disease risk and may necessitate referral for genetic counseling and hereditary testing.
- Other Considerations:
    - Clonal hematopoiesis (CHIP/CCUS): Identify alterations that may be indicative of clonal hematopoiesis rather than derived from the tumor. Somatic mutations, typically of myeloid malignancy associated genes (e.g. *DNMT3A*, *TET2*, and *ASXL1*) derived from a non-tumor source, such as the blood are an indication of CHIP or CCUS based on the absence (CHIP) or presence (CCUS) of persistent cytopenias[2].
    - Re-testing or molecular profiling: Determine if and when re-testing or additional molecular profiling is needed (e.g., disease progression, treatment failure, targetable acquired resistance mutations).
- Engage with a Molecular Tumor Board (MTB)
    - Collaboration: Work with the multidisciplinary MTB to discuss complex NGS results and refine treatment options.
    - Treatment refinement: Incorporate MTB consensus on potential therapies, trial eligibility, and novel treatment strategies based on the patient's unique molecular profile.
- Summarize and Communicate Results
    - Clear and concise summary: Present NGS findings in a clear, actionable format for the oncology care team.
    - Actionable insights: Highlight clinically relevant alterations and therapeutic options, emphasizing those that may significantly impact therapy selection.
    - Implications for further testing: Communicate the need for any follow-up testing (e.g., germline mutations) and how the results may affect ongoing treatment decisions.

Patient-Centered Activities:

- Somatic vs. Germline Mutations: Explain the difference between somatic mutations (acquired mutations specific to the cancer cells) and germline mutations (inherited mutations potentially affecting personal/family risk).
- Cancer Therapies: Clarify the differences between targeted therapy, chemotherapy, and immunotherapy, and how NGS results may guide specific treatment choices.
- Clinical Trials: Discuss potential clinical trial opportunities based on NGS findings and how they may offer access to new therapies.

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2. Khoury JD, Solary E, Abla O, et al. The 5th edition of the World Health Organization Classification of Haematolymphoid Tumours: Myeloid and Histiocytic/Dendritic Neoplasms. Leukemia. 2022 Jul;36(7):1703-1719.