A Paradigm Shift in Non-Small-Cell Lung Cancer (NSCLC) Diagnostics: From Single Gene Tests to Comprehensive Genomic Profiling

Cancer Informatics
Volume 23: 1–2
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DOI: 10.1177/11769351241243243

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ABSTRACT: Lung cancer imposes a burden on the health care system worldwide affecting 2 million people and causing 1.8 million deaths in 2021.More than 85% of all lung cancer cases are reported under Non-small-cell lung cancer (NSCLC). It is critical to discover gene alterations to treat non-small cell lung cancer successfully. The CAP/IASLC/AMP recommendations supported use of polymerase chain reaction (PCR) and fluorescent in situ hybridization (FISH) *EGFR* (epidermal growth factor receptor) mutations and *ALK* (Anaplastic lymphoma kinase) rearrangements, respectively. A study presented in the annual meeting of the American Society of Clinical Oncology (ASCO) in Chicago emphasized the need for comprehensive genomic profiling (CGP) before single gene tests (SGTs) since it demonstrated that SGT can result in the depletion of precious biopsy samples. As a result, the efficacy of thorough genetic Profiling (CGP) is reduced, preventing patients from receiving valuable genetic information about their tumors.

KEYWORDS: Comprehensive genomic profiling, lung cancer, single gene test, NSCLC, diagnostics

RECEIVED: December 1, 2023. **ACCEPTED:** March 4, 2024.

TYPE: Short Communication

FUNDING: The author(s) received no financial support for the research, authorship, and/or publication of this article.

DECLARATION OF CONFLICTING INTERESTS: The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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One of the most common causes of cancer-related deaths worldwide is lung cancer, which has a significant impact on global health.[1] In both men and women, neoplasms of the lungs rank as the second most prevalent cancer diagnosis.[2] Based on histology there are 2 types of lung cancers, small-cell lung cancer and non-small cell lung cancer (NSCLC).[1] More than 80% to 85% of all lung cancer cases are caused by non-small-cell lung cancer (NSCLC). NSCLC is a broad term that includes adenocarcinoma, squamous cell carcinoma, and large cell carcinoma.[1] Mutations in the genes that are associated with includes *EGFR* (epidermal growth factor receptor), *ALK* (Anaplastic lymphoma kinase), *BRAF* (v-raf murine sarcoma viral oncogene homolog B), *MET* (mesenchymal epithelial transition), *ROS1* (c-ros oncogene 1), and *RET* (rearrangement during transfection) pathways are found in NSCLC.[3] NSCLC can be diagnosed by using imaging techniques (CT scan, PET-CT scan, MRI, and bone scan), biopsy, bronchoscopy, needle aspiration, thoracocentesis, thoracoscopy, mediastinoscopy, and thoracotomy.[4] Tissue biopsies are the gold standard test for diagnosing NSCLC but there is no gold standard test for detecting biomarkers. For an effective and successful treatment of NSCLC, it is essential to identify gene mutations. To identify these mutations several molecular testing techniques have been developed such as single gene diagnostic assays and multiplex testing for gene mutation.[5]

Single gene diagnostic assays use a single test to look for single gene mutation; it includes techniques like Sanger sequencing, immunohistochemistry (IHC), Reverse transcriptase-polymerase chain reaction (RT-PCR), and fluorescence in situ hybridization (FISH). Sanger sequencing was one of the earliest techniques to detect *KRAS* (Kirsten rat sarcoma viral oncogene homolog) and *EGFR* mutations. Sanger sequencing can determine the sequence of nucleotides in a DNA fragment but is inefficient for sequencing whole genes or cancer genomes.[6] IHC is used for identifying *EGFR* mutations. RT-PCR for fusion genes, it is specific for predefined fusion and can not detect alternate fusion partners. FISH can detect *ALK* and *ROS1* rearrangements, unlike RT-PCR it can detect fusion with variant partners.[6] As multiple mutations are found in cancer, single-gene tests result in the loss of valuable information from the sample of patients. In cancers like NSCLC obtaining biopsies from these patients is challenging. Single gene tests might be ineffective because of inadequate biopsy samples or DNA for diagnosis. So this reduces the chances of patients to get more personalized and effective treatment for his/her cancer type.

While multiplex panels with multiple hot spot tests use a single test to look for multiple gene mutations. It includes PCR, FISH, or NGS-based assays (Next-generation sequencing). The chances of failure to detect new mutations are high in multiplex hotspot testing as it is more focused toward a limited number of genes. It is worth noting that hotspot platforms are unable to detect 4 types of DNA cancer-related mutations, which include point mutations, small indels, copy number changes, and rearrangements. But these mutations can be diagnosed by hybrid capture-based NGS platforms, also called comprehensive genomic profiling (CGP) with great sensitivity and specificity making it an effective alternative to multiplex or hotspot testing.[7]

CGP assesses hundreds of genes looking for mutations and relevant biomarkers in a single assay.[8] Moreover, it has the ability to detect genomic signature burden of tumor mutational burden (TMB), microsatellite instability (MSI), and loss of heterozygosity (LOH) thereby maximizing the ability to identify actionable alterations.[9] It can identify most prevalent and rare mutations by comprehensive testing of genes thus reducing the need for sequential testing.[9] Although there are mutations that are shared by many tumors, an individual tumor may have distinct mutations. Therefore, a comprehensive screening of a wide range of mutations, which is tissue agnostic, can be helpful for a better understanding of disease progression and to inform more precise and effective personalized therapeutic interventions. Since CGP is used for the identification of effective therapy, it is ordered after a single gene test (SGT) when either it has negative results or the treatment has failed, this is a common practice observed in the oncology community.[10]

A study presented in June 2023 at the Annual Meeting of the American Society of Clinical Oncology (ASCO) Annual Meeting in Chicago emphasized the importance of CGP before SGTs as it showed that SGT can result in a depletion of valuable biopsy samples. As a consequence, this can hinder the efficacy of CGP, ultimately preventing patients from obtaining a comprehensive understanding of the genomic information relating to their tumors.[8] The study revealed that CGP was utilized as a secondary diagnostic method in 29% of the participants. Among these cases, 89% of the CGP tests used the same tumor sample as the primary SGT, leading to a decrease in the effectiveness of CGP. This was primarily due to the insufficient availability of viable tumor tissue for comprehensive testing. However, when SGT was not performed before CGP or when CGP utilized a distinct sample, it gave more comprehensive insights into the genomic makeup of the tumor.[8] Since CGP assesses the biomarkers in one glance and more clinical variants than SGT and hotspot NGS panels, this not only provides results faster but also uses limited biopsy samples therefore decreasing the costs and risks related to rebiopsy.[9]There may be some differences in the implementation of CGP between eastern and western countries due to variations in healthcare systems, regulations, and infrastructure. So, collaboration between researchers, clinicians, and policymakers from both eastern and western countries is essential for harmonizing CGP practices worldwide.

To summarize, the complex terrain of NSCLC, which includes several subtypes and genetic variants, needs a multifaceted approach to diagnosis and therapy selection. The identification of particular gene mutations is critical for guiding focused therapeutics, improving patient outcomes, and reducing the possibility of unsuccessful treatments. The use of CGP allows for the simultaneous examination of many biomarkers, resulting in a more complete picture of the tumor's genetic landscape. Healthcare providers may enhance patient outcomes by expediting the implementation of personalized treatment plans, lowering the need for repeat biopsies, and minimizing the need for repeated biopsies by integrating CGP as a primary diagnostic tool. Rapid advancement in diagnostic molecular profiling techniques helps us treat lung cancer according to the genetic profile of the patient. This provides a comprehensive picture of tumor markers making us one step closer toward effective and targeted treatment of cancer. This approach will reduce the burden of NSCLC worldwide. Hence new guidelines for the diagnosis of NSCLC should be formed.

Author Contributions

Ushna Zameer: reviewing. Wajiha Shaikh: writing. Abdul Moiz Khan: final reviewing.

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