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Comparative Evaluation of IHC and Molecular Techniques in Identifying Oncogenic Pathways

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Introduction

The identification of oncogenic pathways is fundamental to cancer diagnosis, classification, prognosis and targeted therapy. As the landscape of cancer diagnostics evolves, the integration of histological and molecular approaches has become increasingly essential. Among the most widely used methods are Immunohistochemistry (IHC) and molecular diagnostic techniques such as Polymerase Chain Reaction (PCR), Fluorescence *In Situ* Hybridization (FISH), Next-Generation Sequencing (NGS) and Comparative Genomic Hybridization (CGH). Each technique offers unique insights into tumor biology, but they also differ in sensitivity, specificity, contextual relevance and clinical applicability. A comparative evaluation of IHC and molecular techniques is crucial for understanding their complementary roles and selecting the most appropriate tools for identifying and characterizing oncogenic pathways across cancer types [1].

Description

Immunohistochemistry serves as a tissue-based assay that utilizes antigen–antibody interactions to detect specific proteins within Formalin-Fixed, Paraffin-Embedded (FFPE) tissue sections. IHC offers spatial resolution, enabling visualization of protein expression within the cellular and tissue architecture, which is particularly useful in heterogeneous tumors. This method is widely employed in routine pathology to assess markers such as HER2, p53, Ki-67 and PD-L1, which inform about oncogenic activation, proliferation status and immune checkpoint activity. IHC is relatively inexpensive, accessible and rapid, making it suitable for widespread clinical application. Moreover, it is especially valuable when protein expression itself is indicative of pathway activation, such as nuclear accumulation of β-catenin in Wnt pathway dysregulation or overexpression of EGFR in receptor tyrosine kinase signaling. In contrast, molecular techniques provide a direct assessment of genetic and epigenetic alterations that underlie oncogenesis. These include point mutations, insertions, deletions, gene fusions, copy number variations and aberrant methylation patterns. PCR-based assays are widely used for detecting hotspot mutations, such as those in KRAS, BRAF and EGFR. FISH enables visualization of gene amplifications or translocations, such as ALK rearrangements in lung cancer or HER2 amplification in breast cancer. More advanced platforms like NGS offer high-throughput, multiplexed analysis of entire oncogenic pathways by sequencing hundreds of genes simultaneously, revealing mutational signatures, clonal architecture and therapeutic vulnerabilities. NGS is particularly powerful in precision oncology, where matching targeted therapies to genomic profiles has transformed treatment paradigms [2,3].

While molecular techniques offer superior sensitivity and genetic granularity, they often lack spatial information, requiring dissociation of tissues or nucleic acid extraction that obliterates histological context. IHC, by contrast, preserves this context but may be limited by semi-quantitative interpretation and variable antibody specificity. Furthermore, IHC detects protein expression, which may not always correlate with genetic alterations. For instance, a gene mutation may not result in detectable protein changes, or post-translational modifications may activate oncogenic pathways without altering gene sequence. Conversely, protein overexpression detected by IHC may result from upstream signaling alterations, gene amplification, or epigenetic deregulation, not always captured by sequencing. These discrepancies underscore the importance of using both IHC and molecular techniques in a complementary fashion. For example, in breast cancer, HER2 status is initially assessed by IHC, with equivocal cases resolved by FISH. In colorectal cancer, mismatch repair protein expression is evaluated by IHC to screen for Lynch syndrome, followed by microsatellite instability testing or germline mutation analysis for confirmation. Similarly, the diagnosis of Ewing sarcoma often involves detection of EWSR1 translocations *via* FISH or RT-PCR, accompanied by IHC for CD99 and FLI1. These multimodal diagnostic strategies improve diagnostic accuracy, stratify patients for targeted treatments and avoid both overtreatment and undertreatment [4].

One of the most clinically impactful areas of convergence between IHC and molecular testing is in the detection of actionable mutations and pathway activity. For instance, IHC for phosphorylated mTOR or ERK may reflect PI3K/AKT/mTOR or RAS/MAPK pathway activation, providing functional readouts of upstream genetic changes. Similarly, IHC for IDH1 R132H in gliomas correlates with mutations identified via sequencing, allowing rapid screening before confirmatory molecular tests. In non-small cell lung cancer, IHC is increasingly used to detect ALK, ROS1 and NTRK fusions, with positive cases undergoing molecular confirmation. This tiered approach optimizes resource utilization while maintaining diagnostic robustness. Nevertheless, both IHC and molecular techniques face limitations. IHC interpretation may be subject to interobserver variability, influenced by staining quality, antigen retrieval and subjective scoring. Molecular methods, while highly sensitive, may suffer from false positives, especially in low-allele frequency variants or degraded samples. Turnaround time, cost and tissue requirements also influence their feasibility in clinical workflows. Therefore, selecting the appropriate method depends on clinical context, test availability, tumor type and the specific oncogenic alteration under investigation [5].

Conclusion

In conclusion, immunohistochemistry and molecular techniques offer distinct but complementary approaches to identifying oncogenic pathways. IHC provides valuable protein-level insights with histological resolution, while molecular diagnostics unveil the genetic architecture underlying tumor biology. When integrated thoughtfully, these methods enhance diagnostic precision, inform therapeutic decisions and facilitate biomarker-driven cancer care. As technology continues to evolve, the convergence of histopathology and genomics promises to redefine oncologic diagnostics, enabling more accurate, personalized and effective cancer management.

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Conflict of Interest

None.

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