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Commentary

Next-Generation Sequencing for Personalized Cancer Genomics

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DESCRIPTION

In the age of precision medicine, one technology stands at the forefront of cancer innovation: Next-Generation Sequencing (NGS). This revolutionary genomic tool has transformed the way we diagnose, classify, and treat cancer, offering unprecedented insight into the genetic underpinnings of tumors. But beyond being a research tool, NGS is now redefining clinical care ushering in an era of personalized cancer genomics, where treatment is tailored not to the tumor's location, but to its unique molecular fingerprint.

A genomic lens moving beyond traditional cancer classification

Traditionally, cancer has been classified by its anatomical origin lung, breast, colon, etc. and assessed by histology. While these methods have guided therapy for decades, they offer only a limited view. Two breast cancers may appear identical under the microscope, yet respond differently to treatment due to differences in their genomic makeup. NGS allows us to peer deeper, offering a high-resolution view of the mutations, copy number alterations, gene fusions, and expression profiles driving individual cancers.

NGS works by rapidly sequencing millions of DNA fragments in parallel, enabling comprehensive analysis of entire genomes (whole-genome sequencing), all coding regions (whole-exome sequencing), or targeted panels of cancer-related genes. This technology enables the detection of actionable mutations those that can be matched with existing targeted therapies or clinical trials. For example, identification of *EGFR* mutations in non-small cell lung cancer has led to the widespread use of *EGFR* inhibitors, drastically improving outcomes in selected patients.

Importantly, NGS doesn't just uncover well-known oncogenes or tumor suppressors it can also reveal rare or novel mutations that may otherwise go undetected. It can identify mutations associated with drug resistance, allowing oncologists to anticipate treatment failure and pivot to alternative therapies. In short, NGS provides a molecular blueprint of each patient's cancer one that's essential for precision medicine.

From bench to bedside personalizing treatment with NGS

The clinical impact of NGS is already evident across multiple cancers. In melanoma, sequencing for *BRAF* mutations guides the use of *BRAF* and MEK inhibitors. In colorectal cancer, NGS is used to identify *KRAS*, *NRAS*, and *BRAF* mutations, which influence eligibility for anti-*EGFR* based monoclonal antibody therapies. And in breast cancer, profiling *HER2* amplification, *PIK3CA* mutations, and *BRAC* 1/2 alterations informs a spectrum of targeted and PARP-inhibitor therapies.

Perhaps the most striking example of personalized genomics is seen in the approval of tissue-agnostic therapies. The U.S. FDA has approved drugs like pembrolizumab for tumors with high microsatellite instability or deficient mismatch repair, and larotrectinib for tumors harboring NTRK fusions regardless of tumor origin. These landmark decisions underscore a shift in cancer treatment: from organ-based models to molecularly defined categories. NGS also plays a crucial role in liquid biopsy, where tumor DNA fragments are sequenced from a blood sample. This minimally invasive approach can be used to monitor disease progression, detect minimal residual disease, and identify emerging resistance mutations in real time. This is a game-changer, especially for patients unable to undergo repeated tissue biopsies.

Moreover, in hematologic malignancies like leukemia and lymphoma, NGS has improved risk stratification and helped guide bone marrow transplant decisions, particularly through the detection of specific translocations and gene fusions. This enables clinicians to better assess prognosis and personalize therapeutic approaches early in the disease course.

Despite its promise, widespread adoption of NGS in clinical oncology is not without challenges. One key issue is interpretation. Sequencing data can reveal hundreds of mutations, many of which are classified as Variants of Unknown Significance (VUS). Determining which mutations are actionable and clinically relevant requires specialized expertise and curated databases. Another concern is cost and accessibility. While the price of NGS has dropped dramatically in the past decade, the infrastructure and expertise needed to implement

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and interpret sequencing remains a barrier in many healthcare systems, particularly in low- and middle-income countries.

There are also ethical and psychological implications. Incidental findings, such as germline mutations in cancer predisposition genes, may impact not only the patient but also their family members. Clinicians must be equipped to offer genetic counseling and navigate these sensitive situations. Artificial intelligence and machine learning are being employed to further interpret NGS data, integrate it with other clinical information, and predict outcomes. As these tools evolve, they will likely become indispensable in translating complex genomic data into real-time, actionable insights.

CONCLUSION

Next-generation sequencing is not just a technological advance it is a paradigm shift in how we understand and treat cancer. By revealing the molecular individuality of tumors, NGS has laid the foundation for personalized cancer genomics an approach that promises more effective treatments, fewer side effects, and better outcomes for patients. As we look ahead, the challenge will be to democratize access, improve interpretation, and integrate genomic insights seamlessly into routine care. If we meet these goals, we won't just treat cancer better we'll understand it more deeply, and one day, perhaps even outsmart it.