Harnessing the Power of Predictive Biomarkers in Precision Oncology

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Presenter's disclosures of conflicts of interest are found at the end of this article.

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Abstract

At JADPRO Live 2024, J. Kevin Hicks, PharmD, PhD, FCCP, highlighted advances in targeted therapies, liquid biopsies, and genetic profiling to improve outcomes in patients. He discussed the impact of trials such as FLAURA2 and MARIPOSA on refining treatment for *EGFR*-mutated NSCLC and the use of pharmacogenomics to guide dosing. Dr. Hicks also described the creation of an innovative cloud-based platform at Moffitt Cancer Center designed to organize genetic testing data and streamline clinical decisions.

In the era of precision medicine, molecular and genetic profiling is used to match therapies to individual patients based on unique characteristics. At JADPRO Live 2024, J. Kevin Hicks, PharmD, PhD, FCCP, Associate Member, Attending in the Precision Medicine Clinical Service, Director of Pharmacogenomics, and Chair of the Thoracic Molecular Tumor Board at Moffitt Cancer Center, explored the evolving role of biomarkers in guiding personalized treatment for cancer patients.

THE IMPORTANCE OF BIOMARKER TESTING

"Biomarker testing is important because it guides both therapeutic decision-making and clinical trial matching," Dr. Hicks stated.

With advances in somatic DNA sequencing, it is now possible to analyze hundreds to thousands of cancer-related genes to identify targetable mutations. RNA sequencing further aids in detecting fusion variants, while immunohistochemistry (IHC) markers such as PD-L1 and mismatch repair (MMR) help determine eligibility for immunotherapy.

Recent breakthroughs, such as the DESTINY-PanTumor02 trial, have expanded the role of HER2 IHC 3+ testing, allowing for trastuzumab deruxtecan (Enhertu) to be used across multiple solid tumors (Meric-Bernstam et al., 2024). Other biomarkers, including microsatellite instability (MSI) and tumor mutation burden (TMB), indicate favorable responses to immunotherapy, such as pembrolizumab (Keytruda). Emerging markers like loss of heterozygosity (LOH) are gaining prominence, particularly in gynecological cancers where they inform the use of PARP inhibitors.

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Germline testing, although sometimes overlooked, is also important to perform. Germline variants, such as *BRCA1/2* mutations, can inform treatment in pancreatic, prostate, breast, and gynecological cancers (Figure 1).

"In most instances, germline assays and somatic assays are not interchangeable, and we need to perform both," Dr. Hicks emphasized.

Pharmacogenetics is another consideration. One topic of current debate is dihydropyrimidine dehydrogenase (DPYD) testing, which helps guide fluoropyrimidine dosing to prevent severe toxicity and potential fatal outcomes in patients with *DPYD* mutations.

WHO SHOULD UNDERGO SOMATIC NGS?

Guidelines from the American Society of Clinical Oncology (ASCO) and National Comprehensive Cancer Network (NCCN) recommend NGS for patients with advanced or metastatic cancer, particularly when a targeted therapy is available or when test results could indicate resistance to certain treatments.

"These recommendations are constantly evolving, so for whichever tumor type you cover, it's a good idea to look at the updated NCCN Guidelines to determine if you should be doing somatic NGS for your patients," advised Dr. Hicks.

In addition to identifying eligible patients, there is the choice between tissue-based and liquid NGS. Tissue-based NGS remains the gold standard, offering higher accuracy and the ability to detect RNA fusions, which are especially relevant in lung adenocarcinoma. However, it requires an invasive biopsy, has a longer turnaround time, and can be difficult to repeat.

Liquid biopsies, which analyze circulating tumor DNA (ctDNA), are less invasive, quicker (often 7–10 days for results), and easier to repeat, making them useful for monitoring resistance mutations. Despite its advantages, liquid biopsy carries a higher risk of false negatives, especially when tumor DNA levels are low.

Some assays now report tumor fraction, indicating whether a low fraction increases the likelihood of a false negative. In such cases, tissue-based testing is needed to confirm the results.

"Within our thoracic clinic at Moffitt, we do both assays," Dr. Hicks commented.

TARGETABLE GENETIC ALTERATIONS IN LUNG CANCER

Targetable alterations in lung adenocarcinoma can serve as an example for understanding how biomarker testing is evolving and leading to more personalized treatment.

"One of the things about *EGFR* mutations that we realized is that one size doesn't fit all anymore," Dr. Hicks said. "Now, we have different classifications that are driving the different drugs that we select."

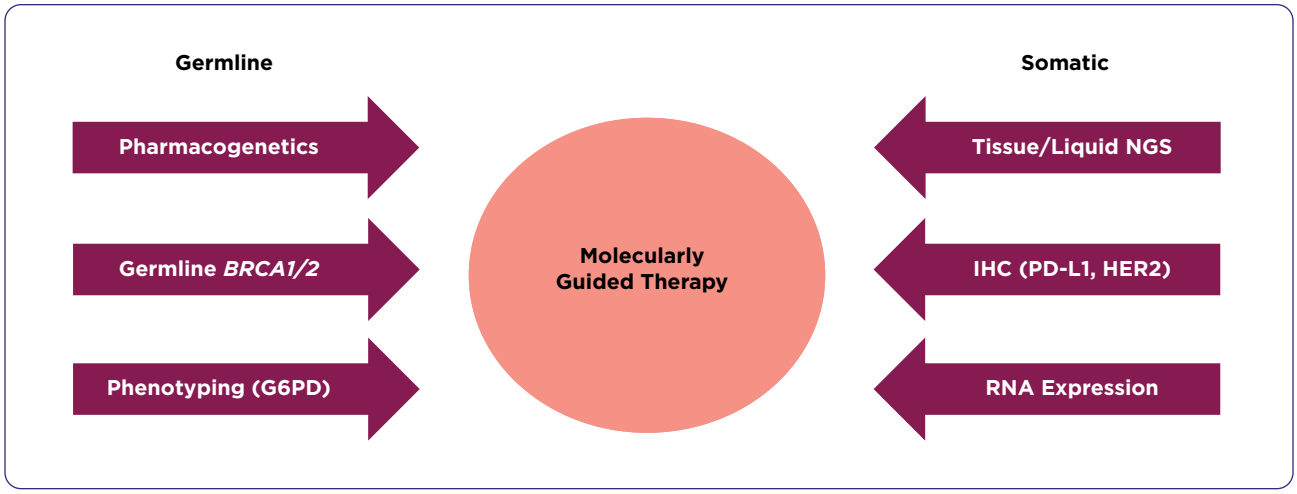

Figure 1. Precision medicine in oncology: consider both tumor and germline genomes. NGS = next-generation sequencing. Reproduced from Wang et al. (2011).

The most common *EGFR* mutations, L858R and exon 19 deletions, are classified as classical mutations, and almost any EGFR inhibitor is effective for these patients. EGFR exon 20 insertions and P-loop αC-helix compressing (PACC) mutations pose more treatment challenges.

Several recent trials have reshaped frontline treatment for *EGFR*-mutated NSCLC. The FLAURA trial showed that osimertinib (Tagrisso) significantly improved progression-free survival (PFS) compared to earlier EGFR tyrosine kinase inhibitors (TKIs) like erlotinib (Tarceva) and gefitinib (Iressa; 18.9 vs. 10.2 months) in the first line (Soria et al., 2018). The FLAURA2 trial showed that osimertinib with platinum/pemetrexed chemotherapy nearly doubled PFS in patients with brain metastases (24.9 months vs. 14 months with osimertinib alone; Planchard et al., 2023). The MARIPOSA trial introduced a new regimen, amivantamab (Rybrevant) plus lazertinib (Lazcluze), which showed superior PFS (23.7 months) over osimertinib (16 months) and improved outcomes in patients with brain metastases (18.3 vs. 13 months; Cho et al., 2024).

Selecting a frontline regimen remains challenging. The choice depends on patient preference, tumor characteristics, and the presence of brain metastases. Patients who want to avoid chemotherapy may opt for osimertinib alone, while those seeking aggressive treatment may benefit from combination therapies. Patients with co-mutations such as *TP53* or bypass signaling mutations (e.g., *ERBB2, NRAS, PIK3CA*) may benefit from combination therapies.

"In my opinion, where the data may be the clearest is if patients present with brain involvement and they have good performance status," Dr. Hicks noted. "That could be an indication to think about combination therapy in those patients, either osimertinib and chemotherapy, or amivantamab and lazertinib."

EGFR PACC mutations, including G719X, pose a challenge, as they reduce osimertinib binding efficiency. Although NCCN guidelines suggest any EGFR TKI, studies indicate that afatinib (Gilotrif) may offer greater sensitivity, with response rates around 70% compared to 35% to 55% with osimertinib. However, afatinib has poor CNS penetration, making osimertinib a preferred option for patients with brain metastases.

For *EGFR* exon 20 insertions, amivantamab, an EGFR-MET bispecific antibody, was initially approved for second-line therapy after platinum-based chemotherapy. The PAPILLON trial demonstrated that amivantamab and chemotherapy significantly improved PFS (11.4 months) compared to chemotherapy alone (6.7 months), making it a preferred frontline option (Zhou et al., 2023).

THE ROLE OF PHARMACOGENOMICS

Pharmacogenomics is the study of how genetic variations affect drug response. By identifying patients at risk of poor drug response, clinicians can adjust doses or select alternative treatments to optimize efficacy and minimize adverse effects.

One example Dr. Hicks presented was the impact of CYP2C19 genetic variants on voriconazole metabolism. Voriconazole is an antifungal used for prophylaxis and treatment in neutropenic acute myeloid leukemia patients undergoing induction or reinduction therapy.

Dr. Hicks explained, "Voriconazole is metabolized by CYP2C19 into less active compounds. CYP2C19 rapid or ultra-rapid metabolizers are at an increased risk of having low voriconazole levels."

It is estimated that 20% to 30% of patients are CYP2C19 rapid or ultra-rapid metabolizers, and therefore have an increased risk of breakthrough fungal infections. A plan at Moffitt started with obtaining support from providers to do CYP2C19 genotyping, asking pharmacy colleagues to manage dose adjustments independently, and requesting the pathology department to handle in-house CYP2C19 testing. This led to increased therapeutic levels of voriconazole in the population, prevention of breakthrough fungal infections, cost savings from preventing those infections, and no increase in toxicities (Hicks et al., 2019).

PRECISION MEDICINE AND CLINICAL WORKFLOW INTEGRATION

Moffitt Cancer Center has developed a structured approach to integrating precision medicine into clinical workflows.

As Dr. Hicks described, "Our solution at Moffitt is what's called the Moffitt Cancer Analytics Platform. This is a cloud-based data platform that has discrete data, designed to improve data curation, integration, and access."

The system extracts and organizes data from sources such as the EHR and NGS results, while an interpretive database helps match results with clinical trials. It also streamlines consult notes, reducing manual data entry. Weekly tumor board meetings including oncologists, advanced practitioners, pharmacists, molecular pathologists, and trial navigators facilitate collaborative decision-making.

CONCLUSION

Molecular profiling enables personalized treatment selection, leading to improved patient survival and quality of life. By harnessing the power of predictive biomarkers, precision oncology continues to evolve to offer patients better options for their disease. ●

Disclosure

Dr. Hicks has served on advisory boards for ARUP and Bristol Myers Squibb, and acted as a consultant for Jackson Laboratories.

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