EGFR Gene Testing
Routinizing genetic testing in clinical practice

Back in 2003, based on retrospective analysis on efficacy of gefitinib/erlotinib, in a single arm study of non-small cell lung cancer (NSCLC) patients, it was discovered that patients who had activating mutations in the kinase domain of EGFR responded well to targeted therapy with tyrosine kinase inhibitors as compared to those patients who did not have EGFR mutations. Also, the study noted that these mutations were common in never-smokers with adenocarcinoma histology. The most common mutations were exon 19 deletions and exon 21 L858R.

MedGenome testing for EGFR gene involves the analysis of tumor specimen to detect mutations in EGFR gene region of tumor DNA. It has become a gold standard technique for stratifying NSCLC patient to tyrosine kinase inhibitor.

Key Features of the test:

The exon 19 in-frame deletions and a point mutation in exon 21, L858R, account for >75% of the activating mutations, which are sensitive to Erlotinib, Gefitinib, Afatinib, Osimertinib and Dacomitinib.

Next generation sequencing (NGS) makes detection of rare activating mutations of EGFR, particularly the exon 19 deletions that are activating and equally sensitive to the TKI drugs.
Therapeutic Implications:

- Activation of EGFR signaling by mutations in the receptor drives tumor growth by promoting cell proliferation, invasion, angiogenesis, metastasis and inhibition of cell death.
- EGFR Mutation status can predict response to Tyrosine Kinase Inhibitors (TKIs)
- Activating EGFR mutations are more sensitive to TK inhibitors Gefitinib, Erlotinib, Afatinib, Osimertinib and Dacomitinib than wild-type receptor
- TKIs are transforming the treatment of non-small cell lung cancer by increasing survival of patients who carry mutant EGFR gene, an example of widely accepted application of genetic testing and personalized medicine in NSCLC for the last decade.

Reference:

1. https://science.sciencemag.org/content/304/5676/1497?ijkey=81d79adf5d70bab1c500fab66a7fbb095cfbf794&keytype2=tf_ipsecsha
2. https://www.pnas.org/content/101/36/13306

Comparison of testing techniques:

<table>
<thead>
<tr>
<th>Particulars</th>
<th>Sanger Sequencing</th>
<th>Real-Time PCR</th>
<th>NGS</th>
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</thead>
<tbody>
<tr>
<td>Tumor content required in the tumor biopsy sample for accurate detection of mutations</td>
<td>&gt;30%</td>
<td>5%</td>
<td>5%</td>
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<tr>
<td>Sensitivity (% of mutant gene required for reliable detection against the wild type background)</td>
<td>Low (10-20%)</td>
<td>High (1-2%)</td>
<td>High (1-2%)</td>
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<tr>
<td>Accuracy</td>
<td>Low</td>
<td>High</td>
<td>Very High</td>
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<tr>
<td>Mutation types tested</td>
<td>All mutations present in the exons</td>
<td>Only specific hotspot mutations (covers 95% of all mutations)</td>
<td>All mutations present in the entire gene</td>
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