Hereditary Lung Cancer Risk
EGFR c.2369C>T (T790M)

Genotyped Variants: *EGFR* c.2369C>T (T790M)

Clinical Features:
In the general population, approximately 1 in 16 individuals (6.2%) will develop lung or bronchial cancer in their lifetime.[1] Most cases of lung cancer are due to individual risk factors and exposures such as age, tobacco use, and exposures to secondhand smoke, radiation, asbestos, arsenic and other carcinogens.[1] Genetic factors are also known to contribute to lung cancer risk.[2] Although many of these genetic factors are unknown, germline variants in the *EGFR* gene have been observed in multiple familial lung cancer kindreds.[3,4]

While *EGFR* Thr790Met is commonly observed as an acquired somatic variant in lung tumors, this variant has been observed as germline in up to 1% of individuals with non-small cell lung cancer and segregated with disease in several families.[3,5–11] A preliminary study reviewing published families harboring *EGFR* Thr790Met reported that the penetrance of lung cancer among heterozygotes is 0.15-0.31.[5] This penetrance was dependent upon smoking history, with never smokers associated with a higher disease penetrance. However, the authors state that these numbers may be overestimates due to ascertainment bias and that additional studies are needed to clarify risks.

Inheritance Pattern:
EGFR Thr790Met is associated with an autosomal dominant cancer risk.

Test Methods:
Using genomic DNA from the submitted specimen, the relevant portion of the requested gene is PCR amplified and capillary sequencing is performed. Bi-directional sequence is assembled, aligned to reference gene sequences based on human genome build GRCh37/UCSC hg19 and analyzed for only the requested variant(s). Sequence alterations are reported according to the Human Genome Variation Society (HGVS) nomenclature guidelines.

Test Sensitivity:
The clinical sensitivity of targeted analysis of *EGFR* Thr790Met depends in part on the patient's clinical phenotype and family history. Features increasing the likelihood of a germline *EGFR* Thr790Met variant in an individual include: multiple primary lung cancers in a single individual, several relatives affected with lung cancer spanning multiple generations, and the presence of *EGFR* Thr790Met in a lung tumor prior to treatment. In a small cohort, fifty percent

of patients (5/10) whose tumors harbored the *EGFR* Thr790Met variant prior to receiving treatment were found to carry this variant in the germline.[6]

References:

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