render the GTPase insensitive to GTPase-Activating Proteins (GAPs) stimulation, constitutive activation of these protein in the GTP-bound form, constitutive activation of RAS downstream effector pathways, and resistance to inhibition of EGFR[10] [Figure 6]. Activating *KRAS* mutations are encountered at a frequency of 36-40% in CRC; approximately 90% of these are seen in codons 12 and 13 of exon 2 of the *KRAS* gene. The most frequently observed types of mutations are point mutations [G>A transitions and G>T transversions]. NRAS mutations in CRC are encountered at a frequency of 3%–5%, while somatic mutations in HRAS are anecdotal. About 5% of CRC cases show BRAF mutations, and 15% manifest *PIK3CA* mutations.[11]

Conventional molecular testing for CRC entailed screening for *KRAS* exon 2 (codons 12 and 13). It was mandated that only patients with normal (wild-type) *KRAS* tumours should receive anti-EGFR monoclonal antibodies [cetuximab (Erbitux), and panitumumab (Vectibix)].[12] However, 20% of *KRAS* exon 2 wild-type tumors did not respond to anti-EGFR therapies.[13] Thus additional genotyping of *BRAF, NRAS, PIK3CA, PTEN, AKT1, SMAD4*, and *TGFBR2* was proposed in such a scenario.[13,14] The recent American Society of Clinical Oncology (ASCO) recommendations stipulate extended *RAS* testing as a predictive biomarker of response to anti-EGFR monoclonal antibodies.[8] This testing is recommended by European Society for Medical Oncology (ESMO), National Cancer Comprehensive Network (NCCN), the European Society of Pathology, and the Association of Clinical Pathologists Molecular Pathology and Diagnostics Group (United Kingdom) as well.[3,4,15,16] The expanded *RAS* testing entails testing for *KRAS* exon 2 (codons 12 and 13), exons 3 (codons 59 and 61) and 4 (codons 117 and 146), along with *NRAS* exon 2 (codons 12 and 13), 3 (codons 59 and 61), and 4 (codons 117 and 146).11 Concomitant testing for mutations in *BRAF*, *PIK3CA*, loss of *PTEN*, and MMR are also carried out in CRC.[8]

KRAS and *NRAS* mutations are mutually exclusive, as too are mutations in *BRAF* and *KRAS/NRAS*.[17] This report profiles a highly interesting case wherein concomitant *KRAS* and *NRAS* mutations were seen in the same CRC patient. The incidence of the *KRAS* c.38G>A (G13D) mutation in CRC is 18.9–19.2%. This mutation results in a *KRAS* substitution at position 13, such that a glycine (G) changes to an aspartic acid (D). It confers decreased response to cetuximab/panitumumab, while the response to erlotinib/gefitinib is unknown at this juncture.[11] *NRAS* mutations are rare in CRC, but common in myeloid leukemias and cutaneous melanomas. The c.34G>T (G12C) mutation leads to *NRAS* substitution at position 12, from a glycine (G) to a cysteine (C). Its frequency in *NRAS* mutated CRC is 11.1%. Activating mutations in *NRAS* are associated with relative resistance to anti-EGFR therapy, and sensitivity to the MEK inhibitors, AZD6244 and CI-1040.[18] *RAS* mutations beyond