TP53 **mutation** (Non-core)

Reason/Evidentiary Support

Mutations of the *TP53* gene, which encodes the p53 protein, are found in approximately two-thirds of all diffuse astrocytic gliomas[1] and in over 80% of IDH-mutant diffuse astrocytic gliomas.[2] *TP53* mutations are less common in IDH-wildtype glioblastomas (23-28%), and are notably uncommon in oligodendrogliomas, showing a strong inverse relationship with 1p/19q codeletion. *TP53* mutations are thus used as diagnostic markers for diffuse astrocytic gliomas, and have been used to distinguish low-cellularity diffuse astrocytic gliomas from reactive gliosis.[3] Evaluation of *TP53* mutation may also be used to rule out the possibility of oligodendroglial tumours among IDH-mutant gliomas. Furthermore, *TP53* mutations are important for subclassifying medulloblastomas with SHH pathway activation, dividing them into high-risk *TP53*-mutant cases in older children versus lower-risk *TP53*-wildtype cases in young children and adults. *TP53* mutations are common in some other types of brain tumours, but are not used diagnostically as in the above situations.

Different DNA sequencing techniques may be used for detecting *TP53* mutations. Screening can be accomplished via sequencing of all exons or just exons 5 through 8, where most mutations occur; the great majority of mutations are missense.

<u>p53 Expression (Immunohistochemistry)</u>

Immunohistochemistry is a useful screening tool, given that most missense *TP53* mutations result in increased p53 protein half-life that produces strong immunoreactivity in the majority of tumour cell nuclei (rather than scattered positivity and/or light nuclear staining). Strong p53 positivity in >10% of the tumour cell nuclei has been found to have a sensitivity of 77.4-78.8% and a specificity of 78.6-96.7% when compared to sequencing.[4,5] Positive nuclear p53 staining correlates well with missense mutations with a sensitivity of 92% and a specificity of 79.4%, whereas only 33% of tumours with truncating mutations show p53 positivity,[5] with such mutations typically leading to negative staining.[6]

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