Clinical Whole Genome DNA methylation profiling improves the diagnostics of brain tumors

Brain tumors are clinically and biologically highly diverse, encompassing a wide spectrum of diseases. Molecular profiling has established several distinct subgroups within each histological type of tumor. Methylation of CpG dinucleotides is a key epigenetic regulator of gene function during development and disease and DNA methylation can be used for molecular subclassification of brain tumors. In 2014, Snuderl Laboratory and NYU Molecular Pathology and Diagnostics started developing epigenetic DNA methylation based map of brain tumors to improve diagnostics and classification of brain tumors. In April 2019, NYU finished full clinical validation and received regulatory approval for DNA methylation. **This is the first clinical test utilizing whole genome DNA methylation and machine learning** for diagnostics approved in the CLIA laboratory by the NY State department of Health. We created an epigenetic map of all brain cancers and deployed it into the clinic, as the first CLIA laboratory in the world to receive such regulatory approval.

This is a paradigm shifting approach in diagnosing cancer, as we have shown retrospectively that traditional diagnostics has 12-14% of misdiagnosis rate (Figure 1). Consequences of over/under diagnosis in pediatric brain tumors are severe. A wrong diagnosis can lead to wrong treatment including unnecessary radiation, or a wrong chemotherapy regimen with worse than expected survival. Misdiagnosis and grading can also lead to unnecessary overtreatment. Long-term morbidity of radiation and chemotherapy is well-established including secondary cancers, cognitive and IQ decline and neuroendocrine deficits. It must also be noted that unnecessary treatment and unnecessary follow up by MRI or CT scans increase costs of health care. Brain tumors are often difficult to diagnose requiring variety of immunohistochemical and molecular tests, while DNA methylation is one-size-fits-all molecular test that can save time and resources delineating the accurate tumor type with a single test. Accurate diagnostics at the time of presentation can therefore also has a significant potential to reduce healthcare costs. NYU is currently the only CLIA certified lab with clinically validated DNA methylation test and can provide this testing to centers that currently do not have this testing available.
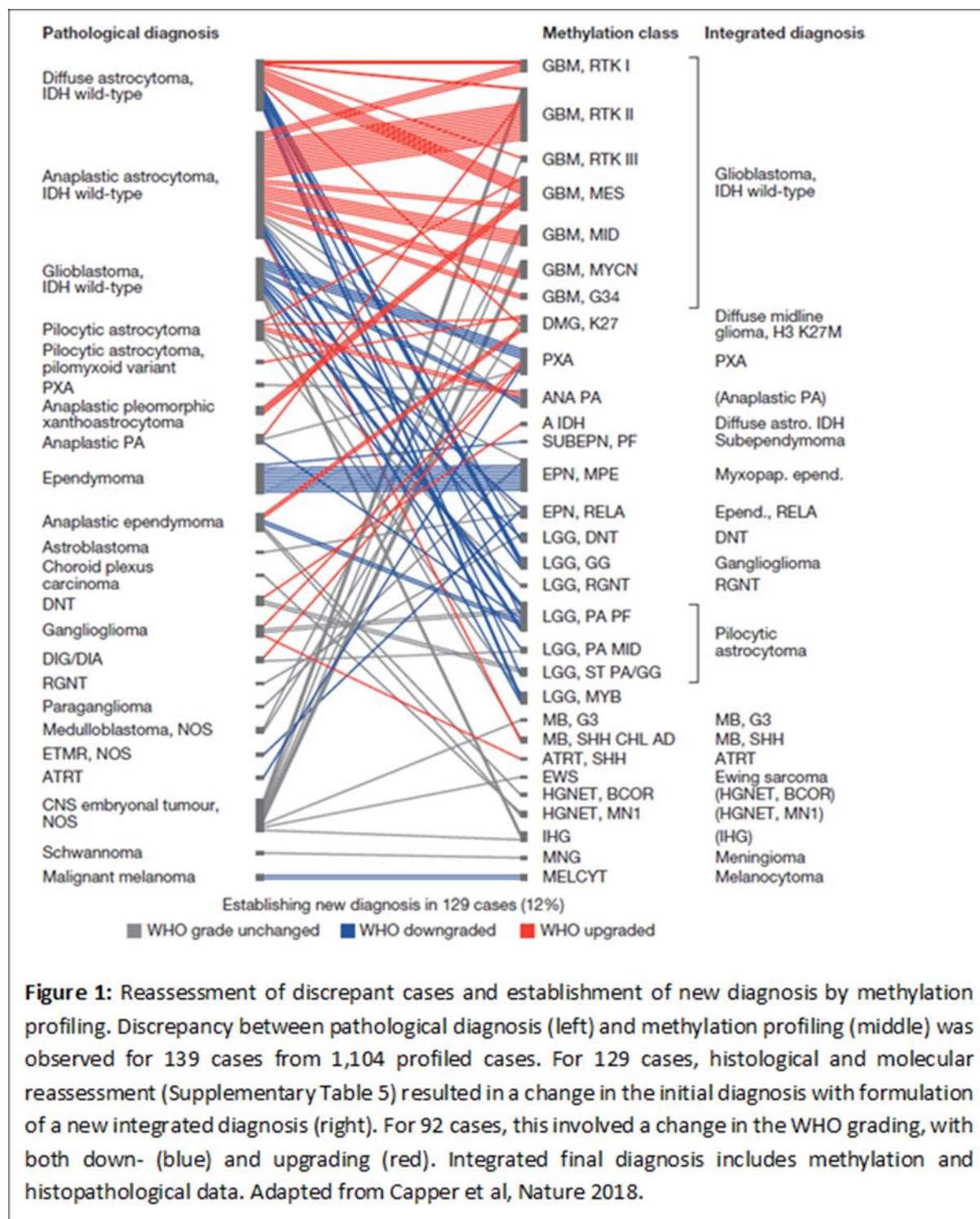
Figure 1: Reassessment of discrepant cases and establishment of new diagnosis by methylation profiling. Discrepancy between pathological diagnosis (left) and methylation profiling (middle) was observed for 139 cases from 1,104 profiled cases. For 129 cases, histological and molecular reassessment (Supplementary Table 5) resulted in a change in the initial diagnosis with formulation of a new integrated diagnosis (right). For 92 cases, this involved a change in the WHO grading, with both down- (blue) and upgrading (red). Integrated final diagnosis includes methylation and histopathological data. Adapted from Capper et al, Nature 2018.