PATH-10. Accelerating comprehensive CNS tumor molecular diagnostics with Rapid-CNS2 and MNP-flex: a prospective multi-center validation [Abstract]

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PATH-10. ACCELERATING COMPREHENSIVE CNS TUMOR MOLECULAR DIAGNOSTICS WITH RAPID-CNS^2 AND MNP-FLEX: A PROSPECTIVE MULTI-CENTER VALIDATION

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BACKGROUND: The 2021 WHO classification update highlights the necessity of integrating molecular alterations for precise central nervous system (CNS) tumor diagnoses. However, current molecular reporting methods are hindered by significant initial investment, labor-intensive protocols, and lengthy turnaround times. Methylation-based classification has emerged as a pivotal diagnostic tool but is currently limited to array-based techniques. This necessitates exploration of novel technologies to streamline molecular analysis. METHODS: We implemented Rapid-CNS^2 - our adaptive sampling-based nanopore sequencing workflow- on 190 adult and pediatric samples at University Hospital Heidelberg and University of Nottingham. Intraoperative potential was assessed through real-time analysis followed by 24-hour sequencing for comprehensive genomic insights. Additionally, we developed MNP-Flex, a platform-agnostic version of the Heidelberg methylation classifier covering 184 CNS tumor classes. We evaluated MNP-flex on a global cohort of over 78,000 samples from methylation arrays, whole genome bisulfite sequencing, nanopore whole genome sequencing, methylation panels and Rapid-CNS^2. RESULTS: Rapid-CNS^2 validation yielded accurate integrated diagnoses in all 190 samples. Within a crucial 30-minute timeframe, we reported accurate methylation families and arm-level copy number profiles followed by next-day reporting of fine-grained methylation classification, SNVs, focal CNVs, MGMT status, fusions and novel structural variants. Moreover, MNP-Flex achieved 92% accuracy over the validation dataset spanning over 78,000 samples from five different technologies. CONCLUSIONS: The adoption of Rapid-CNS^2 and MNP-Flex enables rapid intraoperative broad methylation classification and copy number alteration reporting within 30 minutes, with additional clinically relevant, fine-grained molecular insights available the following day. It offers clinicians rapid access to comprehensive molecular information critical for treatment decisions. Furthermore, MNP-Flex extends the utility of the Heidelberg methylation classifier to diverse sequencing-based data. By overcoming the limitations of currently available methods, our workflow represents a paradigm shift in the field, promising improved management of CNS tumor patients. Rapid-CNS^2 can be executed with a single command, while MNP-Flex is publicly available as a web service, enhancing accessibility and usability for clinical applications.