A community-wide comparison of DNA methylation assays for biomarker development and clinical applications

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Abstract
DNA methylation patterns are altered in numerous diseases and often correlate with clinically relevant information such as disease subtypes, prognosis, and drug response. After validation in large cohorts, such associations can be exploited for clinical diagnostics and personalized treatment decisions. Several technologies are now available that seem fit for routine clinical use. However, to date no comprehensive comparison of these technologies has been performed, and potential users are left to their own devices to choose a suitable assay.
Here we describe the results of a community-wide benchmarking study comparing the performance of all widely used methods for DNA methylation analysis that are compatible with routine clinical use. We shipped 32 reference samples to 18 laboratories in 7 different countries. These laboratories collectively contributed 21 locus-specific assays for an average of 27 predefined genomic regions, as well as 6 global assays.
We evaluated assay sensitivity on low-input samples and assessed the assays' ability to discriminate between cell types. Good agreement was observed across all tested methods, with amplicon bisulfite sequencing and bisulfite pyrosequencing showing the best all-round performance. Our benchmarking analysis can inform the selection, optimization, and use of DNA methylation assays in large-scale validation studies, biomarker development, and clinical diagnostics.

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