Detecting the undetectable with AI-enabled nanotechnology

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AI-assisted material selection is on the rise, but the design and optimization of sensing materials based on disease-related molecules and material interfaces have not yet emerged. Here, we proposed an AI-assisted design of copper nanoplasmonic substrate for enhanced Raman analysis of metabolic disease related urine organic acids. The AI-designed carboxylate affinity copper nanoplasmonic substrate demonstrated 15 times greater Raman enhancement than commonly used gold nanomaterials. We combined Raman spectroscopic analysis of clinical urine samples with machine learning to identify urinary markers of inborn errors of metabolism (IEM). IEM encompasses a spectrum of deficiencies in processing nutrients affecting about 0.04% of the population. Due to the nontargeted nature and simplicity in operation of Raman spectroscopy, the spectral data of urine samples can be acquired within 10 min. Trained with a small dataset of 60 clinical samples, the decision model showed a 95.4% sensitivity at a specificity of 80.5% in distinguishing normal and abnormal samples, and a mean 85% accuracy for categorizing abnormal subtypes. Further blinded sample tests demonstrated that the pretrained model could predict with an accuracy of 87.5%. This study presents a novel design of surface enhanced Raman spectroscopic analysis coupled with machine learning that offers simplified and prompt identification of IEMs including ornithine transcarbamylase (OTC) deficiency and maple syrup urine disease (MSUD), demonstrating its potential to improve care and address diagnostic challenges in IEM, and to enable broader screening.