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NETest® 2.0 – A Decade of Innovation in Neuroendocrine Tumor/Neoplasm Diagnostics

Mark Kidd¹, Ignat Drozdov², Alin Chirindel³, Guillaume Nicholas³, David Imagawa⁴, Anthony Gulati⁵, Takahiro Tshuchikawa⁶, Abdel Halim¹, Jonathan Strosberg⁷, Nicholas Wright⁸.

¹Wren Laboratories, CT; ²Bering Research, London, UK; ³University of Basel, Basel Switzerland; ⁴University of California Irvine, CA; ⁵Bennett Cancer Center, CT; ⁶Hokkaido University, Sapporo, Japan; ⁷Moffitt Cancer Center, FL; ⁸Barts Cancer Institute, London, UK.

BACKGROUND

Gastroenteropancreatic neuroendocrine neoplasms (GEP-NENs) are challenging to diagnose and manage. We introduced the NETest in 2013, a liquid biopsy that quantifies mRNA expression of 51 NET-specific genes in blood using real-time PCR (NETest® 1.0). The test leverages a proprietary blood collection to stabilize RNA and perform RT-PCR on RNA isolated from whole blood, followed by supervised machine learning (ML) algorithms. The 0-100 algorithm was scaled to adjudicate patient results against cutoffs of 20, 40, and 80. A result >20 correlated with a NET diagnosis a result of 40-79 correlated with a high probability of disease progression, with >80, identifying those most at risk. Over the next decade, we continued efforts to train the ML classifiers to simplify test outputs, optimize sensitivity and specificity of NET diagnosis and prognostication (NETest 2.0).

METHODS

qPCR measurements were used to train two supervised classifiers for diagnostic and prognostic scores. Unlike NETest 1.0, the algorithms used were different. The diagnostic classifier was trained on 78 controls (healthy individuals) and 162 NETs to distinguish NETs from controls; the prognostic classifier was trained on 134 patients with stable disease (SD) and 61 patients with progressive disease (PD) to differentiate stable from progressive NET. In all cases, 80% was retained for model training; 20% was used for performance evaluation. The predictive performance was assessed using sensitivity, specificity, and Area under Received Operating Characteristic Curve (AUROC). Trained models were validated in two independent sets of patients. Validation Set I (Controls vs. NETs) consisted of 555 NETs and 186 controls, while Validation Set II (Stable vs. Progressive) comprised 294 patients with image-confirmed SD and 149 with PD.

RESULTS

Results are reported from the two validation sets (Set I-Diagnostic: $n=741$; Set II-Prognostic: $n=443$). The diagnostic algorithm achieved an AUROC of 0.92, 93% sensitivity, 82% specificity, and 90% overall accuracy for distinguishing NETs from controls. The prognostic algorithm demonstrated an AUROC of 0.81, 67% sensitivity, 87% specificity and 80% overall accuracy for distinguishing stable from progressive disease. In head-to-head comparisons versus NETest 1.0, the overall diagnostic accuracy was significantly better using NETest 2.0 ($p=1 \times 10^{-16}$) as was the prognostic accuracy ($p=1.5 \times 10^{-5}$).

CONCLUSIONS

NETest 2.0 was trained on 240 samples and validated in 741 (diagnostic) and 443 (prognostic) patients, respectively. NETest 2.0 simplified the disease scoring system exhibiting improved diagnostic and prognostic capabilities over NETest 1.0. This optimized, validated blood-based molecular tool provides a powerful approach for diagnostic, prognostic and patient monitoring.

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