Biomarkers Driving Precision Medicine in Nonfunctioning Pituitary Neuroendocrine Tumors: A Systematic Review of Recent Literature

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Abstract Nonfunctioning pituitary neuroendocrine tumors (NF-PitNETs) display considerable biological heterogeneity, posing challenges for accurate prognostication and personalized management. This systematic review, conducted in Scopus and Web of Science in accordance with PRISMA 2020, identified 29 primary studies and categorized all molecular findings into 3 core themes: (1) invasion biology and epithelial-mesenchymal transition (EMT); (2) noncoding RNAs and liquid biopsy markers; and (3) multiomics, epigenetic, and prognostic signatures.Within the invasion/EMT theme, gonadotroph tumors consistently demonstrated the strongest EMT-linked activity, including SNAI-mediated transitions, Vimentin upregulation, and beta-catenin alterations. Corticotroph tumors showed intermediate EMT involvement, while null-cell tumors exhibited invasion patterns driven mainly by hypoxia-related protease dysregulation rather than EMT. In the noncoding RNA and circulating biomarker theme, several candidates, including exosomal miR-486-5p, miR-151a-5p, and exosomal MMP1, have shown diagnostic or prognostic value, although subtype specificity remains limited. The multiomics and epigenetic theme revealed subtype-dependent molecular programs: gonadotroph tumors were associated with PI3K-AKT pathway enrichment and SF-1 labeling heterogeneity; recurrent lesions showed elevated nuclear pEGFR T693 and MCM7; while DNA methylation mapping identified subtype-relevant loci such as NUP93, LGALS1, and GABRA1. Phosphoproteomic and acetylomic profiling further highlighted alterations in metabolic, kinase-driven, and cell-adhesion pathways linked to invasion and recurrence. Overall, the lineage-aligned synthesis indicates that NF-PitNETs progress through diverse molecular pathways, with each subtype dominated by distinct regulatory networks. Although many biomarkers show promise, most remain exploratory, highlighting the need for harmonized methods and multicenter validation to support precision diagnostics and prognostic modeling.

Keywords **Author Keywords:** nonfunctioning pituitary neuroendocrine tumors; NF-PitNETs; NFPA; pituitary tumors; biomarkers; precision medicine

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All data analyzed are included in this article or listed in the references.

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