Stepwise refinement refers to the progressive refinement in small steps of a program specification into a program. Sometimes, it is called top-down design.

While accumulating studies have investigated coding gene-associated biomarkers in malignant glioma, research on comprehensive coding and non-coding RNA-associated biomarkers is lacking. Furthermore, few studies have illustrated the crosstalk signaling pathways among these biomarkers and mechanisms in detail.

Huang et al. identified differentially expressed genes and Competing endogenous RNA (ceRNA) networks in malignant glioma and then constructed Cox/Lasso regression models to further identify the most valuable genes through stepwise refinement. Top-down comprehensive integrated analysis, including functional enrichment, SNV, immune infiltration, transcription factor binding site, and molecular docking analyses, further revealed the regulatory maps among these genes. The results revealed a novel and accurate model (AUC of 0.91 and C-index of 0.84 in the whole malignant gliomas, AUC of 0.90 and C-index of 0.86 in LGG, and AUC of 0.75 and C-index of 0.69 in Glioblastoma) that includes twelve ncRNAs, 1 MicroRNA, and 6 coding genes. Stepwise logical reasoning based on top-down comprehensive integrated analysis and references revealed crosstalk signaling pathways among these genes that were correlated with the circadian rhythm, tumor immune microenvironment, and cellular senescence pathways. In conclusion, the work reveals a novel model where the newly identified biomarkers may contribute to a precise diagnosis/prognosis and subclassification of malignant glioma, and the identified cross-talk signaling pathways would help to illustrate the noncoding RNA-associated epigenetic regulatory mechanisms of glioma tumorigenesis and aid in targeted therapy [1].

1)
Huang Y, Gao X, Yang E, Yue K, Cao Y, Zhao B, Zhang H, Dai S, Zhang L, Luo P, Jiang X. Top-down stepwise refinement identifies coding and noncoding RNA-associated epigenetic regulatory maps in malignant glioma. J Cell Mol Med. 2022 Feb 22. doi: 10.1111/jcmm.17244. Epub ahead of print. PMID: 35194922.