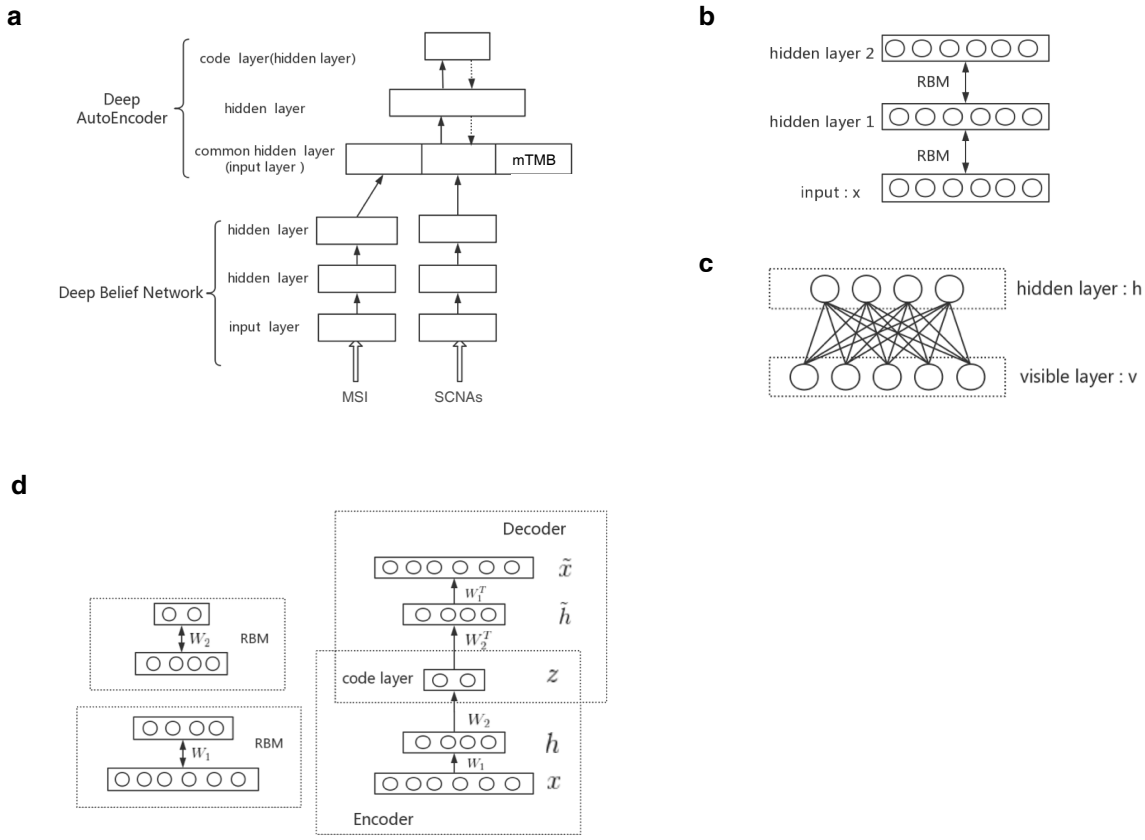

Figure S1. Multifactorial deep learning model structures. **a**, Multi-modal network with three modalities. The bottom level contains three separate deep belief network (DBN) which take three modalities as input respectively. Then the top hidden layer of DBNs is jointed together to form common hidden layer. The top level is a deep AutoEncoder which takes common hidden layer as input. **b**, DBN, stacked by restricted Boltzmann machine (RBMs). **c**, RBM, bi-directionally connected neural network. **d**, Deep AutoEncoder structure.

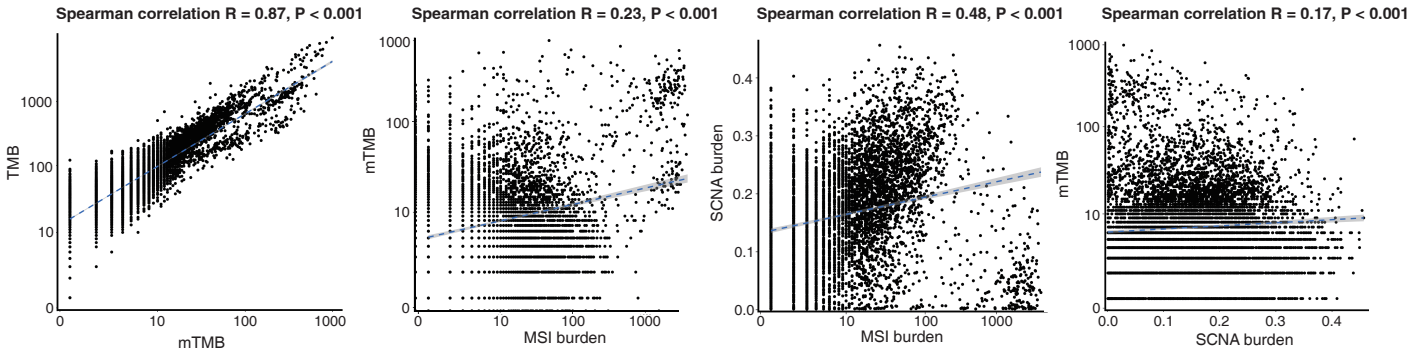

Figure S2. Correlations of three types of genomic alterations.

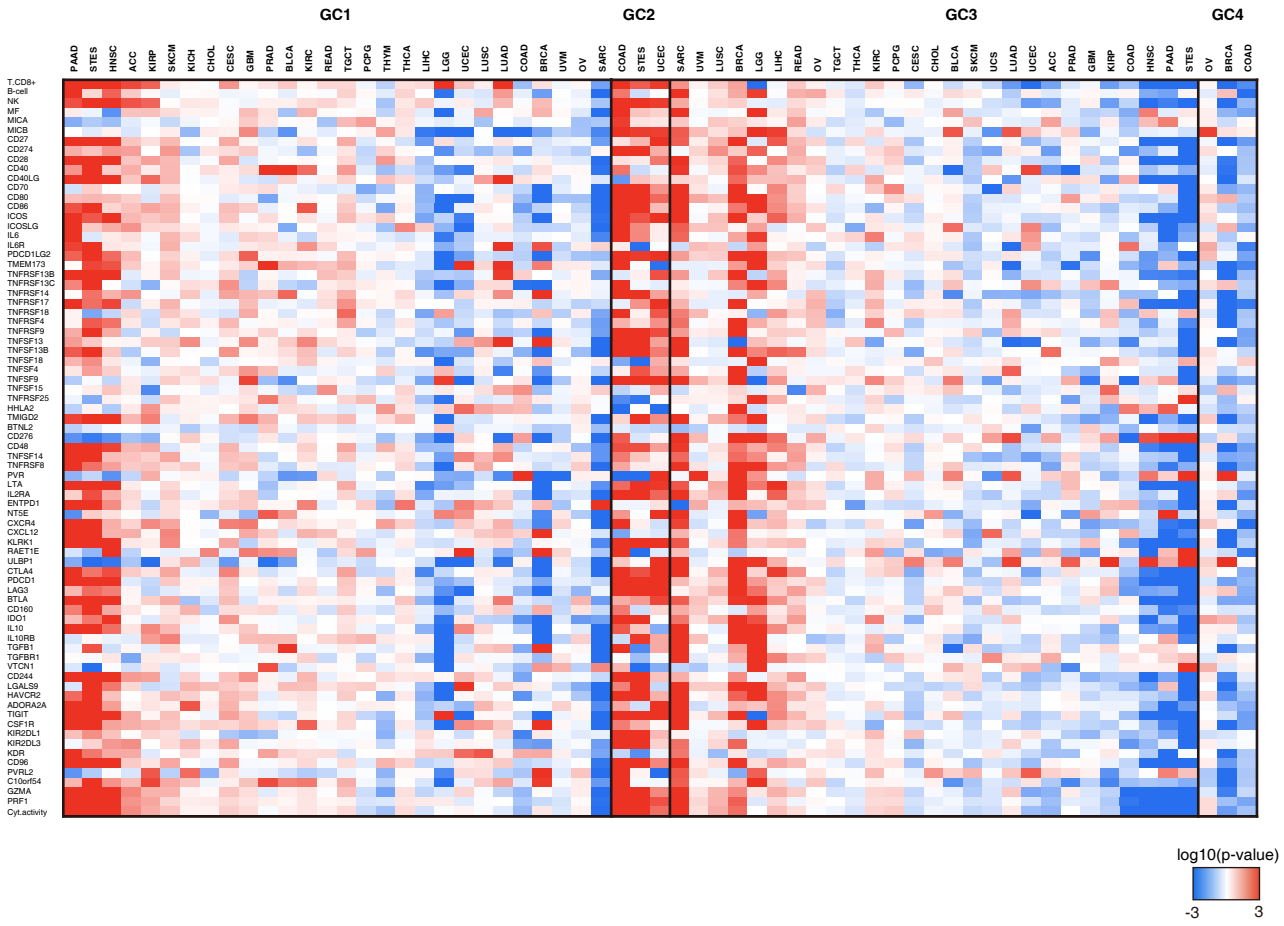

Figure S3. Immune gene panel profile difference between GCs. Comparisons of immune gene expression between samples of a given cancer type in a specific GC and samples of the same cancer type not in that GC. Color intensities in boxes represent the log10(p-value) calculated from a Wilcoxon test comparing the given immune feature between each group of samples. The higher red intensity and positive numbers indicate a more significant level of enrichment while the higher blue intensity and negative numbers indicate a more significant level of depletion.

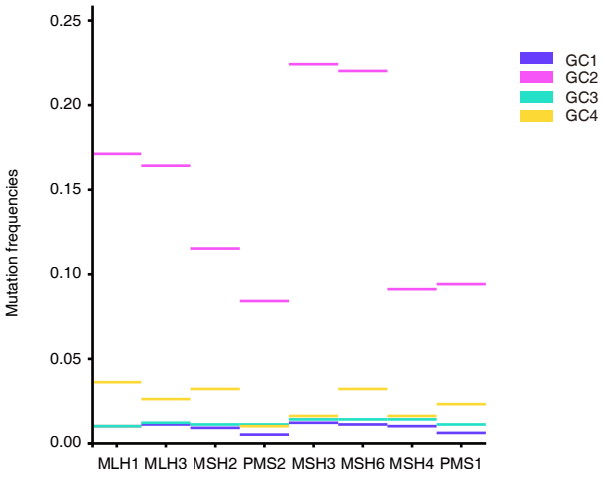

Figure S4. Mismatch repair gene mutation frequency of each GC. The mutation frequency of the DNA mismatch repair (MMR) genes (MLH1, MLH3, MSH2, PMS2, MSH3, MSH6, MSH4, PMS1) is calculated as the number of mutation events in a GC divided by the product of the number of MMR genes and the sample size of this GC.

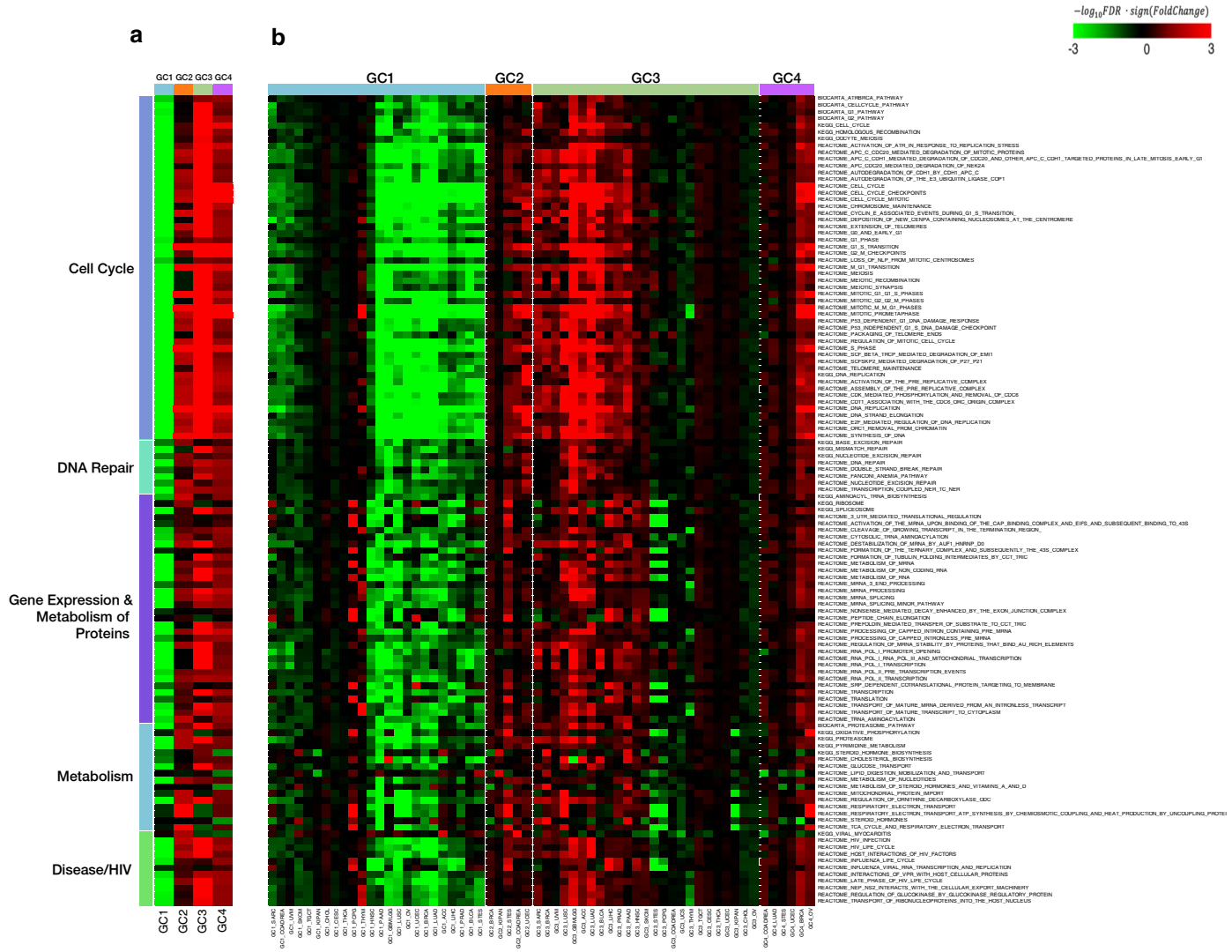

Figure S5. Gene Set Enrichment Analysis (GSEA) enriched pathways analysis for the stratification. **a**, GSEA was performed to identity the gene sets that are over-expressed or under-expressed in one GC compared to other GCs across all tumor types and **b**, Within each tumor type, GSEA was performed across GCs. The higher red intensity indicates a more significant level of high expression while the higher green intensity indicates a more significant level of low expression. The pathways from KEGG, Reatome, BioCarta pathways downloaded from MSigDB were used for test.

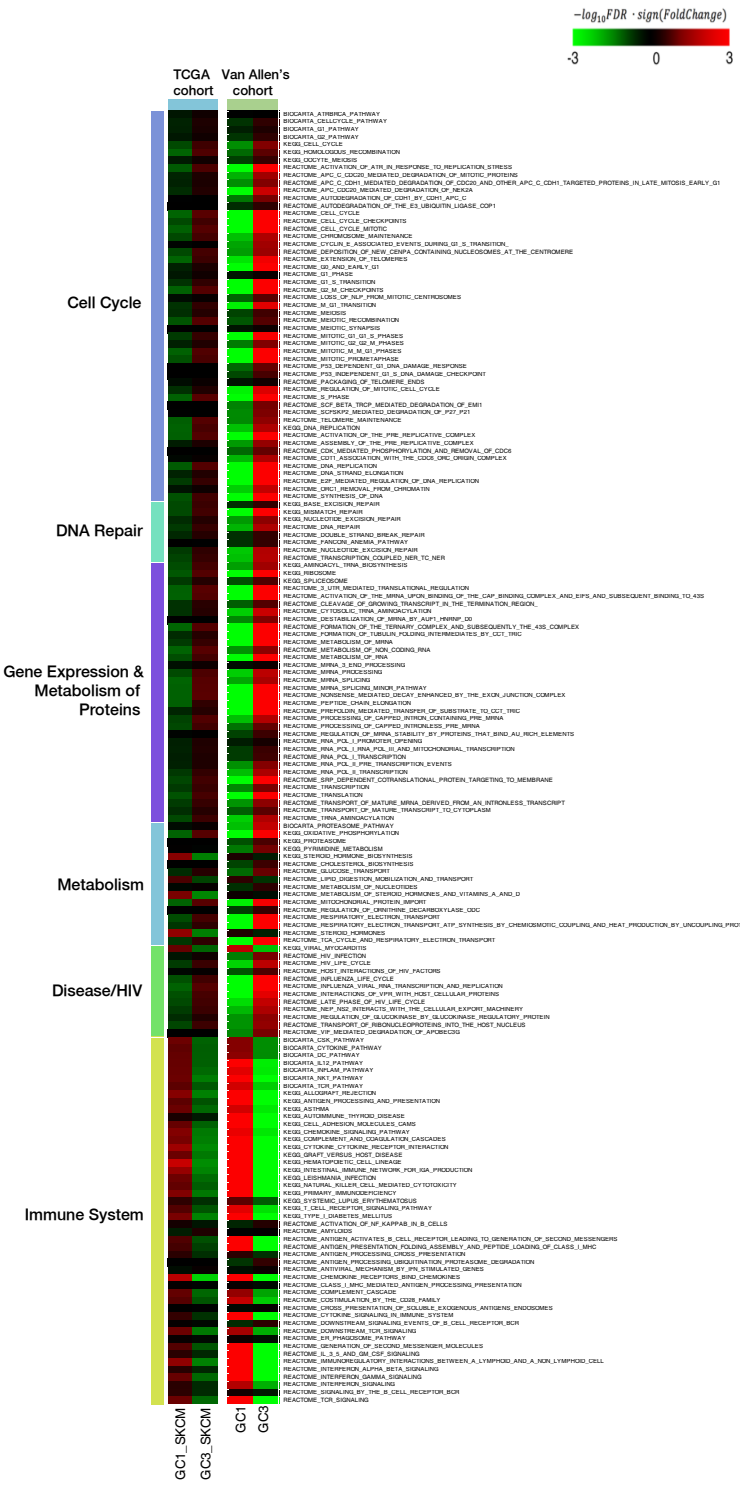

Figure S6. GSEA analysis results of Van Allen's and TCGA melanoma cohorts.The pathways in GC1 and GC3 in two cohorts were shown. The higher red intensity indicates a more significant level of high expression while the higher green intensity indicates a more significant level of low expression. The pathways from KEGG, Reatome, BioCarta pathways downloaded from MSigDB were used for test.

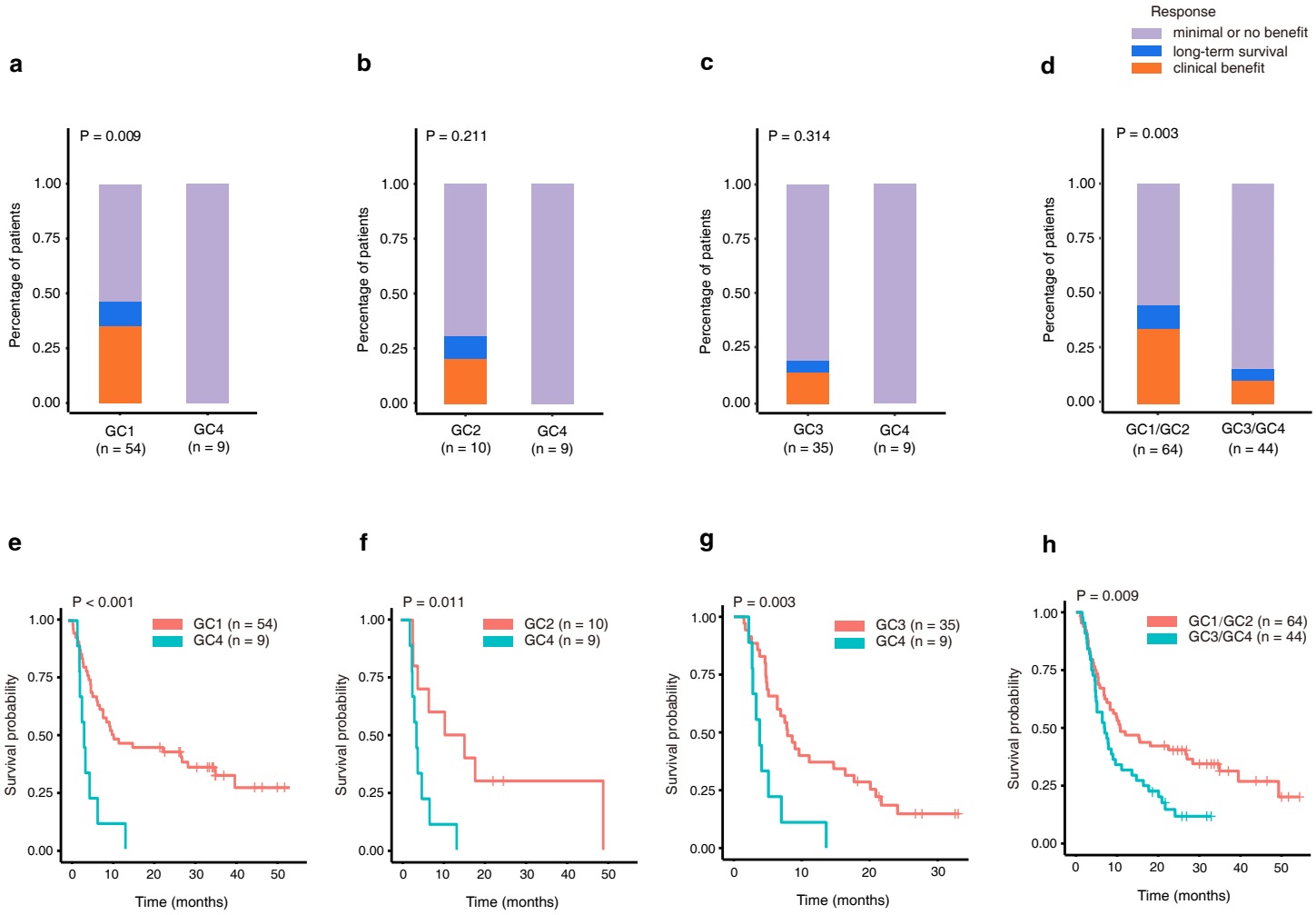

Figure S7. Immunotherapy response and prediction survivals of Van Allen's cohort. **a-d**, Clinical response. The clinical response of patients with minimal or no benefit (n=73), long-term survival (n=9), clinical benefit (n=26) were defined in Van Allen's study as described in methods. The association of clinical response with GCs was tested using two-tailed Fisher exact test and p value was shown. **e-h**, Overall survival. P value was calculated by the log-rank test.

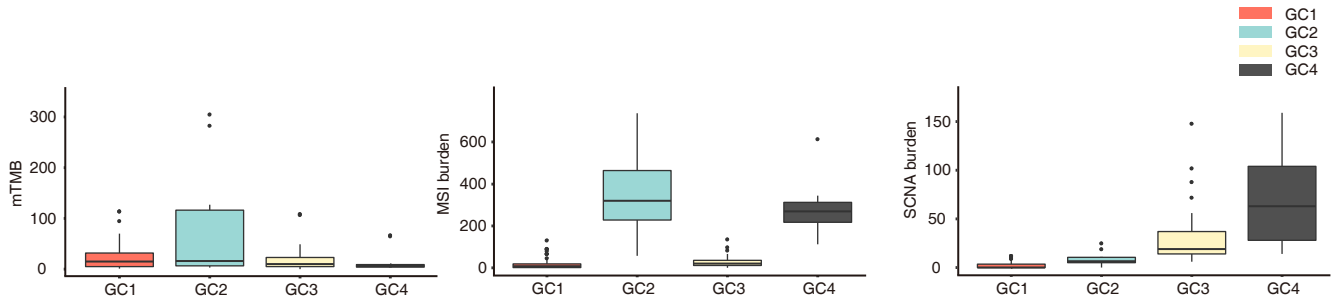

Figure S8. The mTMB, MSI burden, SCNA burden of Van Allen's cohort in each GC.

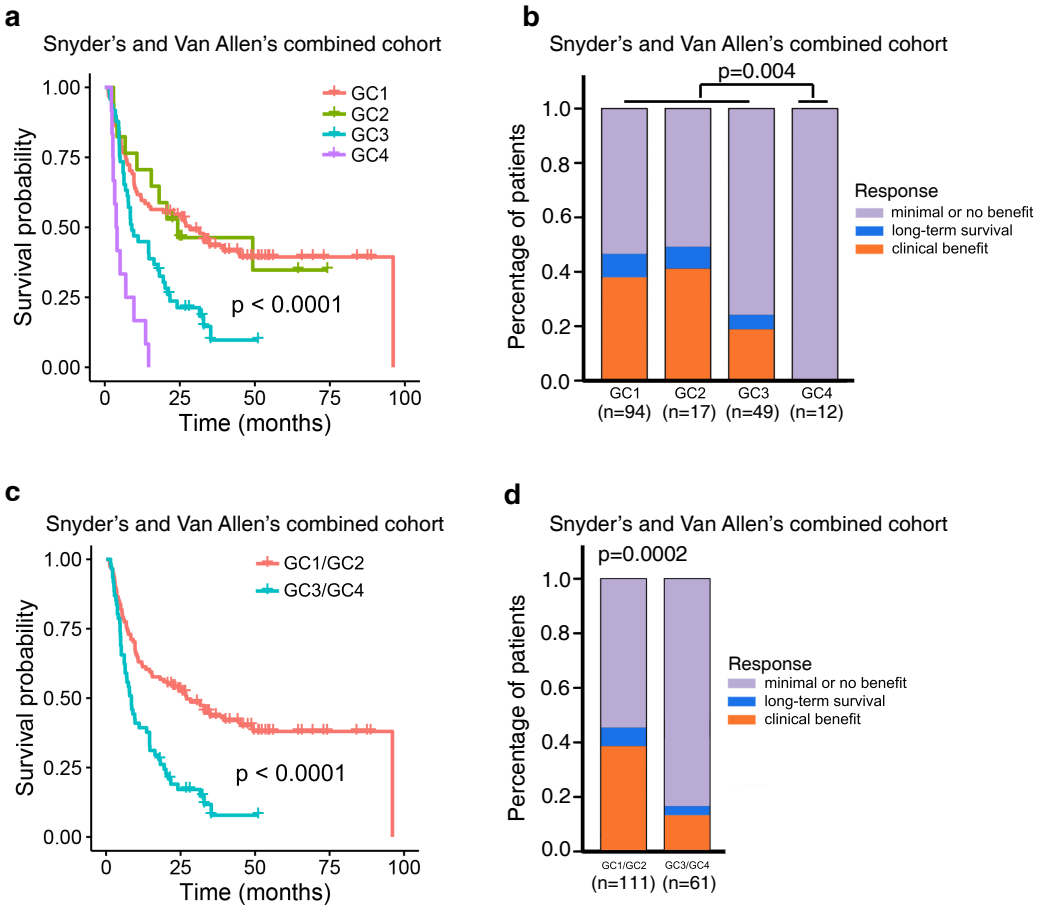

Figure S9. Deep learning model analysis for combined Van Allen's and Snyder's cohorts. The clinical response of patients with clinical benefit, long-term survival, minimal or no benefit were defined in Van Allen's and Snyder's studies as described in methods. **a**, Overall survival of combined cohort. P value was calculated by the log-rank test. **b**, Clinical response of the combined cohort to immunotherapy in patients with metastatic melanoma. The association of clinical response with GCs was tested using two-tailed Fisher exact test and p value was shown. **c**, Overall survival of patients in GC1/GC2 vs GC3/GC4. P value was calculated by the log-rank test. **d**, Clinical response of patients in GC1/GC2 vs GC3/GC4. The association of clinical response with GCs was tested using two-tailed Fisher exact test and p value was shown.

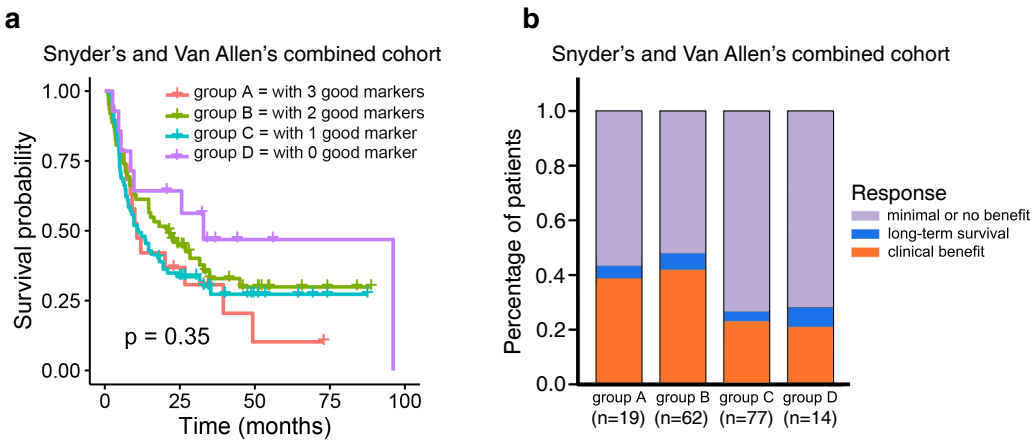

Figure S10. Simple multivariable analysis for combined Van Allen's and Snyder's cohorts. **a**, Overall survival of combined cohort. P value was calculated by the log-rank test. **b**, Clinical response of the combined cohort to immunotherapy in patients with metastatic melanoma. The clinical response of patients with clinical benefit, long-term survival, minimal or no benefit were defined in Van Allen's and Snyder's studies as described in methods. Using medain as cutoffs, we defined the genomic features reportedly associated with benefit from ICB as good markers including TMB-high (>medain), MSI-high (>median) and CNV-low (<median). Groups: A=with 3 good markers, B=with 2 good markers, C=with one good marker and D=with 0 good marker.

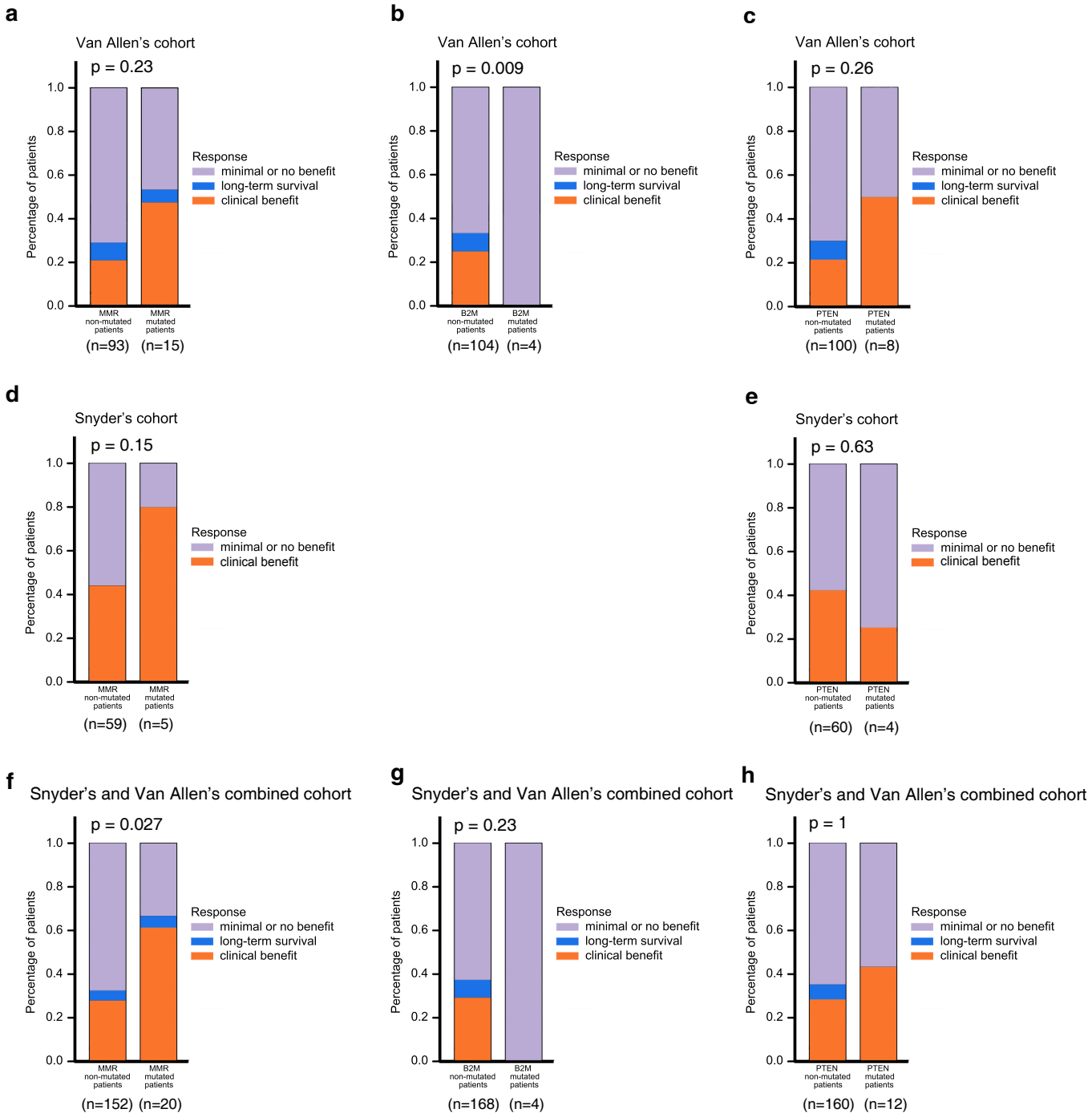

Figure S11. **a-h**, Clinical response analyzed based on gene biomarkers in Van Allen's cohort, Snyder's cohort and combined cohort. The clincial response of patients with clinical benefit, long-term survival, minimal or no benefit were defined in Van Allen's and Snyder's studies as described in methods. The association of clinical response with groups was tested using two-tailed Fisher exact test and p value was shown.

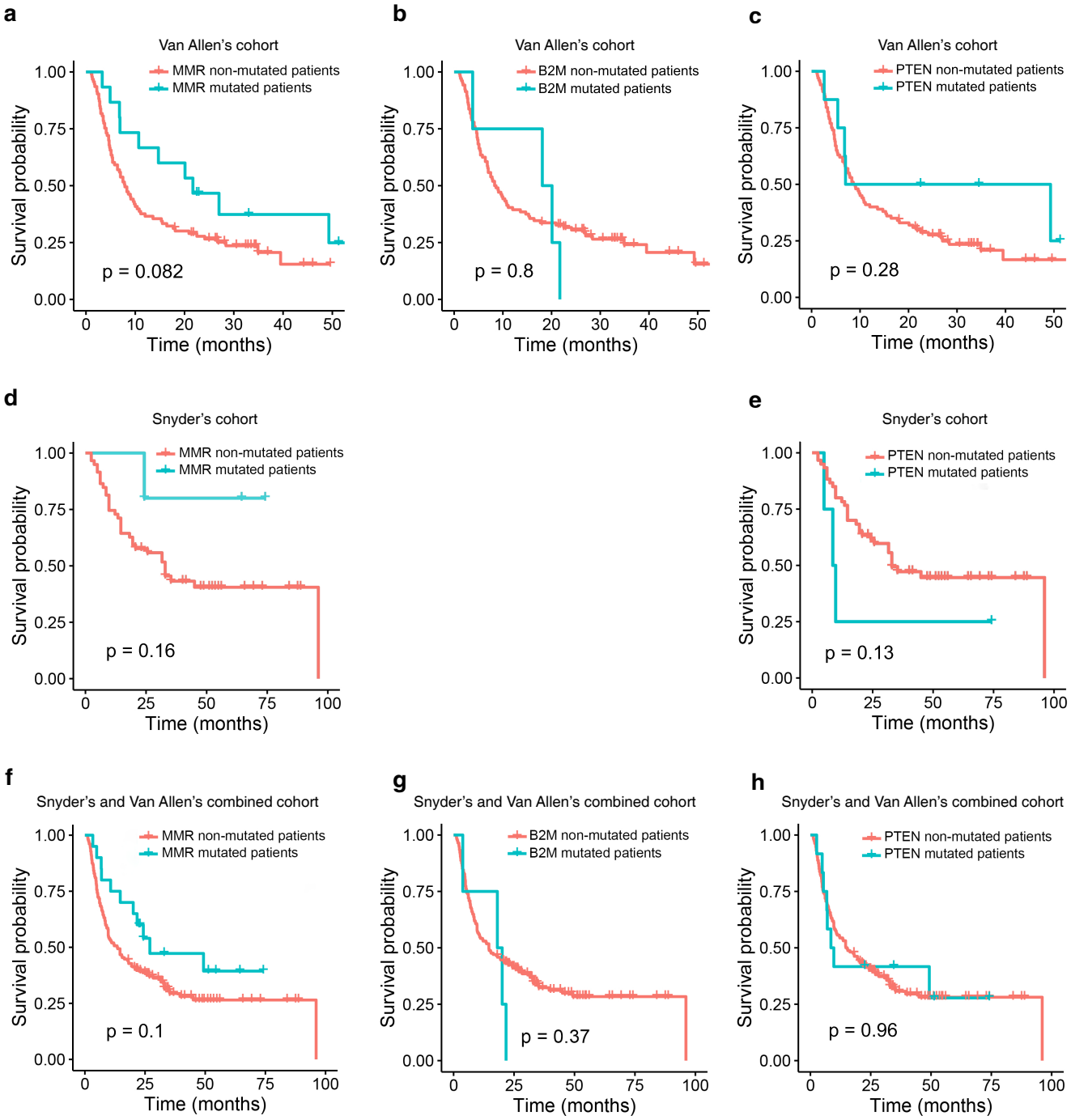

Figure S12. **a-h**, Overall survival analyzed based on gene biomarkers in Van Allen's cohort, Snyder's cohort and combined cohort. P value was calculated by the log-rank test.