

The combined signatures of the tumour microenvironment and nucleotide metabolism-related genes provide a prognostic and therapeutic biomarker for gastric cancer

Jifeng Liu<sup>1†</sup>, Lei Zhong<sup>1†</sup>, Dawei Deng<sup>2†</sup>, Yunshu Zhang<sup>3\*</sup>, Qihang Yuan<sup>1\*</sup>, Dong Shang<sup>1\*</sup>

<sup>1</sup>Department of General Surgery, The First Affiliated Hospital of Dalian Medical University, Dalian, Liaoning, China

<sup>2</sup>Department of Hepato-Biliary-Pancreas, Affiliated Hospital of North Sichuan Medical College, Nanchong, China

<sup>3</sup>Department of Traditional Medicine, The First Affiliated Hospital of Dalian Medical University, Dalian, Liaoning, China

†These authors have contributed equally to this work and share first authorship

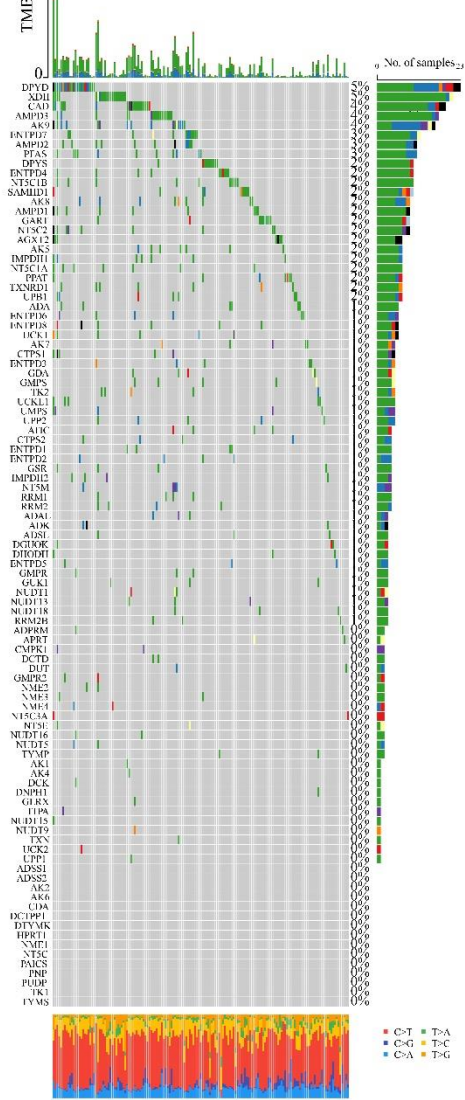
**\*Correspondence:**

Prof. Dong Shang, E-mail: shangdong@dmu.edu.cn;

Dr. Qihang Yuan, E-mail: qihangdy@163.com;

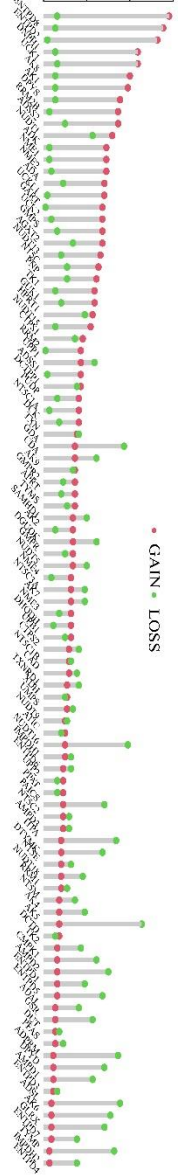
Dr. Yunshu Zhang, E-mail: zys1986062186@163.com.

A 5612 Altered in 161 (37.18%) of 433 samples.

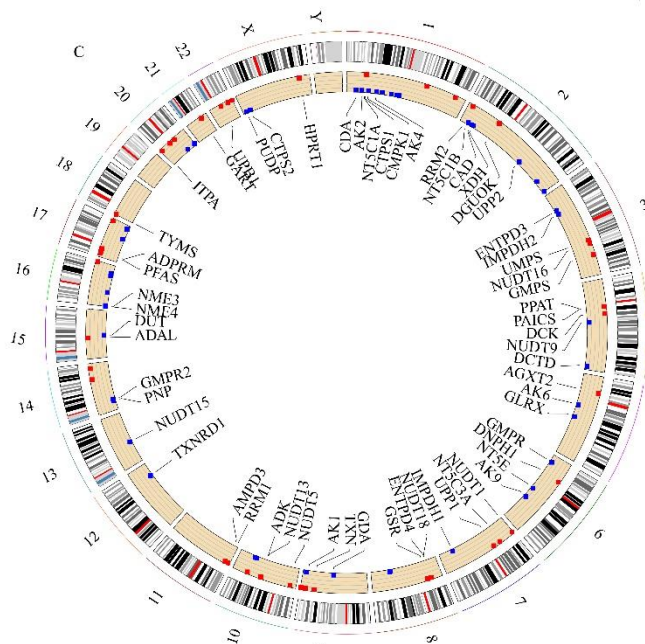
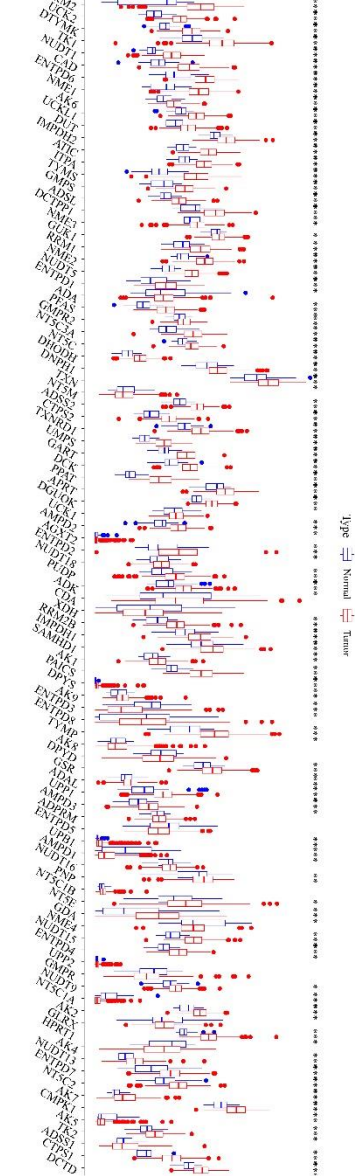


■ Missense Mutation ■ Nonsense Mutation  
 ■ Frame Shift Del ■ In Frame Del  
 ■ Spike Site ■ Nonstop Mutation  
 ■ Frame Shift Ins ■ Multi Hit

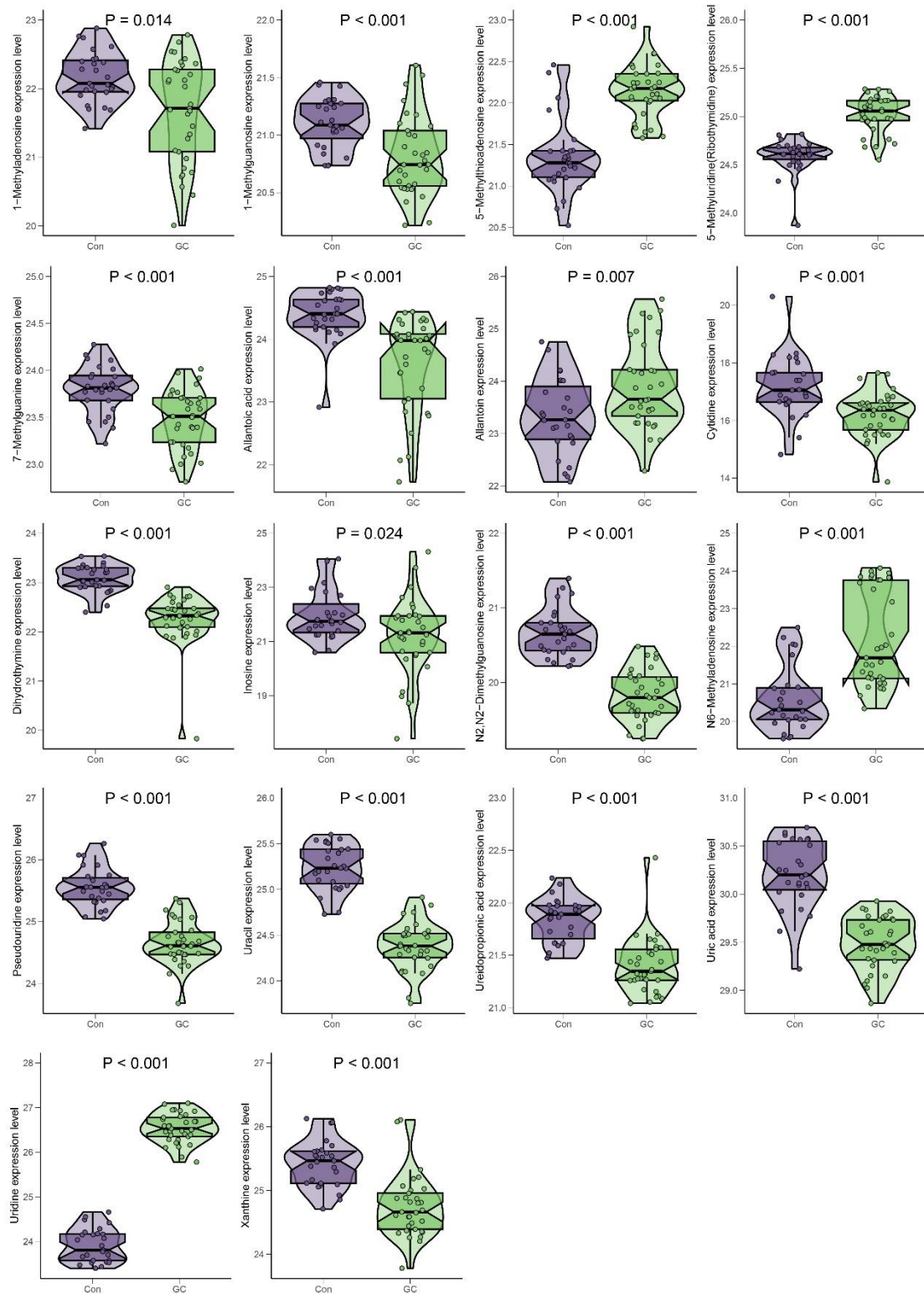
B CNV frequency (%)



D Gene expression

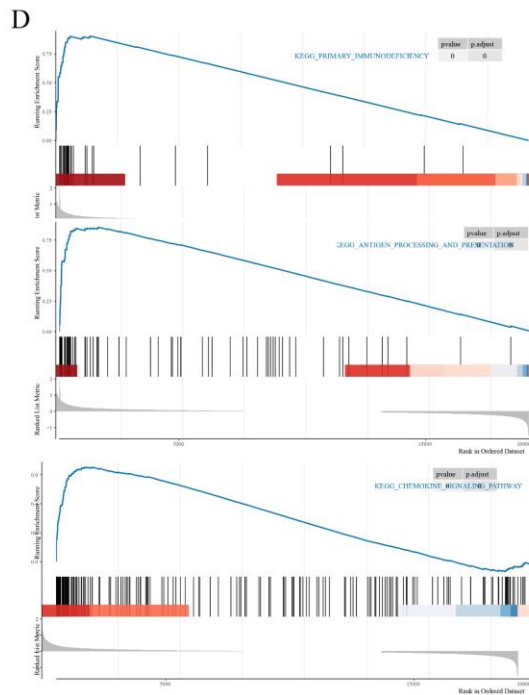
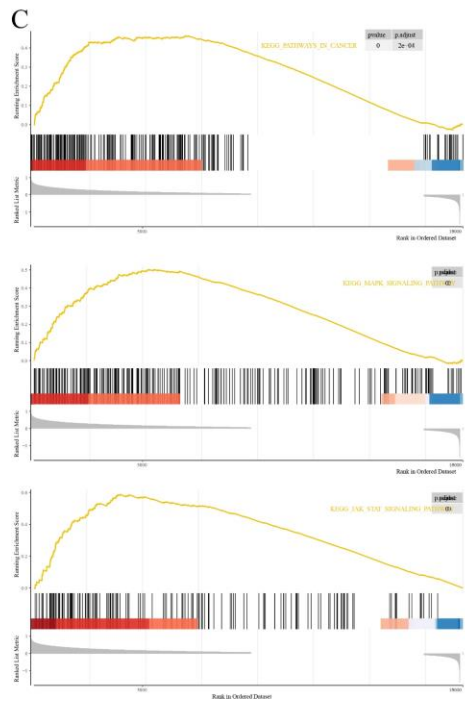
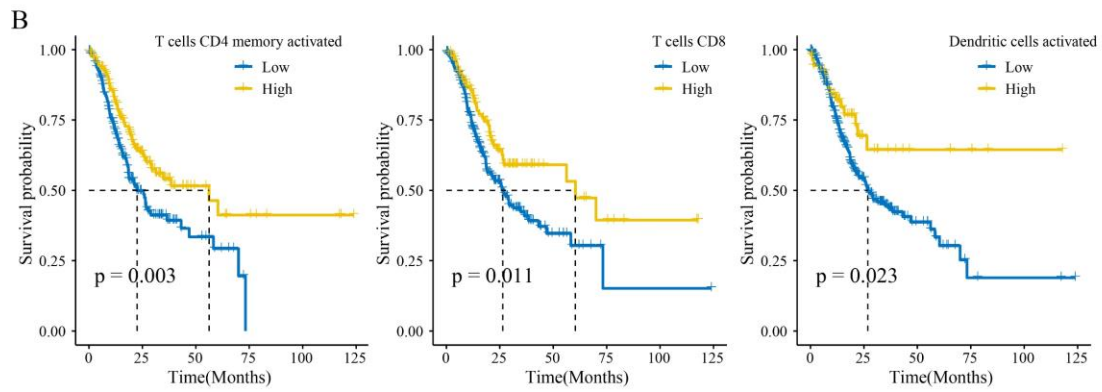
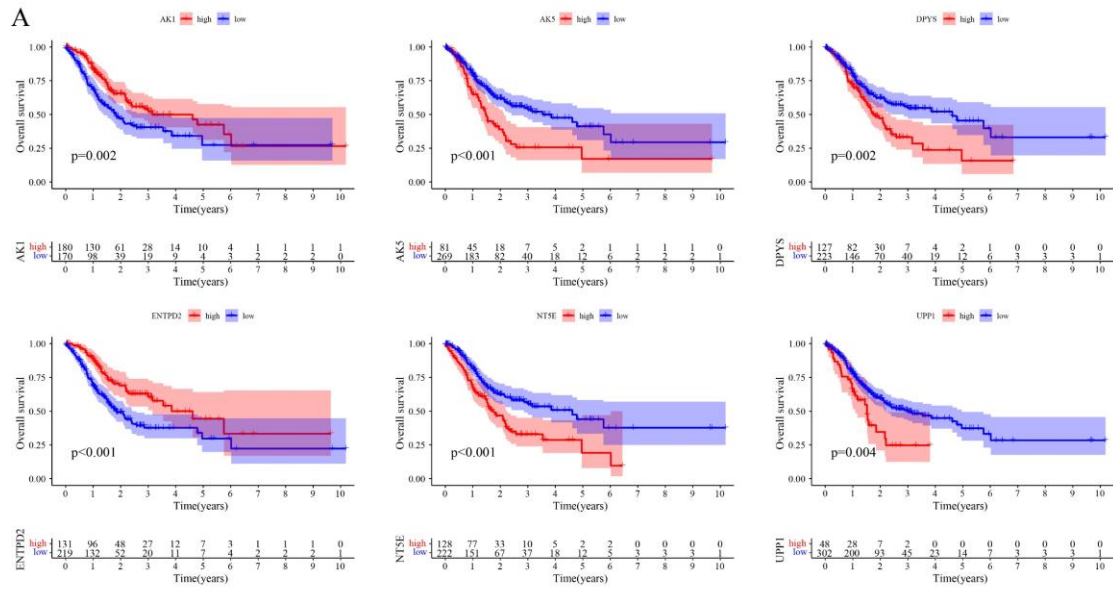


**Supplementary Figure 1.** Genetic variation of NMRG in GC. (A) 161 of 433 patients have genetic alterations of NMRG. (B) CNV mutation frequency of NMRGs. (C) Position of CNV change of NMRG on chromosome. (D) Difference in NMRG expression between normal and GC.

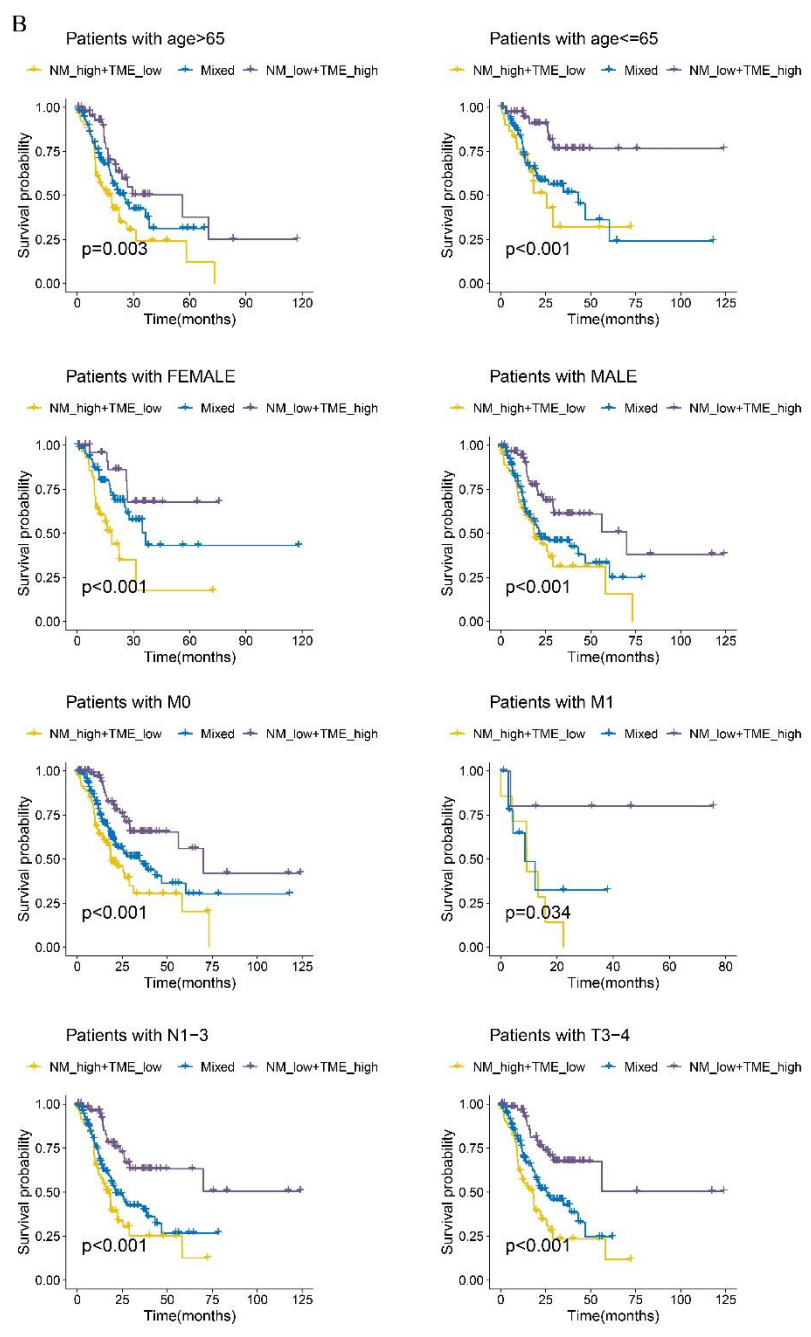
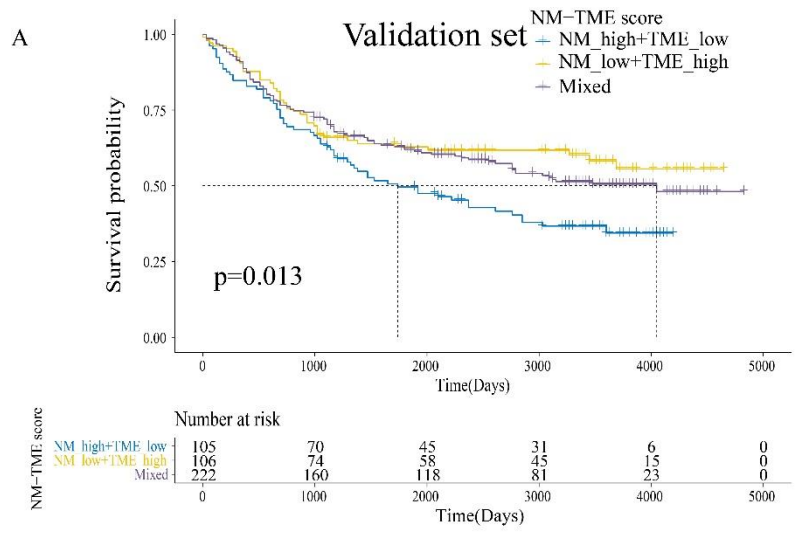


**Supplementary Figure 2.** 18 differentially expressed nucleotide metabolites (1-Methyladenosine, 1-Methylguanosine, 5-Methylthioadenosine, 5-Methyluridine (Ribothymidine), 7-Methylguanine, Allantoic acid, Allantoin, Cytidine,

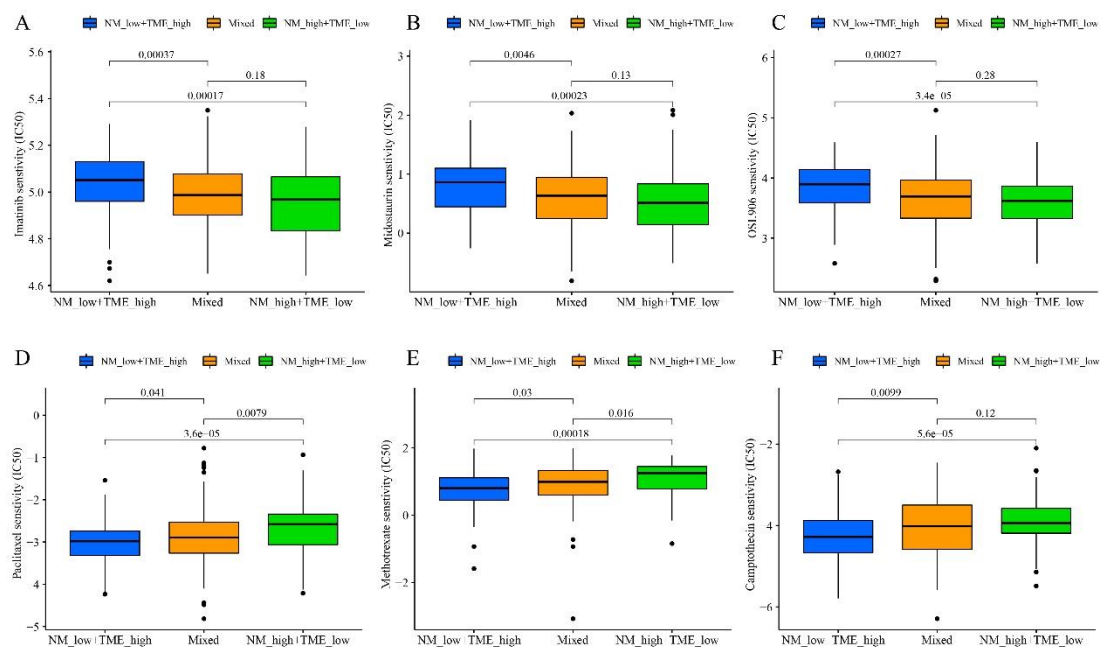
Dihydrothymine, Inosine, N<sup>2</sup>, N<sup>2</sup>-Dimethylguanosine, N<sup>6</sup>-Methyladenosine,  
Pseudouridine, Uracil, Ureidopropionic acid, Uric acid, Uridine, Xanthine).



**Supplementary Figure 3.** (A) KM analysis of 6 NMRGs. (B) KM analysis of 3 immune cells. (C-D) GSEA analysis



**Supplementary Figure 4. (A) Survival analysis in GEO cohort. (B) Survival analysis of patients with different clinical characteristics.**



**Supplementary Figure 5. Drug sensitivity analysis.**

## REACTOME\_METABOLISM\_OF\_NUCLEOTIDES

ADA  
 ADAL  
 ADK  
 ADPRM  
 ADSL  
 ADSS1  
 ADSS2  
 AGXT2  
 AK1  
 AK2  
 AK4  
 AK5  
 AK6  
 AK7  
 AK8  
 AK9  
 AMPD1



AMPD2  
AMPD3  
APRT  
ATIC  
CAD  
CDA  
CMPK1  
CTPS1  
CTPS2  
DCK  
DCTD  
DCTPP1  
DGUOK  
DHODH  
DNPH1  
DPYD  
DPYS  
DTYMK  
DUT  
ENTPD1  
ENTPD2  
ENTPD3  
ENTPD4  
ENTPD5  
ENTPD6  
ENTPD7  
ENTPD8  
GART  
GDA  
GLRX  
GMPR  
GMPR2  
GMPS  
GSR  
GUK1  
HPRT1  
IMPDH1  
IMPDH2  
ITPA  
NME1  
NME2  
NME3  
NME4  
NT5C

NT5C1A  
NT5C1B  
NT5C2  
NT5C3A  
NT5E  
NT5M  
NUDT1  
NUDT13  
NUDT15  
NUDT16  
NUDT18  
NUDT5  
NUDT9  
PAICS  
PFAS  
PNP  
PPAT  
PUDP  
RRM1  
RRM2  
RRM2B  
SAMHD1  
TK1  
TK2  
TXN  
TXNRD1  
TYMP  
TYMS  
UCK1  
UCK2  
UCKL1  
UMPS  
UPB1  
UPP1  
UPP2  
XDH

**Supplementary Table 1.** Gene list of 97 NMRGs.

	GC (n=33)	Healthy individuals (n=27)	p-value
Gender (n, %)			P=0.957
Male	21 (63.6%)	17 (63.0%)	
Female	12 (36.3)	10 (37.0%)	
Age (years, mean±SD)	61.58±11.13	52.70±12.68	P=0.005
Hemoglobin (g/L, mean±SD)	117.79±25.33	125.59±47.19	P=0.009
Creatinine (umol/L, mean±SD)	63.69±15.48	70.67±14.69	P=0.081
Urea (mmol/L, mean±SD)	4.98±1.40	5.29±1.49	P=0.395
Blood glucose (mmol/L, mean±SD)	5.21±1.18	5.16±0.53	P=0.353

**Supplementary Table 2. Clinical characteristics of the GC patients used for untargeted metabolomics.**

gene	HR	HR.95L	HR.95H	pvalue
UPP1	1.360831931	1.08027011	1.714259728	0.008912236
AK5	1.344861349	1.028789416	1.758039129	0.030188605
ENTPD2	0.870614574	0.783846926	0.966986934	0.009690446
NT5E	1.240146195	1.087312493	1.414462351	0.001339277
DPYS	1.5210553	1.042302924	2.219709043	0.029644217
AK1	0.783698577	0.630616399	0.973941464	0.027942729

**Supplementary Table 3. Univariate Cox regression analysis of 97 NMRGs.**

	Coef	boot_SD	Coef..boot_SD
UPP1	0.327541121	0.130596641	2.508036325
AK5	0.182223238	0.220334768	0.827028976
ENTPD2	-0.098240668	0.064524876	-1.522523947
NT5E	0.145816291	0.072871783	2.000998002
DPYS	0.312228438	0.189556705	1.647150587
AK1	-0.278087858	0.129053973	-2.154818257

**Supplementary Table 4.** Correlation coefficients of six NMRGs.

	Coef	boot_SD	Coef..boot_SD
T cells CD8 <sup>+</sup>	-1.34185683	1.26755862	-1.058615207
T cells CD4 memory activated <sup>+</sup>	-2.653592836	2.572796514	-1.031404086
Dendritic cells activated <sup>+</sup>	-3.925520195	4.568644586	-0.859230811

**Supplementary Table 5.** Correlation coefficients of three immune cells.