A Prognostic Nomogram for Predicting Overall Survival in Pediatric Wilms Tumor Based on an Autophagy-related Gene Signature

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Abstract: Background: Wilms Tumor (WT) is the most common primary renal malignancy in children. Autophagy plays dual roles in the promotion and suppression of various cancers.

Objective: The goal of our study was to develop a novel autophagy-related gene (ARG) prognostic nomogram for WT.

Methods: The Cancer Genome Atlas (TCGA) database was used. We screened the expression profiles of ARGs in 136 WT patients. The differentially expressed prognostic ARGs were evaluated by multivariate Cox regression analysis and survival analysis. A novel prognostic nomogram based on the ARGs and clinical characteristics was established using multivariate Cox regression analysis.

Results: First, 69 differentially expressed ARGs were identified in WT patients. Then, multivariate Cox regression analysis was used to determine 4 key prognostic ARGs (CC3CL1, ERBB2, HIF-α, and CXCR4) in WT. According to their ARG expression levels, the patients were clustered into high- and low-risk groups. Next, survival analysis indicated that high-risk patients had significantly poorer overall survival than low-risk patients. The results of functional enrichment analysis suggested that autophagy may play a tumor-suppressive role in the initiation of WT. Finally, a prognostic nomogram with a Harrell's concordance index (C-index) of 0.841 was used to predict the survival probability of WT patients by integrating clinical characteristics and the 4-ARG signature. The calibration curve indicated its excellent predictive performance.

Conclusion: In summary, the ARG signature could be a promising biomarker for monitoring the outcomes of WT. We established a novel nomogram based on the ARG signature, which accurately predicts the overall survival of WT patients.

Keywords: Wilms tumor, autophagy, gene signature, prognostic model, nomogram, TCGA.

1. INTRODUCTION

Wilms tumor (WT), or nephroblastoma, is a type of renal cancer that mainly occurs in the pediatric age group. The incidence of WT is 1 in 10,000, which accounts for 6-14% of malignant tumors in children [1]. WT can be highly cured with a survival rate of 90% [2]. However, the overall survival rate (OS) of some patients with tumor relapse (15-20%) is only 50-60% [3, 4]. Although previous clinical and molecular studies on WT have been reported, effective WT targeted treatment and prognostic biomarkers are still lacking.

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Autophagy is a process that delivers cytoplasmic components to lysosomes for degradation [5, 6] and has been verified to play an important role in various biological and pathological processes, especially in cancer [7]. Autophagy has also been shown to be a mechanism involved in the development of multiple tumors [8, 9]. Autophagy protects cells from programmed cell death, which may partially explain the association between tumor cell survival and autophagy [10]. Early clinical trials have demonstrated the feasibility and promising survival benefit of therapeutics that target autophagy in multiple cancer models [11, 12].

In recent years, some studies have reported a correlation between autophagy and WT. These ARGs may be regulated by multiple signaling pathways and may regulate multiple signaling pathways [13, 14]. For example, the current study...
aimed to investigate the expression of ARGs (BECN1 and ATG4B) in WT, its association with several clinical characteristics and its effect on patient survival [15]. Another study also showed that autophagy deregulation is involved in WT, and targeting autophagy may potentially improve the clinical outcomes of resistant and refractory cases [13]. Therefore, ARGs may be ideal therapeutic targets and prognostic markers in WT.

Since high-throughput expression data are available, it is feasible to use these data to determine whether the overall gene expression patterns of ARGs can predict the survival outcomes of WT patients. In our research, we analyzed the differential expression of ARGs between WT and normal samples to identify their functional enrichment. We also investigated 4 ARGs associated with WT prognosis. A novel nomogram that consists of the screened pivotal ARGs and clinical information was developed. Our nomogram introduces a novel perspective and a promising tool for the prognostic assessment of WT patients.

2. MATERIALS AND METHODS

2.1. Data Acquisition

The general process of our study is shown in Fig. (1). A total of 232 ARGs were obtained from The Human Autophagy Database (http://www.autophagy.lu/). This database aims to reserve human genes involved in autophagy based on PubMed and other biological public databases [16]. The RNA-sequencing (RNA-seq) data and corresponding clinical information of pediatric WT patients in the Therapeutically Applicable Research to Generate Effective Treatments (TARGET) cohort were downloaded and extracted from The Cancer Genome Atlas (TCGA, https://portal.gdc.cancer.gov/) data portal. A total of 136 cases were investigated in this study, including 6 normal samples and 130 WT samples. In the construction of prognostic prediction models, 8 WT cases were excluded due to incomplete clinical information.

Fig. (1). Flowchart of the study design and analysis.
2.2. Differential Autophagy Gene Expression Analysis

The "edgeR" package in R was used to screen differentially expressed ARGs in the normal and WT samples in the TARGET-WT cohort [17]. False Discovery Rate (FDR) < 0.05 and \[\log_2 \text{(fold change)}\] > 1 were considered the cutoff values for identifying significantly differentially expressed ARGs [18]. The ARGs in the TARGET-WT cohort are displayed in volcano plots and box plots.

2.3. ARG-related Prognostic Risk Scoring System Construction and Evaluation

Univariate Cox regression analysis was used to determine the correlation between the ARG signature and OS with the “survival” package in R [19]. Then, genes were further screened by multivariate Cox regression analysis. Only optimal prognosis-related genes in the multivariate Cox regression model were determined to further calculate the risk score [20]. We used the following formula to calculate the risk score of each patient: \( \text{risk score} = \sum_{j=1}^{n} \text{Coef}_j \times x_j \), where \( \text{Coef}_j \) indicates the coefficient and \( x_j \) represents the relative expression level of each ARG. The risk score was standardized by the z-score [21]. Based on the median risk score, we divided the patients into a high-risk group and a low-risk group. Then, the prognosis of the high-risk and low-risk groups was determined by Kaplan-Meier (K-M) survival analysis, and a two-sided log-rank test was used to test the survival differences between the high-risk and low-risk groups. Furthermore, Least Absolute Shrinkage and Selection Operator (LASSO) regression was used to screen clinicopathological factors (including race, ethnicity, age, sex, stage, first event and histologic classification) for inclusion in the Cox regression analyses, and the results are presented as a heat map. By applying univariate and multivariate Cox regression analyses, we established a predictive model. Receiver Operating Characteristic (ROC) curve analysis was performed to evaluate the predictive accuracy of the prognostic risk score model and clinical factors with the “survivalROC” package in R [22, 23]. An area under the ROC curve (AUC) greater than 0.5 indicated good specificity and sensitivity of the model.

2.4. Functional Enrichment Analysis and GSEA

Gene Ontology (GO) functional annotation and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway analyses were performed with the “clusterProfiler” package in R. An FDR < 0.05 was considered statistically significant [24, 25]. Next, we used Gene Set Enrichment Analysis (GSEA, v.4.0, http://software.broadinstitute.org/gsea/index.jsp) software to uncover the biological processes and signaling pathways in which the differentially expressed genes of the high- and low-risk groups were enriched. GSEA was performed at the whole transcriptome level. One thousand permutations were selected, and Affymetrix was used as the chip platform to calculate the Normalized Enrichment Score (NES). \( P < 0.05 \) and FDR \( q \)-value < 0.25 were used to select significant items [26].

2.5. Nomogram Construction and Performance Evaluation

According to the results of the multivariate Cox regression analyses of the risk score and clinicopathological factors, we then constructed a nomogram that predicted the 1-, 3-, and 5-year OS of WT via the “rms” package in R [27]. The nomogram was constructed by integrating clinical pathological variables such as the first event, stage, histology and risk score derived from the prognostic signature. Harrell’s concordance index (C-index), which ranges from 0.5 (representing random chance) to 1.0 (representing a perfectly discriminating model), was used to evaluate the performance of the nomogram [28]. A calibration curve was used to evaluate agreement between the predicted probabilities and the actual outcomes. The degree of calibration of a model reflects the degree of consistency between its predicted and actual values. The consistency of a model is better when its calibration curve is closer to the 45-degree standard line [29]. The AUC was calculated to evaluate the discriminatory capacity of the nomogram. Decision Curve Analysis (DCA) was used to evaluate the clinical effectiveness of the nomogram [30]. The abscissa and ordinate of a DCA curve represent the threshold probability and net benefit, respectively, of the model. A model with a higher DCA curve indicates a greater net benefit.

2.6. Statistical Analysis

All analyses were conducted using R version 3.6.2 (https://www.r-project.org/), and \( P < 0.05 \) was considered statistically significant. In multivariate Cox regression analysis, statistical significance was defined as \( P < 0.10. * P < 0.05, ** P < 0.01 \) and *** \( P < 0.001 \) are shown in the figures.

3. RESULTS

3.1. Differentially Expressed ARG Selection

The expression profiles of 232 ARGs were downloaded from the TCGA database. The TARGET-WT cohort consisted of a total of 130 WT tissues and 6 normal tissues. According to the criteria of FDR <0.05 and \[\log_2 \text{(fold change)}\] >1, a total of 29 upregulated and 40 downregulated ARGs were obtained (Table S and Fig. 2A, B). Furthermore, a box plot was used to show the expression patterns of the 69 differentially expressed ARGs between WT samples and normal samples (Fig. 2C).

3.2. Identification of prognostic ARGs

Due to incomplete clinicopathological or follow-up data, 8 WT cases were excluded. In the TARGET-WT cohort composed of 122 WT patients, we performed univariate Cox regression analysis on the 69 differentially expressed ARGs, and then we identified 6 genes that were shown to have significant prognostic value (\( P<0.05 \), Fig. 3A). Further multivariate Cox regression analysis showed that only CX3CL1 (hazard ratio (HR)=0.724, 95% confidence interval (CI)=0.509-1.030, \( P=0.072 \), ERBB2 (HR=0.583, 95% CI=0.385-0.881, \( P=0.011 \), HIF-1α (HR=0.527, 95% CI=0.291-0.953, \( P=0.034 \), and CXCR4 (HR=0.737, 95% CI=0.558-0.971, \( P=0.030 \) exhibited significant prognostic value for WT. From the forest map of the HRs, we can conclude that all these genes are protective factors (Fig. 3B). The K-M analysis of these genes indicated that the downregulation of CXCR4 was correlated with worse OS (\( P=0.06 \), Fig. 3F). There was no significant difference in the results of CX3CL1, ERBB2, and HIF-1α (Fig. 3C-F).
Fig. (2). Differentially expressed ARGs between WT and normal tissues. (A) Volcano plot of the 232 ARGs from the TARGET-WT cohort. (B) Heatmaps of the 69 differentially expressed ARGs. Red indicates higher gene expression values, while blue indicates lower gene expression values. Black shows indicate genes showing no difference between WT and normal tissues. (C) Boxplot of the 69 differentially expressed ARGs between WT and normal tissues. N indicates normal tissues; T indicates tumor tissues. Gene expression is represented by count values. *$P < 0.05$, **$P < 0.01$, ***$P < 0.001$. (A higher resolution / colour version of this figure is available in the electronic copy of the article).

Fig. (3). Contd…
According to the results of the multivariate Cox regression analysis, we constructed a prognostic risk scoring system based on the expression of the ARGs (Risk score = \sum_{j=1}^{n} Coefj \times Xj), which was then standardized by the z-score. We divided the patients into high-risk and low-risk groups according to their risk score value. Fig. (4) shows the distribution of the prognostic risk score in the TARGET-WT cohort (Fig. 4A), the survival outcomes of the patients in the two groups (Fig. 4B), and a heatmap of the expression levels of the 4 ARGs and clinicopathological factors (Fig. 4C). K-M analysis indicated that the survival rate of patients in the high-risk group was significantly better than that of patients in the low-risk group (P=0.010, n=122). The 1-year OS rates of the high-risk and low-risk groups were 83.4% and 93.4%; the 3-year OS rates were 55.5% and 76.0%; and the 5-year OS rates were 49.7% and 73.9%, respectively (Fig. 4D).

Furthermore, after adjusting for clinicopathological factors such as race, ethnicity, age, sex, stage, first event and histologic classification, the risk score remained an independent prognostic factor for WT patients in the multivariate Cox regression model (HR = 1.505, 95% CI=1.215-1.865, P <0.001, Fig. 5A-B). The AUCs based on the risk score for 1-, 3-, and 5-year survival were 0.755, 0.706, and 0.698, respectively (Fig. 5C-E). These results indicated that the risk score based on the ARGs has certain potential in survival prediction.

### 3.3. Functional Enrichment Analysis

We performed functional enrichment analysis to identify the biological functions and pathways associated with the differentially expressed ARGs. The top 30 enriched GO terms and KEGG pathways are listed in Fig. (6A-B). GO enrichment analysis suggested that the biological processes of the differentially expressed genes were mainly related to “autophagy”, “macro-autophagy” and “regulation of autophagy”. The cellular components of the differentially expressed genes were mainly related to “autophagic vacuole”, “pre-autophagosomal structure” and “vacuolar membrane”. The molecular functions of the differentially expressed genes were mostly enriched in the terms “ubiquitin protein ligase binding”, “small conjugating protein ligase binding” and “phosphatase binding” (Fig. 6A). We identified the top 30 KEGG pathways with an FDR < 0.05, including “autophagy”, “platinum drug resistance”, “NOD-like receptor signaling pathway”, “FoxO signaling pathway” and “p53 signaling pathway”, which were related to WT (Fig. 6B).
Fig. (4). Characteristics of the prognostic gene signature. (A) Distribution of the prognostic index. (B) Survival status of patients in the two groups. (C) The heat map shows the expression profiles of the 4 ARGs and the distribution of clinicopathological variables between the high- and low-risk groups. (D) The relationship between the risk score and the OS of WT patients. (A higher resolution / colour version of this figure is available in the electronic copy of the article).

Fig. (5). The ARG signature was significantly related to survival in WT. Univariate (A) and multivariate (B) Cox regression analyses indicated that first event, stage, histology and ARG signature were independent predictors of prognosis in WT. The 1- (C), 3- (D) and 5-year (E) survival time-dependent ROC curves to evaluate the prognostic significance of the ARG signature and clinicopathological parameters. (A higher resolution / colour version of this figure is available in the electronic copy of the article).
A Prognostic Nomogram for Wilms Tumor

3.4. GSEA

We aimed to investigate possible differences between the high-risk and low-risk groups by using GSEA, which verified that the autophagy-related signature was enhanced in the high-risk group. The results suggested that the enriched GO terms of the high-risk group included “DNA replication initiation”, “mitotic recombination”, “small nucleolar ribonucleoprotein complex” and “ATP-dependent chromatin remodeling” (Fig. 6C-F). Consistently, in the KEGG pathway analysis, we observed that “DNA replication”, “cell cycle”, “aminoacyl tRNA biosynthesis” and “mismatch repair” were enriched in the high-risk group (Fig. 6G-J). In summary, the GSEA results showed the existence of a significant regulatory role for autophagy in high-risk WT patients. This result can provide strong evidence for the targeted therapy of WT.

3.5. Nomogram Construction and Evaluation

According to the results of multivariate Cox proportional hazards regression, we generated a nomogram to predict the probability of 1-, 3- and 5-year OS by incorporating risk score, first event, stage and histology (Fig. 7A). In multivariate Cox proportional hazards regression, there was no significant difference between stages I and II, so we merged stages I and II in the nomogram and compared them with stages III and IV. The C-index of our nomogram was 0.841. Calibration curves indicated that the actual and predicted survival outcomes matched very well for 1-, 3-, and 5-year survival (Fig. 7B-D). The AUC was used to evaluate the predictive accuracy of the nomogram. The AUC values based on the nomogram for 1-, 3-, and 5-year survival were 0.871, 0.879, and 0.856, respectively (Fig. 7E-G). DCA was used to evaluate the clinical effectiveness of the nomogram. According to the DCA results, the net
Fig. (7). Nomogram predicting the 1-, 3- and 5-year survival probability of WT patients. (A) Prognostic nomogram to predict the survival of WT patients. Calibration curves of the nomogram for predicting survival at 1 (B), 3 (C) and 5 years (D). The x-axis is the predicted survival, and the y-axis is the actual survival. ROC curves were used to evaluate the performance of the nomogram at 1 (E), 3 (F) and 5 years (G). Decision curve analysis of the nomogram for predicting the 1- (H), 3- (I) and 5-year (J) cancer-specific survival probabilities. The x-axis is the threshold probability, and the y-axis is the net benefit rate. The horizontal line indicates that all WT patients will survive. The oblique line indicates that none of the WT patients will survive. The dashed line indicates the net benefit. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).
benefits of the nomogram were significantly higher than those of the two extreme cases (Fig. 7H-J).

4. DISCUSSION

It has been reported that autophagy plays a vital role in tumorigenesis, progression, aggressiveness, and resistance to treatment [31, 32]. Autophagy can be targeted for both stimulation and inhibition. Nutrition deprivation, cell stress and mTOR inhibition can achieve stimulation [33], while inhibition can be achieved through multiple targets both upstream (Beclin 1 [34], ULK1 [35] and VPS34 inhibitors [36]) and downstream of the site of lysosomal fusion with the autophagosome [7]. Correcting the dysregulation of autophagy-associated pathways can suppress tumor development and enhance treatment sensitivity [6]. Therefore, it is necessary to elucidate the underlying influence of autophagy regulators on WT.

Recently, multiple studies have explored a large number of molecular biomarkers for WT [37-40]. Some of these studies have investigated a variety of WT gene expression patterns that can be used for risk stratification, targeted treatment, and prognosis prediction [37, 39, 40]. Linjie et al. [13] reported that autophagy deregulation is involved in WT, which is consistent with our findings. However, the sample size of the study was small, with only 3 patients having primary WT, and a larger number of samples is needed for further verification. Maha et al. [15] reported that the ARGs BECN1 and ATG4B were statistically significant discriminators of survival in WT, which is consistent with our result that tumors are probably suppressed by autophagy in the initiation of WT. However, in our study, three was no difference in the expression of BECN1 and ATG4B in tumor patients. In view of the fact that none of the studies incorporated global expression patterns according to ARGs to accurately predict the prognosis of WT patients, based on the TARGET-WT cohort, we first confirmed 69 differentially expressed ARGs. Then, after further multivariate Cox regression analysis, we identified 4 genes that were significantly associated with prognosis. Lower expression levels of CX3CL1, ERBB2, HIF-1α, and CXCR4 were associated with poor prognosis in WT patients. CX3CL1 belongs to the CX3C subgroup of chemokines. Kim et al. [41] reported that CX3CL1 was directly regulated by WT1 and strongly implicated in WT tumorigenesis. Tardáguila et al. [42] found that CX3CL1 expression was downregulated in HER2/neu tumors and acts as a positive modifier of breast cancer in concert with ErbB receptors. ERBB2, commonly known as HER2, encodes a member of the Epidermal Growth Factor (EGF) receptor family of receptor tyrosine kinases. Diseases associated with ERBB2 include glioma, breast cancer and gastric cancer. Salem et al. [43] suggested that the extent of ERBB2 expression is associated with epithelial differentiation in WT. Ragab et al. [44] reported that early stages, homologous epithelial differentiation and ERBB2-positive tumors were associated with an OS advantage in WT patients. HIF-1α encodes the alpha subunit of the transcription factor hypoxia-inducible factor-1. It plays a vital role in embryonic angiogenesis, tumor angiogenesis and hypoxic pathogenesis [45]. Shi et al. [46] found that HIF-1α inhibits the growth of the WT cell line SK-N-NEP-1 in vitro and suppresses tumorigenesis and angiogenesis in vivo. Madan et al. [47] reported that HIF-1α transcriptionally upregulates WT by binding to five response elements in the p53 promoter. This finding has an important implication in the design of anticancer strategies. CXCR4 encodes a CXC chemokine receptor specific for stromal cell-derived factor-1. Lee et al. [48] suggested that the expression of CXCR4 was decreased in WT vessels. This indicates that the downregulation of CXCR4 expression is linked to potential cancer progression, such as infiltration and metastasis. Chatterjee et al. [49] found that CXCR4 antagonism disrupted the interaction between tumors and stroma; it can make cancer cells sensitive to cytotoxic drugs, slow tumor growth and inhibit metastasis. Next, GSEA of the 4 ARGs was also conducted in this study. A series of cancer biological processes and pathways were found to be dysregulated in WT development, which provides proven evidence that autophagy disorders play a vital role in promoting the pathogenesis and progression of WT. Several studies have reported that mismatch repair deficiency was associated with WT [50, 51]. Diets et al. [52] found the loss of heterozygosity of the TRIM28 locus by mitotic recombination in seven WT samples, suggesting that mitotic recombination is linked to WT development and progression. In summary, CX3CL1, ERBB2, HIF-1α, and CXCR4 may play an inhibitory role in tumors by regulating autophagy in WT. These ARGs can be regarded as new targets for treatment and promising prognostic biomarkers in WT.

Then, we constructed a novel risk scoring system based on the expression levels of the 4 ARGs. Compared with clinicopathological parameters, this scoring system improves the ability to predict OS in WT patients. The WT patients were divided into low-risk and high-risk groups based on the risk scoring system. Patients in the high-risk group had significantly poorer OS than patients in the low-risk group. Nomograms have been widely used in patient management and personalized medical assistance, such as for predicting the OS of cancer patients [53]. Here, we developed a nomogram containing the ARG signature, first event, stage and histology. We removed sex from the nomogram variables, although its P value in the multivariate Cox proportional hazards regression analysis was 0.061. Many studies have shown that sex is not associated with OS in WT or the incidence of WT [54, 55]. Calibration curves, ROC curves and DCA based on the TARGET-WT cohort indicated that the 1-, 3- and 5-year survival outcomes corresponded closely with the predicted survival outcomes, which indicates that the prognostic nomogram constructed in this study had high calibration, strong predictive ability and clinical validity. In conclusion, we incorporated ARG expression patterns for predicting the survival of patients with WT for the first time and found a significant relationship between decreased ARG expression levels and poorer OS. The nomogram established in the present study may be beneficial for both physicians and patients to more precisely estimate individualized survival predictions, which would help design better treatment plans.

However, the present study has several limitations. First, the number of normal and WT samples was small, which may affect the reliability of our results. Second, some important clinical information downloaded from TCGA,
such as treatment strategy and vascular invasion, was limited and incomplete. Third, the prognostic nomogram needs further validation in experimental and clinical studies.

CONCLUSION

Here, we identified a reliable 4-ARG risk score model that was significantly associated with the prognosis of WT patients. Furthermore, a novel prognostic nomogram based on the ARG signature and clinicopathological factors could accurately predict the 1-, 3- and 5-year survival probabilities of individual WT patients. Our study provides important evidence for further exploration of the role of autophagy in WT.

LIST OF ABBREVIATIONS

ARG = Autophagy-related Gene  
AUC = Area Under the Receiver Operating Characteristic Curve  
CI = Confidence Interval  
C-index = Harrell's Concordance Index  
DCA = Decision Curve Analysis  
FDR = False Discovery Rate  
GO = Gene Ontology  
GSEA = Gene Set Enrichment Analysis  
HR = Hazard Ratio  
KEGG = Kyoto Encyclopedia of Genes and Genomes  
K-M = Kaplan-Meier  
LASSO = Least Absolute Shrinkage and Selection Operator  
NES = Normalized Enrichment Score  
OS = Overall Survival  
RNA-seq = RNA-sequencing  
ROC = Receiver Operating Characteristic  
TARGET = Therapeutically Applicable Research to Generate Effective Treatments  
TCGA = The Cancer Genome Atlas  
WT = Wilms Tumor

AUTHORS’ CONTRIBUTIONS

Study design: LKH & SSH; Study conduct: SSH & GSL; Data collection: LKH, J CW, XTW & WPX; Data analysis and interpretation: LKH, YG & JL; Manuscript writing: LKH & YJ; Revising manuscript content: LKH & SSH; Final approval of manuscript: All authors.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The TCGA database is publicly available; thus, approval from the local ethics committee was not required.

HUMAN AND ANIMAL RIGHTS

No animals/humans were used for studies that are base of this research.

CONSENT FOR PUBLICATION

Not applicable.

AVAILABILITY OF DATA AND MATERIALS

All analyzed data were obtained from the TCGA database. The original data are available upon request to the corresponding author.

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CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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SUPPLEMENTARY MATERIAL

A list of differentially expressed ARGs between normal samples and WT samples in the TARGET-WT cohort. Supplementary material is available on the publisher’s website along with the published article.

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A Prognostic Nomogram for Wilms Tumor

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