

# 膀胱癌患者尿液外泌体中 miR-494-3p, LncRNA MAGI2-AS3 表达水平及临床价值研究

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**摘要:** **目的** 探讨膀胱癌患者尿液外泌体中微小核糖核酸 (microRNA, miR) -494-3p, 长链非编码 RNA (long non-coding RNA, LncRNA) MAGI2-反义 RNA 3 (MAGI2-antisense RNA 3, MAGI2-AS3) 表达水平及临床应用价值。**方法** 选取重庆两江新区第一人民医院 2021 年 7 月~2023 年 6 月收治的 105 例膀胱癌患者为癌变组, 另选取同期膀胱良性疾病患者 101 例作为良性组。实时荧光定量 PCR (qRT-PCR) 检测尿液外泌体 miR-494-3p 和 LncRNA MAGI2-AS3 水平。Kappa 检验分析尿液外泌体 miR-494-3p 和 LncRNA MAGI2-AS3 与病理活检诊断膀胱癌的一致性; 受试者工作特征 (receiver operating characteristic, ROC) 曲线分析尿液外泌体 miR-494-3p 和 LncRNA MAGI2-AS3 水平对膀胱癌的诊断价值。**结果** 癌变组尿液外泌体 miR-494-3p 水平 ( $1.41 \pm 0.32$ ) 高于良性组 ( $1.02 \pm 0.24$ ), LncRNA MAGI2-AS3 水平 ( $0.79 \pm 0.19$ ) 低于良性组 ( $1.05 \pm 0.22$ ), 差异具有统计学意义 ( $t=9.866, 9.089$ , 均  $P < 0.05$ )。miR-494-3p 高表达组肿瘤直径  $> 3$  cm, T3~T4 期以及淋巴结转移的占比显著高于 miR-494-3p 低表达组, 差异具有统计学意义 ( $\chi^2=5.806, 6.999, 8.289$ , 均  $P < 0.05$ )。LncRNA MAGI2-AS3 低表达组 T3~T4 期及发生淋巴结转移的比例明显高于 LncRNA MAGI2-AS3 高表达组, 差异具有统计学意义 ( $\chi^2=9.244, 7.795$ , 均  $P < 0.05$ )。尿液外泌体 miR-494-3p 和 LncRNA MAGI2-AS3 联合与病理活检诊断膀胱癌的一致性较高 (Kappa 值  $=0.718, P < 0.05$ )。ROC 曲线显示, 尿液外泌体 miR-494-3p 和 LncRNA MAGI2-AS3 水平单独诊断膀胱癌的 AUC (95%CI) 分别为  $0.812 (0.752\sim0.863)$  和  $0.779 (0.716\sim0.833)$ , 尿液外泌体 miR-494-3p 和 LncRNA MAGI2-AS3 水平联合诊断膀胱癌的 AUC(95%CI)[ $0.877, (0.824\sim0.918)$ ] 显著高于两者分别单独诊断 ( $Z=2.053, 2.647, P=0.040, 0.008$ )。**结论** 膀胱癌患者尿液外泌体中 miR-494-3p 水平升高, LncRNA MAGI2-AS3 水平下降, 二者联合对膀胱癌的诊断价值较高。

**关键词:** 膀胱癌; 微小 RNA-494-3p; 长链非编码 RNA MAGI2-反义 RNA 3; 外泌体

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## Study on Expression Levels and Clinical Value of miR-494-3p and LncRNA MAGI2-AS3 in Urine Exosomes of Patients with Bladder Cancer

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**Abstract: Objective** To investigate expression level and clinical application value of microRNA(miR)-494-3p and long non-coding RNA (LncRNA) MAGI2-antisense RNA 3 (MAGI2-AS3) in urine exosomes of patients with bladder cancer. **Methods** A total of 105 bladder cancer patients admitted to Chongqing Liangjiang New Area People's Hospital from July 2021 to June 2023 were selected as the cancer group, and 101 patients with benign bladder diseases were as the benign group. Real-time fluorescence quantitative PCR(qRT-PCR) was applied to detect miR-494-3p and LncRNA MAGI2-AS3 levels in urine exosomes. Kappa test was used to analyze the consistency among miR-494-3p, LncRNA MAGI2-AS3 in urinary exosomes and pathological biopsy diagnosis of bladder cancer. Receiver operating characteristic (ROC) curve was applied to analyze the diagnostic value of miR-494-3p and LncRNA MAGI2-AS3 levels in urinary exosomes for bladder cancer. **Results** The level of miR-494-3p ( $1.41 \pm 0.32$ ) in the urine exosomes of the cancer group was higher than that of the benign group ( $1.02 \pm 0.24$ ), while the level of LncRNA MAGI2-AS3 [ $(0.79 \pm 0.19)$  vs ( $1.05 \pm 0.22$ )] was lower than that of the benign group ( $1.05 \pm 0.22$ ), and the differences were statistically significant ( $t=9.866, 9.089$ , all  $P < 0.05$ ). The proportions of tumor diameter  $> 3$  cm, T3~T4 stage, and lymph node metastasis in the high expression group of miR-494-3p were higher than those in the low expression group, and the differences were significant ( $\chi^2=5.806, 6.999, 8.289$ , all  $P < 0.05$ ). The proportions of T3~T4 stages and lymph node metastasis in the low expression group of LncRNA MAGI2-AS3 were higher than those in the high expression group, and the differences were

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significant ( $\chi^2=9.244$ , 7.795, all  $P<0.05$ ). MiR-494-3p and LncRNA MAGI2-AS3 in urine exosomes combined with pathological biopsy showed high consistency in the diagnosis of bladder cancer (Kappa value=0.718,  $P<0.05$ ). ROC curve showed that the areas under the curve(95% confidence interval) [AUC(95%CI)] of miR-494-3p and LncRNA MAGI2-AS3 levels in urinary exosomes alone for diagnosis of bladder cancer were 0.812 (0.752~0.863) and 0.779 (0.716~0.833), respectively. MiR-494-3p and LncRNA MAGI2-AS3 levels in urinary exosomes combined to diagnose the AUC (95%CI) of bladder cancer 0.877(0.824~0.918) were higher than that of AUC(95%CI) diagnosed separately ( $Z=2.053$ , 2.647,  $P=0.040$ , 0.008).

**Conclusion** The level of miR-494-3p in urine exosomes of patients with bladder cancer was increased, while the level of LncRNA MAGI2-AS3 was decreased. The combination of the two may have high diagnostic value for bladder cancer.

**Keywords:** bladder cancer; micro RNA-494-3p; long non-coding RNA MAGI2-antisense RNA 3; exosomes

据统计,膀胱癌在我国的发病率约为5.8/10万,居恶性肿瘤13位<sup>[1]</sup>。膀胱癌的发生与饮食习惯、接触致癌物质、吸烟、慢性感染等多种因素有关,通常表现出尿痛、排尿难、血尿等<sup>[2-3]</sup>。寻找能够准确诊断且无创易测的指标对膀胱癌诊断具有积极意义。外泌体由细胞分泌,在血液、尿液等体液中广泛存在,其中含有大量遗传物质,肿瘤细胞来源的外泌体能够促进肿瘤生长侵袭<sup>[4]</sup>。近年来,微小核糖核酸(microRNA, miRNA)及长链非编码RNA(long non-coding RNA, LncRNA)在肿瘤中的作用倍受关注,且LncRNA通过与miRNA结合调控靶向基因表达<sup>[5-6]</sup>。多项研究报道,微小RNA(miRNA, miR)-494-3p及LncRNA MAGI2-反义RNA 3(MAGI2-antisense RNA 3, MAGI2-AS3)影响着肺癌、乳腺癌等肿瘤的发生发展<sup>[7-9]</sup>。目前,miR-494-3p及LncRNA MAGI2-AS3在膀胱癌中的研究鲜少报道,且诊断价值尚不清楚。因此,本研究通过检测膀胱癌患者尿液外泌体miR-494-3p和LncRNA MAGI2-AS3水平,探讨尿液外泌体miR-494-3p和LncRNA MAGI2-AS3对膀胱癌的诊断价值及与患者分期等病理特征的关系,为膀胱癌的诊断提供参考。

## 1 材料与方法

**1.1 研究对象** 选取本院2021年7月~2023年6月收治的105例膀胱癌患者为癌变组,其中男性61例、女性44例,平均年龄 $56.48 \pm 8.52$ 岁,平均体重指数 $22.47 \pm 2.61$  kg/m<sup>2</sup>。另选取同期101例膀胱良性疾病患者作为良性组(33例膀胱平滑肌瘤,18例膀胱血管瘤,29例膀胱息肉,21例膀胱囊肿),其中男性53例、女性48例,平均年龄 $54.86 \pm 7.53$ 岁,平均体重指数 $22.71 \pm 2.85$  kg/m<sup>2</sup>,两组一般资料具有可比性( $\chi^2=0.658$ ,  $t=1.444$ , 0.631, 均 $P>0.05$ )。收集癌变组肿瘤直径、分期等病理特征。本研究获医学伦理委员会准批(伦理号:2021-083)。

癌变组纳入标准:①经手术病理或膀胱镜检查确诊;②签署知情同意书;③首次确诊,入组前未进行相关治疗。排除标准:①临床资料不全;②并发自身免疫性、血液性、传染性疾病;③并发其它部

位肿瘤;④器官衰竭。

良性组纳入标准:①经膀胱镜和CT等检查确诊为膀胱平滑肌瘤、血管瘤、息肉、囊肿等良性疾病;②其它器官功能正常。排除标准:①近期接受免疫抑制剂等药物治疗;②并发血液性、恶性肿瘤等疾病。

**1.2 仪器与试剂** 流式细胞仪(赛默飞世尔科技);PCR仪(美国Bio-Rad公司);抗人CD63抗体(美国Abcam公司);外泌体提取试剂盒(美国ABI公司);RNA提取试剂盒及逆转录试剂盒(日本TAKARA公司)。

## 1.3 方法

**1.3.1 尿液外泌体的提取与鉴定:** 癌变组及良性组患者均留取晨起中段尿约100 ml,存放于-80℃。外泌体提取试剂盒分离尿液外泌体。流式细胞术检测外泌体标记物CD63表达情况。

**1.3.2 尿液外泌体miR-494-3p和LncRNA MAGI2-AS3水平检测:** 实时荧光定量PCR检测尿液外泌体miR-494-3p和LncRNA MAGI2-AS3水平,提取外泌体中RNA,再合成互补DNA进行RCR反应,反应体系(25 μl): cDNA(2 μl),正义引物(1 μl),反义引物(1 μl), RCR预混液(12.5 μl),去RNA酶水(8.5 μl)。miR-494-3p正义引物: 5'-GATACTC GAAGGAGAGGTTGTC-3',反义引物: 5'-GAGGTT TCCCGTGTATGTTTCAT-3'; LncRNA MAGI2-AS3正义引物: 5'-CACCTTGCTTGACAACCTGA-3',反义引物: 5'-CATTACAGCTCGGCTACTGC-3'。以2<sup>-ΔΔCt</sup>法计算miR-494-3p和LncRNA MAGI2-AS3相对表达水平。

**1.4 统计学分析** SPSS 22.0处理数据,计量资料符合正态分布,以均数±标准差( $\bar{x} \pm s$ )表示,两组间比较采用 $t$ 检验。计数资料以 $n(\%)$ 表示,行 $\chi^2$ 检验。Kappa检验分析尿液外泌体miR-494-3p和LncRNA MAGI2-AS3与病理活检诊断膀胱癌的一致性;受试者工作特征(receiver operating characteristic, ROC)曲线分析尿液外泌体miR-494-3p和LncRNA MAGI2-AS3水平对膀胱癌的诊断价值。以 $P<0.05$ 为差异有统计学意义。

## 2 结果

2.1 外泌体鉴定 见图1。透射电子显微镜下观察外泌体,结果显示提取的外泌体为杯状双层膜结构、直径30~150 nm。流式细胞术结果显示,标记物CD63呈阳性。

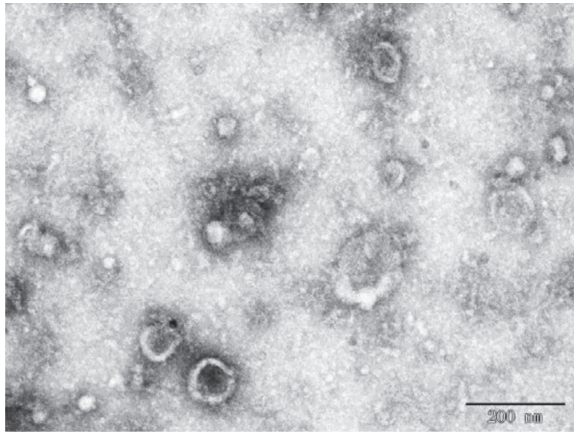


图1 电镜下外泌体形态

2.2 良性组和癌变组尿液外泌体 miR-494-3p 和 LncRNA MAGI2-AS3 水平比较 癌变组尿液外泌体 miR-494-3p 水平 ( $1.41 \pm 0.32$ ) 高于良性组 ( $1.02 \pm 0.24$ ), LncRNA MAGI2-AS3 水平 ( $0.79 \pm 0.19$ ) 低于良性组 ( $1.05 \pm 0.22$ ), 差异有统计学意

义 ( $t=9.866, 9.089$ , 均  $P < 0.05$ )。

2.3 膀胱癌患者尿液外泌体 miR-494-3p 和 LncRNA MAGI2-AS3 水平与临床病理特征的关系 见表1。以膀胱癌患者尿液外泌体 miR-494-3p 水平均值 (1.41) 为界限分为 miR-494-3p 高表达组 ( $n=57, \geq 1.41$ ) 和 miR-494-3p 低表达组 ( $n=48, < 1.41$ )。miR-494-3p 高表达组肿瘤直径  $> 3$  cm, T3~T4 期以及淋巴结转移的占比显著高于 miR-494-3p 低表达组, 差异具有统计学意义 ( $\chi^2=5.806, 6.999, 8.289$ , 均  $P < 0.05$ )。以膀胱癌患者尿液外泌体 LncRNA MAGI2-AS3 水平均值 (0.79) 为界限分为 LncRNA MAGI2-AS3 高表达组 ( $n=50, \geq 0.79$ ) 和 LncRNA MAGI2-AS3 低表达组 ( $n=55, < 0.79$ )。与 LncRNA MAGI2-AS3 高表达组比较, LncRNA MAGI2-AS3 低表达组 T3~T4 期及发生淋巴结转移的比例明显升高, 差异具有统计学意义 ( $\chi^2=9.244, 7.795$ , 均  $P < 0.05$ )。

2.4 尿液外泌体 miR-494-3p 和 LncRNA MAGI2-AS3 与病理活检诊断膀胱癌的一致性 见表2。Kappa 检验显示, 尿液外泌体 miR-494-3p 和 LncRNA MAGI2-AS3 两者联合与病理活检诊断膀胱癌的一致性较高 (Kappa 值  $=0.718, P < 0.05$ )。

表1 膀胱癌患者尿液外泌体 miR-494-3p 和 LncRNA MAGI2-AS3 水平与临床病理特征的关系 [ $\bar{x} \pm s, n(\%)$ ]

类别	miR-494-3p		$t/\chi^2$	$P$	LncRNA MAGI2-AS3		$t/\chi^2$	$P$
	高表达组 ( $n=57$ )	低表达组 ( $n=48$ )			高表达组 ( $n=50$ )	低表达组 ( $n=55$ )		
年龄 (岁)	$57.39 \pm 8.65$	$55.40 \pm 8.37$	1.192	0.236	$55.32 \pm 8.20$	$57.53 \pm 8.81$	1.327	0.188
性别	男	32 (56.14)	0.196	0.658	26 (52.00)	35 (63.64)	1.457	0.227
	女	25 (43.86)			24 (48.00)	20 (36.36)		
肿瘤直径 (cm) $\geq 3$	36 (63.16)	19 (39.58)	5.806	0.016	22 (44.00)	33 (60.00)	2.688	0.101
	$< 3$	21 (36.84)			28 (56.00)	22 (40.00)		
分期	TA	5 (8.77)	6.999	0.030	10 (20.00)	4 (7.27)	9.244	0.010
	T1~T2	24 (42.11)			28 (56.00)	23 (41.82)		
	T3~T4	28 (49.12)			12 (24.00)	28 (50.91)		
淋巴结转移	是	30 (52.63)	8.289	0.004	13 (26.00)	29 (52.73)	7.795	0.005
	否	27 (47.37)			37 (74.00)	26 (47.27)		
远处转移	是	23 (40.25)	2.036	0.154	15 (30.00)	21 (38.18)	0.778	0.378
	否	34 (59.65)			35 (70.00)	34 (61.82)		

表2 尿液外泌体 miR-494-3p 和 LncRNA MAGI2-AS3 与病理活检诊断膀胱癌的一致性

外泌体 miR-494-3p+LncRNA MAGI2-AS3	病理活检	
	膀胱癌 ( $n=105$ )	膀胱良性病变 ( $n=101$ )
膀胱癌 ( $n=108$ )	92	16
膀胱良性病变 ( $n=98$ )	13	85

2.5 尿液外泌体 miR-494-3p 和 LncRNA MAGI2-

AS3 水平对膀胱癌的诊断价值 见表3, 图2。以膀胱癌的发生为因变量, 以尿液外泌体 miR-494-3p 和 LncRNA MAGI2-AS3 水平为检验变量在 SPSS 中绘制 ROC 曲线, 结果显示, 尿液外泌体 miR-494-3p 和 LncRNA MAGI2-AS3 水平联合诊断膀胱癌的曲线下面积 (area under the curve, AUC) 为 0.877, 显著高于两者单独诊断的 AUC ( $Z=2.053, 2.647, P=0.040, 0.008$ )。



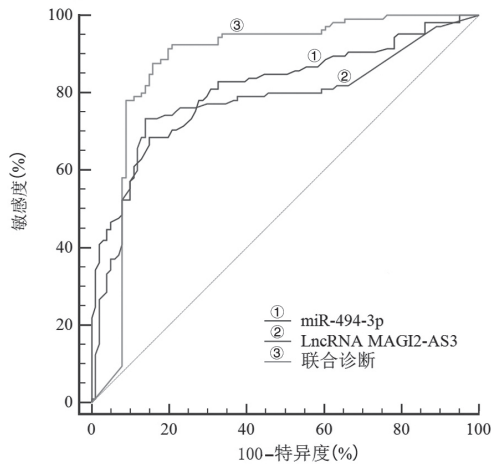


图2 尿液外泌体 miR-494-3p 和 LncRNA MAGI2-AS3 水平诊断膀胱癌的 ROC 曲线

### 3 讨论

与血液相比,尿液受机体其它系统的影响较小,膀胱为尿液储存器官,故尿液标志物比血液标志物更能准确的反映膀胱部位病变<sup>[10]</sup>。外泌体为细胞排泄物,能够参与机体免疫应答、影响肿瘤生长。miR-494-3p 和 LncRNA MAGI2-AS3 影响多种肿瘤的发生发展,因此,探讨尿液外泌体 miR-494-3p 和 LncRNA MAGI2-AS3 水平对膀胱癌的诊断价值具有重要意义。

miR-494-3p 前体是位于染色体 14q32.31 区域的 miR-494,既往研究报道,miR-494-3p 在癌症中

发挥着抑癌或促癌基因的作用<sup>[11]</sup>。郭蕊静等<sup>[12]</sup>研究表明,乳腺癌组织中 miR-494-3p 水平较癌旁组织升高,且 miR-494-3p 被 LncRNA 海绵化后癌细胞增殖受到抑制,即 miR-494-3p 在乳腺癌中发挥着促癌基因作用。本研究结果显示,与良性组相比,癌变组尿液外泌体中 miR-494-3p 水平显著升高,提示 miR-494-3p 可能会影响膀胱癌的发生过程。然而李金昌等<sup>[13]</sup>研究报道,胃癌患者血清外泌体中 miR-494-3p 水平较健康人群降低,即 miR-494-3p 在胃癌中发挥着抑癌基因的作用,与本研究结果相反,这可能是由于 miR-494-3p 在不同肿瘤中的作用机制不同。本研究通过进一步分析膀胱癌患者尿液外泌体 miR-494-3p 水平与其病理特征关系发现,不同肿瘤直径、分期及淋巴结转移患者尿液外泌体 miR-494-3p 水平存在较大差异,提示 miR-494-3p 可能会影响膀胱癌进展程度。此外,Xü 等<sup>[14]</sup>进行的细胞及动物研究表明,抑制 miR-494-3p 表达能够限制膀胱癌细胞生长、迁移,阻碍裸鼠肿瘤生长。结合 Xü 等<sup>[14]</sup>研究推测 miR-494-3p 高表达通过促进肿瘤细胞生长增殖促进人体内膀胱癌发生发展。本研究进一步采用 ROC 分析发现,尿液外泌体 miR-494-3p 水平对膀胱癌具有一定的诊断价值,现有研究中尚无报道,且当患者尿液外泌体 miR-494-3p 水平高于 1.24 时,癌变的可能性较高。

表3 尿液外泌体 miR-494-3p 和 LncRNA MAGI2-AS3 水平对膀胱癌的诊断价值

类别	AUC	截断值	95%CI	敏感度 (%)	特异度 (%)	约登指数
miR-494-3p	0.812	1.24	0.752-0.863	68.57	85.15	0.537
LncRNA MAGI2-AS3	0.779	0.91	0.716-0.833	73.33	86.14	0.595
联合诊断	0.877	-	0.824-0.918	87.62	84.16	0.718

LncRNA MAGI2-AS3 是新发现的 RNA,人类 LncRNA MAGI2-AS3 编码基因位于染色体 7q21.1 区域,目前对 LncRNA MAGI2-AS3 的研究尚不够深入<sup>[15-16]</sup>。王冰等<sup>[17]</sup>研究发现,LncRNA MAGI2-AS3 能够抑制非小细胞肺癌细胞侵袭。本研究发现,癌变组尿液外泌体中 LncRNA MAGI2-AS3 水平显著低于良性组,该结果提示 LncRNA MAGI2-AS3 可能与膀胱癌的发生有关。此外,LncRNA MAGI2-AS3 高表达组患者肿瘤直径小于 LncRNA MAGI2-AS3 低表达组,T3~T4 及淋巴结转移占比低于 LncRNA MAGI2-AS3 低表达组,提示 LncRNA MAGI2-AS3 可能在一定程度上影响膀胱癌进展,有望成为膀胱癌潜在治疗靶点。SHEN 等<sup>[18]</sup>报道,LncRNA MAGI2-AS3 与膀胱癌分期呈负相关,与本研究结果相一致。本研究进

一步分析尿液外泌体 LncRNA MAGI2-AS3 水平对膀胱癌的诊断价值发现其诊断价值较高,且当患者尿液外泌体 LncRNA MAGI2-AS3 水平低于 0.91 时,膀胱癌的发生几率较高。结合相关报道推测 LncRNA MAGI2-AS3 可能通过调节上皮间质转化等过程影响膀胱癌发生进展,具体机制有待进一步探讨。

TANG 等<sup>[19]</sup>的研究报道,LncRNA MAGI2-AS3 通过靶向调节 miR-31-5p 抑制膀胱癌进展。结合前人研究<sup>[19-20]</sup>推测,miR-494-3p 有可能作为 LncRNA MAGI2-AS3 的下游基因,二者共同影响膀胱癌细胞增殖、侵袭,从而共同调节膀胱癌发生发展,但二者的具体信号通路有待细胞及动物实验明确。本研究 Kappa 检验显示,尿液外泌体 miR-494-3p 和 LncRNA MAGI2-AS3 两者联合与病理活

检诊断膀胱癌的一致性较高,因此,miR-494-3p和LncRNA MAGI2-AS3有望成为临床诊断膀胱癌的标记物。进一步比较发现,尿液外泌体miR-494-3p和LncRNA MAGI2-AS3联合诊断膀胱癌的AUC及敏感度均优于两者单独诊断,提示联合诊断价值更高,建议临床上同时检测尿液外泌体miR-494-3p和LncRNA MAGI2-AS3水平对膀胱良性疾病及癌变患者进行区分诊断。

综上所述,膀胱癌患者尿液外泌体中miR-494-3p水平升高,LncRNA MAGI2-AS3水平下降,miR-494-3p和LncRNA MAGI2-AS3联合对膀胱癌的诊断价值较高,有助于膀胱癌的临床诊疗。但由于经费、时间限制,本研究尚未检测健康人群尿液外泌体miR-494-3p和LncRNA MAGI2-AS3水平,尿液外泌体miR-494-3p和LncRNA MAGI2-AS3对膀胱癌的诊断价值有待验证。

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