·特约综述·

尿液检测技术在膀胱癌无创诊断中的研究进展

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摘 要:膀胱癌是泌尿系统最常见的肿瘤之一,当前膀胱镜检查加病理活检是确诊和随访观察治疗后肿瘤复发进展的金标准,但该检查技术有创且存在有时因尿道狭窄、肿瘤出血致视野不清、取材不充分而影响判断等缺点。因此开发能媲美于膀胱镜检查的无创诊断方法一直是研究者们关注的热点。本文通过文献检索分析归纳总结近10年关于膀胱癌尿液无创诊断研究现状,并简要介绍本团队在该领域的相关研究进展。

关键词:膀胱癌;无创诊断;尿液
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The Advances on Urine Testing Technology in Noninvasive Diagnosis of Bladder Cancer

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Abstract: Bladder cancer is one of the most commonly seen tumors in the urinary system, cystoscopy and biopsy currently remain the gold standard procedure for diagnosis and surveillance. Yet, they are invasive and may undermine the diagnosis due to unclear vision and insufficient depth of biopsy caused by urethral stricture or tumor bleeding. Therefore, it has been a hotspot issue for researchers to explore noninvasive diagnostic methods comparable to the conventional cystoscopy. This paper reviews the literature regarding the noninvasive urinary biomarkers for the detection of bladder cancer in the latest decade and briefly introduces the relevant research of our team.

Key words: bladder cancer; noninvasive diagnosis; urine
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膀胱癌是男性第四大常见癌症,女性第十二大常见癌症。2019年美国新增膀胱癌病例80 470人,死亡17 670人[1]。大部分罹患浅表性膀胱癌的临床病例经积极治疗后预后良好,但对于晚期膀胱

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癌治疗效果却不佳。因此通过肿瘤早诊理论上可提升该疾病的治疗效果。血尿是膀胱癌最常见的症状,但对于膀胱癌的阳性预测值仅有8%[2]。指南推荐对血尿患者首先进行泌尿系超声和/或CT检查,膀胱镜检查和活检是初发诊断和术后复发监测的"金标准"[3]。膀胱癌患者中,大约有75%为非肌层浸润性膀胱癌(Ta/T1期,NMIBC),25%为肌层浸润性膀胱癌(T2-T4期,MIBC)[3]。非肌层浸润性膀胱癌通常行经尿道膀胱肿物电切术(transurethral resection of bladder tumor, TURBt),根据不同的危险分层,术后5年内有31%~78%患者出现膀胱肿瘤复发需再次或多次行TURBt手术,有0.8%~45%患者因未及早发现肿瘤复发而进展为肌层浸润性膀胱癌[4]。因此,非肌层浸润性膀胱癌患者TURBt术后每3~6个月需做一次膀胱镜检查[3]。但膀胱镜检查为有创性检查,有可能导致泌尿系感染、前列腺损伤、尿道狭窄等,且临床应用受到外科医生经验水平及场地设备等制约,不利于肿瘤早期筛查和术后监测。因此,研究者们致力于寻求无创、便捷、准确的诊断方法辅助和改进膀胱肿瘤的检测,以期最终补充甚至取代膀胱镜检查。我们使用"(bladder cancer OR transitional cell carcinoma OR urothelial cell carcinoma) AND (detection OR diagnosis) AND urine AND (biomarker OR assay)"关键词进行了MEDLINE/Pubmed系统检索,对近10年相关临床研究及荟萃分析进行归纳总结,对尿液检测技术在膀胱癌无创诊断中的研究进展做一综述,并介绍我们团队在该领域的相关研究。

1 尿细胞学

从尿液或膀胱冲洗液标本中检测脱落癌细胞是首个广泛应用于临床的膀胱癌无创诊断方法。这一方法检测膀胱癌的特异度高达99%(95% CI: 83% ~ 99.7%)[5],而灵敏度因肿瘤分级而异,检测高级别肿瘤灵敏度较高(84%),低级别肿瘤灵敏度却低至16%[6]。炎症、上皮不典型增生以及放化疗后组织改变等因素,导致其存在12%的假阳性率[7]。尿脱落细胞学对于低级别肿瘤检测的低敏感性是其临床应用的主要限制因素,这主要是因为低级别肿瘤具有更强的细胞间粘附性,且缺乏显著的细胞不典型性和明确统一的诊断标准[8-9]。近年来一些多中心研究结果表明,即使是高级别肿瘤,尿细胞学也显示出了比既往数据更低的灵敏度[10-11]。因此指南推荐尿液细胞学仅作为膀胱镜的辅助手段来更准确地检测高级别肿瘤[3]。

2 FDA认证的尿液生物标志物检测方法

由于尿脱落细胞学检测灵敏度低,且阅片依赖于病理医生的主观经验,容易产生偏倚。因此探索具有高敏感性及特异性,且客观性更强的检查方法成为膀胱癌早期诊断的研究热点问题。随着尿液肿瘤标记物研究的不断发展,目前用于诊断膀胱癌的尿液肿瘤标记物层出不穷。美国食品和药物管理(The U.S. Food and Drug Administration, FDA)认证了6种尿液生物标志物检查方法,用以诊断或监测膀胱癌:定量NMP22(NMP22 BC),定性NMP22(NMP22 BladderChek),定量BTA(BTA TRAK),定性BTA(BTA stat),荧光原位杂交(FISH, UroVysion),荧光免疫组化(uCyt+/Immuno-Cyt),其中定性NMP22与BTA可做床边检测,其他则为实验室检测[12]。

2.1 核基质蛋白22

核基质蛋白22(nuclear matrix protein 22, NMP22)是构成细胞核网状支架结构的重要成分,它在DNA复制、转录以及RNA的加工和调控基因表达等方面发挥生物功能。细胞死亡后释放NMP22,以可溶性复合物或片段形式存在于人尿液中。研究表明,膀胱癌患者尿中NMP 22浓度显著高于正常人[13-14]。根据一项荟萃分析,定量(临界值>10 U/mL)和定性NMP22灵敏度分别为0.69 (95% CI: 0.62 ~ 0.75)与0.58 (95% CI: 0.39 ~ 0.75),特异度分别为0.77 (95% CI: 0.70 ~ 0.83)、0.88 (95% CI: 0.78 ~ 0.94)[12]。与尿液细胞学相比,NMP22检测低级别肿瘤(G1)的敏感性较高(NPM22:83%;尿液细胞学:38%; $P<0.05$),而总体特异性较低(NPM22:68%;尿液细胞学:96%; $P<0.05$)[15],引起假阳性的原因主要有以下几种:泌尿系感染、尿路结石、近期留置尿管、肠代膀胱、其它泌尿生殖系统肿瘤和接受器械检查等,研究表明,当排除以上这六类原因导致血尿的病例后,NMP22检测膀胱癌的特异性达95.6%[16]。

2.2　膀胱肿瘤相关抗原

膀胱肿瘤相关抗原(bladder tumor antigen，BTA)试验是采用单克隆抗体检测尿中的补体因子H或补体因子H相关蛋白，它们可影响补体激活途径，使肿瘤免受免疫攻击，促进肿瘤生长[17]。定量(BTA TRAK)和定性(BTA stat)BTA灵敏度分别为0.65（95% CI：0.54～0.75）、0.64（95% CI：0.58～0.69），特异度分别为0.74（95% CI：0.64～0.82）、0.77（95% CI：0.73～0.81）[12]。一项对比BTA与尿脱落细胞学诊断效能的荟萃分析提示，BTA stat的灵敏度和特异度分别为70%和75%，BTA TRAK的灵敏度和特异度分别为66%和65%，而尿脱落细胞学的灵敏度和特异度分别为55%和94%[18]。尤其在检测低级别肿瘤方面，BTA stat显示出了比尿脱落细胞学更高的灵敏度（分别为58%与21%）[19]。BTA与NMP22检测尿路上皮癌的优缺点及导致假阳性的因素相似，较低的特异性及较高的假阳性率成为了限制这两者独立应用于临床的原因。

2.3　荧光原位杂交技术

膀胱肿瘤的发生与3、7、17号染色体非整倍性及9号染色体P16抑癌基因位点缺失密切相关，荧光原位杂交技术(fluorescence in situ hybridization，FISH)可通过荧光标记的核酸探针检测肿瘤细胞染色体的改变[20]。一项涵盖了15项研究的荟萃分析显示，FISH（UroVysion)的灵敏度和特异度分别为0.72（0.69~0.75)和0.83（0.82~0.85)[21]。另一项研究表明UroVysion检测低级别肿瘤的敏感性为40.8%，高于脱落细胞学(14.3%)[22]。此外，Skacel等报道，对尿脱落细胞学检查未能确定或非典型性改变标本再行FISH检测，敏感性及特异性分别达100%与89%，提示对细胞学检查无法确诊的肿瘤病例，FISH可作为有效的补充检测手段[23]。

2.4　荧光免疫组织化学染色技术

荧光免疫组化(uCyt+/ImmunoCyt)利用三种荧光单克隆抗体(M344、LDQ10和19A211)检测尿脱落细胞中膀胱癌特有的三种抗原，其中M344、LDQ10是膀胱癌粘蛋白抗原，在正常尿路上皮细胞中不表达，19A211是糖基化癌胚抗原的高分子量成分[24]。uCyt+/ImmunoCyt的灵敏度和特异度分别为0.725(95%CI：0.683~ 0.765)、0.657(95%CI：0.629～0.685)[25]。检测低级别肿瘤的敏感性为0.65（95%CI：0.47~0.80)，不仅高于脱落细胞学，且高于FISH(0.42，95%CI：0.25~0.60)[12]。多项研究表明，uCyt+/ImmunoCyt结合尿脱落细胞学显示出了比二者单独应用更高的灵敏性，而特异性却远低于脱落细胞学单独应用[25-26]。

表1总结了尿液细胞学及FDA认证的六种尿液检测方法的诊断效能。FDA认证的这六种尿液检测方法均显示出比尿细胞学更高的敏感性，尤其是在诊断低级别肿瘤方面，但其特异性却普遍低于尿细胞学检查[12]，并且操作复杂、价格高。目前已有多种商品化的FISH试剂盒用于临床，但尚无足够的临床资料证明上述检测方法可取代传统镜检和尿液细胞学在膀胱肿瘤诊断中的作用。

3　新型尿液生物标志物检测方法

由于FDA认证的膀胱癌尿液无创检测方法未能广泛应用于临床，研究者们致力于探索新型尿液生物标志物，包括蛋白标志物和遗传物质相关

表1　尿液细胞学及FDA认证的生物标志物

Table 1　Cytology and FDA-approved biomarkers

Marker	Method	Sensitivity/%(95%CI)	Specificity/%(95%CI)
Cytology[5]	Giemsa or HE	34（20-53）	99（83-100）
NMP22 BC[12]	ELISA	69（62-75）	77（70-83）
NMP22 BladderChek[12]	Point-of-care office test	58（39-75）	88（78-94）
BTA TRAK[12]	ELISA	65（54-75）	74（64-82）
BTA stat[12]	Point-of-care office test	64（58-69）	77（73-81）
UroVysion[12]	FISH	72（69-75）	83（82-85）
uCyt+/ImmunoCyt[25]	ICC	73（68-77）	66（63-69）

HE：hematoxylin-eosin staining；ELISA：enzyme linked immunosorbent assay；FISH：fluorescence in situ hybridization；ICC：immunocytochemistry

的标志物。

3.1 蛋白生物标志物

利用质谱技术和生物信息学等技术,对比膀胱肿瘤组织和癌旁正常组织,研究者们发现了成百上千种差异性表达的蛋白[27],其中大部分已被证实不能有效地检测肿瘤[28],目前只有少数蛋白具有一定诊断价值和应用前景。

生存素(survivin)能够抑制细胞凋亡并诱导细胞增殖,调节细胞周期,支持肿瘤细胞的血管生成,有利于肿瘤干细胞存活[29]。生存素在膀胱癌组织中的表达水平高于癌旁组织,且随着肿瘤分级和分期升高而升高[30]。荟萃分析显示生存素诊断膀胱癌的总体灵敏度和特异度分别为0.79(95%CI:0.73~0.84)、0.87(95%CI:0.79~0.92)[29];另一荟萃分析提示生存素的灵敏度高于细胞学(生存素:0.748;细胞学:0.433),但特异度稍逊于细胞学(生存素:0.942;细胞学:0.983)[31]。

细胞角蛋白(cytokeratins, CK)作为一种中间丝,存在于所有上皮细胞,其中某些角蛋白在尿路上皮肿瘤中高表达[32]。尿膀胱癌抗原(urinary bladder cancer, UBC)检测通过测定尿液中的细胞角蛋白8和18(cytokeratins 8, 18)的片段来检测膀胱癌[33-35],荟萃分析表明其总体灵敏度为0.59(95% CI: 0.55~0.62),特异度为0.76(95% CI: 0.72~0.80)[33]。细胞角蛋白19片段抗原21-1(cytokeratin fragment 21-1, CYFRA 21-1)也是一种诊断膀胱癌的生物标志物,它的总体灵敏度为0.82(95% CI: 0.70~0.90),特异度为0.87(95% CI:0.84~0.90)[35]。

微小染色体维持蛋白5(MCM5)在DNA复制的起始、延伸过程中起重要作用,在正常组织中MCM5仅局限于上皮基底层的增殖区,而在尿路上皮肿瘤组织中,MCM5可扩展到上皮全层,因此可在脱落细胞中检测到。ADXBLADDER是一种商用的MCM5酶联免疫吸附方法,一项大型前瞻性研究表明ADXBLADDER检测膀胱癌复发的总体灵敏度为44.9%(95% CI 36.1~54),特异度为71.1%(95% CI 68.5~73.5),阴性预测值为93%(95% CI 91.2~94.5),排除非低级别pTa肿瘤的阴性预测值高达99.0%(95% CI 98.2~99.5),提示此方法可作为排除性诊断纳入NMIBC随访方案中[36]。

其他正在探索中的蛋白标志物包括转录因子BLCA-1和BLCA-4、抗凋亡蛋白可溶性Fas(sFas)异构体、凝聚素(Clusterin)、透明质酸(HA)、纤维连接蛋白(Fibronectin)、CD44抗原等,这些标志物均需要进一步的研究来评估和确定其临床价值;此外,血管内皮生长因子(VEGF)、白介素(ILs)和端粒酶等蛋白在膀胱癌中的表达也显著升高,但较低的特异性使其无法成为诊断或监测膀胱癌的工具[7]。

真核起始因子5A2(EIF-5A2)是一种对细胞增殖起重要作用的蛋白,研究表明卵巢癌、结直肠癌、胃癌都存在EIF-5A2基因的扩增及过度表达[37]。AIB1是核受体共活化因子SRC-1家族成员,在乳腺癌、前列腺癌、卵巢癌等多种实体癌中过度表达[38]。我团队研究发现EIF-5A2和AIB1基因在膀胱癌组织中的表达较癌旁正常组织有显著性上调,EIF-5A2和AIB1基因的过度表达与膀胱癌术后复发、进展存在显著的相关性,并可作为膀胱癌患者不良预后的独立预测因素[37-40]。此外,AIB1和EIF-5A2在预测上尿路移行上皮癌的预后和复发风险中也具有重要价值[41-42]。体内外实验证实,EIF-5A2可能通过激活TGF-β1表达来促进膀胱癌细胞的侵袭性和转移潜能;敲除内源性AIB1可通过G1阻滞效应抑制膀胱癌细胞株的生长与增殖[43-44]。基于以上基础研究,我们进一步探索了EIF-5A2和AIB1在膀胱癌无创尿液诊断中的作用。研究发现,与对照组相比,膀胱癌患者尿液中EIF-5A2和AIB1浓度显著增高。独立验证队列中,尿AIB1诊断膀胱癌的敏感度为80%,特异度为86%,AUC(受试者工作特征ROC曲线下面积,取值范围在0.5和1之间,越接近1.0,检测方法真实性越高)为0.827,高于NMP22(AUC:0.766);EIF-5A2的敏感度和特异度分别为71%、74%,AUC为0.723。为提高检测效能,我们进一步构建了AIB1、EIF-5A2和NMP22联合检测模型,其灵敏度为92%,特异性为92%,AUC为0.919,优于单一生物标志物[45]。通过以上研究,我们发现EIF-5A2和AIB1能够充当膀胱癌无创诊断的新瘤标,联合AIB1、EIF-5A2和NMP22更能提高膀胱癌的诊断准确度。我团队于2016年申请通过了由AIB1、EIF-5A2和NMP22组成的用于膀胱癌非侵入式诊断的分子标志专利。

3.2 遗传物质生物标志物

膀胱肿瘤发病涉及较多信号通路,通过检测尿液中的遗传物质来诊断肿瘤也成为当下探索新型

肿瘤标志物的热门方向。

成纤维细胞生长因子受体3(fibroblast growth factor receptor 3，FGFR3)在膀胱癌的发生发展中发挥重要作用，它的突变及过表达会过度激活RAS-MAPK，PI3K和STAT6等下游通路，加速细胞增殖分化及血管生成[46]。研究发现pTa、pT1和pT2-4期肿瘤FGFR3突变率分别为80%、21%和16%[46-47]。FGFR3突变用于检测低级别肿瘤复发的灵敏度为58%[48]，对于初发血尿患者，FGFR3诊断肿瘤的灵敏度和特异度分别为25%、99.7%[49]。对比发现，FGFR3突变检测诊断低级别浅表性肿瘤的敏感性优于尿脱落细胞学，与细胞学联合诊断时，灵敏度高达86%[50]。

Cxbladder方法通过检测膀胱癌患者尿液中显著升高的4种mRNA（IGFBP5，HOXA13，MDK，和CDK1)及与良性炎症病变相关的1种mRNA(CXCR2)来诊断膀胱癌[51]。研究表明[52]，当通过调整阈值，使其检测特异度达85%时，Cxbladder检测初发膀胱癌的灵敏度为82%。与细胞学及NMP22相比，Cxbladder具有更高的灵敏度和阴性预测值，在监测膀胱癌复发方面具有比其他两者更高的效能[11]。

端粒酶逆转录酶（telomerase reverse transcriptase，TERT）是端粒酶的活性组分及限速步骤，TERT基因启动子突变参与多种肿瘤的发生发展[53]。膀胱癌TERT的突变率超过70%，其诊断初发和复发膀胱癌的灵敏度分别为62%、42%，特异度分别为90%、73%[54]。

极光激酶A(aurora Kinase A，AURKA)是一种丝氨酸/苏氨酸激酶，参与Wnt等重要的细胞信号通路，直接或间接地调节一些重要蛋白的表达，与人类多种肿瘤的发生发展密切相关[55]。定量检测尿液AURKA mRNA诊断膀胱尿路上皮癌的敏感性为83.6%，特异性为65.2%。与Ta相比，T1和T2期的AURKA表达分别增加了9.31倍和4.78倍；高级别肿瘤的AURKA表达水平比低级别肿瘤高5.33倍。研究结果还提示，AURKA和尿细胞学总体AUC相似(0.744和0.721，P=0.588)。AURKA检测低级别肿瘤更准确，而细胞学诊断高级别病变更准确[56]。

微小RNA（micro RNA，miRNA)在RNA沉默和基因表达转录后调控发挥作用，越来越多的证据表明，异常表达的miRNAs可以作为恶性肿瘤的癌基因或抑癌基因[57]。多种miRNA可在膀胱癌患者的尿液中被检测到，它们的总体灵敏度为71%-94%，特异度为51%-100%，AUC为73%-92%[13]。其中，检测膀胱癌效能较高的单一miRNA有miRNA-155(灵敏度80.2%，特异度84.6%)[58]、miRNA-125-b(灵敏度84.8%，特异度76.2%)[59]、miRNA-99-a(灵敏度74.1~78%，特异度82.6~85.7%)[59-60]及miRNA-96（灵敏度71~72.3%，特异度88.9~89.2%)[61-62]。多种miRNA联合检测可进一步提高诊断效能，miRNA-99-a/125-b联合检测膀胱癌灵敏度为86.7%，特异度为81.1%[59]，6种miRNA(187/18a/25/142-3p/140-5p/204)联合检测的灵敏度为84.4%，特异度为86.5%[63]，而25种miRNA联合检测的灵敏度和特异度分别高达87%、100%[64]。

长链非编码RNA（long noncoding RNA，lncRNA)通过与基因组DNA、mi RNA、m RNA和蛋白质的相互作用来发挥功能，参与了肿瘤的发生、侵袭和转移等过程[65]。lncRNA检测膀胱癌的总体灵敏度和特异度分别为0.73（95% CI：0.58~0.84)、0.78（95% CI：0.62~0.89)[66]。其中研究较多的为UCA1，一项纳入6项研究的荟萃分析表明，尿液UCA1诊断膀胱癌的灵敏度和特异度分别为0.81、0.86[67]。另一项研究使用2种lncRNA(uc004cox.4/GAS5)联合检测，其诊断膀胱癌灵敏度为84.5%，特异度为78.2%，AUC为0.885[68]；3种尿液外泌体来源的lncRNA(MALAT1/PCAT-1/SPRY4-IT1)联合诊断膀胱癌灵敏度为62.5%，特异度为85.0%，AUC为0.813[69]。

DNA甲基化是一种基因表观遗传调控方式，一些尿高甲基化标记物已经被用于膀胱癌的检测。有研究者检测了膀胱癌患者和健康人群尿液DNA甲基化的水平，并建立了一个由150个CpG位点组成的膀胱癌检测生物标记物模块(UroMark)，在后续的验证试验中，UroMark的灵敏度、特异度和阴性预测值分别为98%、97%、97%[70]。但一篇荟萃分析显示，各验证试验间的结果差异性很大，灵敏度为52%~100%，特异度为0~100%[71]。

此外，在遗传物质生物标志物方面，还有DNA微卫星/杂合性缺失检测、XPERT BC Monitor(检测尿液5种mRNA)和拓扑异构酶IIα(Topoisomerase-II alpha，TopoIIA)基因过表达检测等[7, 13, 72]。

上述遗传物质相关的生物标记物在膀胱癌中的研究时间短，各试验结果差异性大，需要进一步

的前瞻性研究来验证其在膀胱癌诊断和监测中的作用。表2总结了一些重要新型生物标志物的检测效能。

3.3 其他新型无创尿液检测方法

拉曼光谱是一种激光照射在物体上发生非弹性散射光线组成的光谱。近期,研究者们尝试将拉曼光谱化学尿液分析方法(Rametrix™)应用于膀胱癌诊断中。当使用尿液中22种主要成分来建立模型时,Rametrix™检测膀胱癌的准确率为80.4%,敏感性为82.4%,特异性为79.5%[73]。电子鼻(eNose)是一种模拟人类嗅觉系统的仪器,它可以嗅出人类排泄物(尿液、呼吸和粪便)散发出来的气体和蒸汽,用于诊断各种疾病。一项研究表明,电子鼻诊断膀胱癌的灵敏度及特异度分别为60.8%、90.2%,AUC达0.909[74]。另一项研究利用荧光光学传感器检测尿液挥发性有机化合物,利用24个传感器点阵列来诊断膀胱癌的灵敏度和特异度分别为84.21%和87.80%,此外,该方法鉴别高、低级别膀胱癌的敏感性为66.67%,特异性为75.00%[75]。新型无创尿液诊断方法层出不穷,与光学等技术结合更是大势所趋,目前,此方面的研究尚处于单中心小型试验探索阶段,随着技术与仪器的发展,可开展更多大型研究进一步验证其膀胱癌诊断价值。

4 结 论

本文归纳总结了现阶段通过尿液来进行膀胱癌无创诊断的检测方法,其中FDA认证的6种检测方法均具有较低的特异性,不足以取代传统膀胱镜检查、活检及尿液细胞学在膀胱癌诊断中的作用;新型尿液生物标志物检测方法包含了蛋白标志物和遗传物质相关标志物等,我团队通过研究发现EIF-5A2和AIB1能够充当膀胱癌无创诊断的新瘤标,联合AIB1、EIF-5A2和NMP22更能提高膀胱癌的诊断准确度。

表2 新型尿液生物标志物

Table 2 Novel urinary biomarkers

Biomarker	Type	Sensitivity/%(95%CI)	Specificity/%(95%CI)
Survivin[29]	Protein	79 (73-84)	87 (79-92)
UBC test[33]	Protein	59 (55-62)	76 (72-80)
CYFRA 21-1[35]	Protein	82(70-90)	87 (84-0.90)
FGFR3[48, 49]	DNA	25-58	99.7
Cxbladder[12]	mRNA	82 (70-90)	85(81-88)
TERT[54, 72]	DNA	42-81	73-90
AURKA[56]	mRNA	83.6	65.2
miRNA[13]	miRNA	71-94	51-100
miRNA-155[56]		80.2	84.6
miRNA-125-b[57]		84.8	76.2
miRNA-99-a[57-58]		74.1-78	82.6-85.7
miRNA-96[61, 62]		71-72.3	88.9-89.2
miRNA-99-a/125-b[57]		86.7	81.1
miRNA187/18a/25/142-3p/140-5p/204[61]		84.4	86.5
25 miRNA[62]		87	100
lncRNA[66]	lncRNA	73 (58-84)	78 (62-89)
UCA1[65]		81	86
uc004cox.4/GAS5[66]		84.5	78.2
MALAT1/PCAT-1/SPRY4-IT1[67]		62.5	85.0
UroMark[71]	DNA methylation	52-100	0-100

寻找无创、便捷、准确的膀胱癌诊断方法仍任重道远,一项调查显示,如果尿液试验灵敏度低于90%,89%的患者仍将选择膀胱软镜作为早期膀胱癌术后监测方法[76]。未来研究者们除了继续探索新的尿液生物标志物外,也可通过多种膀胱肿瘤标志物或多种技术的的联合应用提高诊断的灵敏度及特异性,并且需对有潜力的新型生物标志物展开进一步更大规模的前瞻性验证研究。

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