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Hans汉斯

免疫组化标志物在胰腺导管腺癌临床评估中的应用进展

梁长雄，祖少奇，朱　洪*

昆明医科大学第二附属医院肝胆外科，云南　昆明

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摘　要

胰腺导管腺癌(pancreatic ductal adenocarcinoma, PDAC)是恶性程度最高的消化系统肿瘤之一，侵袭性强，生物学异质性极大，故而现有手段尚难以充分获得患者生存获益。因此，更准确的肿瘤评估及更好的风险分层是推进个体化治疗的前提。免疫组化(immunohistochemistry, IHC)由于可及性好，又对常规病理标本有极好的适用性，在胰腺癌临床管理中已有基础而重要的地位，近年来已从传统的诊断支持技术自然、合理地拓展到预后评估及治疗反应预测领域。近年来学界对PDAC中多种免疫组化标志物的临床价值已有十分系统、充分的讨论，明确指出多指标联合检测有利于提高良恶性病变的鉴别能力，也有利于确定肿瘤来源。更重要的是，与细胞增殖、抑癌通路异常、上皮－间质转化及肿瘤免疫微环境相关的蛋白表达模式在风险评估中已有很好的应用前景。与此形成极好补充的是，免疫相关及分子替代指标正在成为筛选潜在治疗获益人群的新方向。然而，由于目前多数标志物尚无统一检测标准，故现有研究结果有明显异质性，单一指标又不能充分反映PDAC复杂的生物学本质，因此可以很自然、妥帖地预期今后的发展方向是构建多参数整合模型，把免疫组化、分子检测及数字病理技术三者深度融合，由此建立真正精准、临床可操作的综合评估体系。本文对免疫组化标志物在胰腺导管腺癌中的临床应用作了十分清楚、有层次的综述，先总结其在诊断鉴别、预后分层、治疗相关预测诸方面的研究进展，再自然、妥帖地讨论现存问题及今后方向，对胰腺癌的精准管理有极好启示。

关键词

胰腺导管腺癌，免疫组化，生物标志物，风险分层，精准医学

Advances in the Application of Immunohistochemical Markers in the Clinical Evaluation of Pancreatic Ductal Adenocarcinoma

*通讯作者。

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Zhangxiong Liang, Shaoqi Zu, Hong Zhu*

Department of Hepatobiliary Surgery, The Second Affiliated Hospital of Kunming Medical University, Kunming Yunnan

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Abstract

Pancreatic ductal adenocarcinoma (PDAC) is one of the most malignant tumors in the digestive system, with strong invasiveness and significant biological heterogeneity. Therefore, current treatment methods have not been able to fully benefit patients in terms of survival. Thus, more accurate tumor assessment and better risk stratification are prerequisites for advancing personalized treatment. Immunohistochemistry (IHC) has a fundamental and important position in the clinical management of pancreatic cancer due to its good accessibility and excellent applicability to routine pathological specimens. In recent years, it has naturally and reasonably expanded from a traditional diagnostic support technique to the fields of prognosis assessment and treatment response prediction. In recent years, the academic community has had a very systematic and thorough discussion on the clinical value of multiple IHC markers in PDAC, clearly indicating that the combined detection of multiple indicators is beneficial for improving the ability to distinguish between benign and malignant lesions and determining the tumor origin. More importantly, protein expression patterns related to cell proliferation, abnormal tumor suppressor pathways, epithelial-mesenchymal transition, and the tumor immune microenvironment have shown good application prospects in risk assessment. Complementing this, immune-related and molecular surrogate markers are becoming new directions for screening potential treatment-benefited populations. However, due to the lack of unified detection standards for most of the current biomarkers, the existing research results show significant heterogeneity. Moreover, a single indicator cannot fully reflect the complex biological nature of PDAC. Therefore, it is quite natural and appropriate to expect that the future development direction will be to build a multi-parameter integrated model, deeply integrating immunohistochemistry, molecular detection, and digital pathology technologies, thereby establishing a truly precise and clinically operable comprehensive assessment system. This article provides a very clear and well-structured review of the clinical application of immunohistochemical markers in pancreatic ductal adenocarcinoma. It first summarizes the research progress in diagnosis and differentiation, prognosis stratification, and treatment-related prediction, and then naturally and appropriately discusses the existing problems and future directions. It offers excellent guidance for the precise management of pancreatic cancer.

Keywords

Pancreatic Ductal Adenocarcinoma, Immunohistochemistry, Biomarkers, Risk Stratification, Precision Medicine

1. 引言

胰腺癌是目前病死率增长最快的消化系统恶性肿瘤之一，而胰腺导管腺癌(PDAC)占全部胰腺癌病例的90%以上[1]。虽然近年来外科技术、围手术期管理及综合治疗都取得长足进步，但是毋庸讳言，患者

总体生存获益仍十分有限[1]。因此，起病隐匿、早期诊断困难、对现有治疗手段反应差，被公认为制约胰腺癌预后改善的三大核心因素[1]。

由于病理评估在 PDAC 临床决策中具有基础性的地位，故毋庸讳言，实际诊断过程中确有若干重要而棘手的问题：慢性胰腺炎等炎症性病变常伴发导管上皮反应性异型增生，在有限组织标本中极易与浸润性腺癌形成形态学重叠[2] [3]。与此形成极好呼应的是，超声内镜引导下细针穿刺抽吸术(Endoscopic ultrasound-guided fine-needle aspiration, EUS-FNA)等微创取材方式虽然提高了可及性，但是也不可避免地带来了取样偏倚的风险[4]-[7]。因此，在精准医学快速发展的今天，单纯依靠传统组织学特征已不能充分、可靠地回答临床对肿瘤生物学行为的诸种重要问题[1] [8]-[10]。

由于免疫组化操作简便，又十分适合于常规石蜡标本，故其已经成为现代病理诊断体系中极为重要、应用最广的工具之一[7] [11] [12]。更难得的是，某些蛋白表达谱能可靠、直接地反映肿瘤分子改变及生物学特性，因此免疫组化已经从传统的“诊断支持技术”自然、妥帖地发展为目前兼具预后评估及治疗预测价值的综合检测手段。

由于目前有关标志物的报道很多，但是毋庸讳言，其临床转化过程中仍有检测标准不统一、研究异质性大、与分子检测整合不够充分诸种现实问题，故系统、严谨地总结免疫组化标志物在 PDAC 中的应用价值，对规范其临床使用、提高临床决策的科学性都具有十分重要的意义。

2. 诊断相关免疫组化标志物

准确的病理诊断是 PDAC 临床管理的基础[1] [7]，而毋庸讳言，PDAC 常伴有明显的间质反应及炎症背景，故不少病例在形态学上与良性病变有重叠，尤其是小活检或 EUS-FNA 标本中组织量极小，组织结构受限，诊断难度自然大大增加[2] [3]。因此，免疫组化作为形态学极好的补充，在提高 PDAC 诊断准确性方面有极其重要的作用[4] [7]。

由于近年免疫组化在 PDAC 诊断中的应用已从单一标志物检测自然、合理地转向多指标联合检测，故其在良恶性鉴别、肿瘤来源判断及分子替代分型诸方面都有十分明确和重要的应用价值。

2.1. PDAC 与慢性胰腺炎的鉴别

由于慢性胰腺炎时导管上皮常有反应性异型、腺体结构紊乱诸种改变，在有限标本中易与浸润性腺癌混淆，故这是病理诊断中十分典型的难点[2] [3]。因此多标志物联合检测有利于可靠鉴别[4] [13]。

S100 钙结合蛋白 P (S100 calcium-binding protein P, S100P)是目前研究最充分、最明确的 PDAC 相关蛋白之一，文献一致支持其在 PDAC 中呈弥漫强阳性，而在良性/炎症性导管中多为阴性或弱表达，因此敏感性极高[5] [6]。IMP3 是一种胚胎相关的 RNA 结合蛋白，在 PDAC 中常异常高表达，对恶性与良性病变有极好的特异性，故特别适合于细胞学及细胞块材料的诊断[4] [7]。Maspin 在 PDAC 中典型地呈核/胞浆染色，对 PDAC 与慢性胰腺炎的鉴别有直接的临床价值，但使用时也宜注意排除鳞状化生所致的假阳性[14]。与前述肿瘤相关指标不同的是，VHL 肿瘤抑制基因(von Hippel-Lindau tumor suppressor gene, pVHL)在非肿瘤导管中多保留表达，而 PDAC 中常缺失，因此将其作为“反向标志物”纳入检测面板可切实提高判读结果的稳健性[4]。

此外，反映关键通路异常的替代指标有十分明确、重要的辅助意义：SMAD4 蛋白(SMAD family member 4 protein, SMAD4)缺失可可靠地提示抑癌通路失活，而 p53 蛋白(tumor protein p53，p53)异常表达模式可很好地提示 TP53 相关改变，但也毋庸讳言二者敏感性均有局限，故最宜在形态学可疑病例中加以应用[4] [15]。更重要的是，免疫组化结果绝不可脱离组织结构孤立地“只看染色”予以解释[11] [12]。因此，当若干肿瘤相关标志物呈一致阳性时，其诊断价值显然大大超过单一指标[4] [13]。

2.2. 原发性与转移性胰腺肿瘤的鉴别

转移性肿瘤累及胰腺的情况十分常见，因此正确判断原发灶对治疗有直接重大意义[1]。故而临床上常用“谱系分化”免疫表型进行系统、有层次的分型排查[16]。CK7/CK20/CDX2 组合是经典且可靠的基础策略：PDAC 多为 CK7 阳性，而结直肠腺癌典型表现为 CK7 阴性、CK20 及 CDX2 阳性[16]。更重要的是，特殊 AT 序列结合蛋白 2 (special AT-rich sequence-binding protein 2, SATB2)对结直肠分化有极高的特异性，故与尾型同源框转录因子 2 (caudal type homeobox 2, CDX2)联用可极大提高识别转移性结直肠癌的准确性[16]。最后，结合病史及影像学信息选择针对性标志物，显然比无差别大面板更高效，也更少受非特异表达的干扰[7] [11]。

2.3. 基于免疫组化的分子替代分型

PDAC 分子异质性非常强，不同的亚型具有不同的侵袭性以及对不同治疗手段敏感度的不同之处[8]-[10]。如果无法进行测序的话，可能就会转而使用 IHC 来进行分型[17] [18]。在 GATA 结合蛋白 6 (GATA binding protein 6, GATA6)中，它被认为是一个较为可靠地分型标志物：GATA6 高表达时较为接近经典的分型，GATA6 低表达或缺失则偏向于基底样型分型(Basal-like)，并且预后较差并且很可能发生治疗抵抗[18]-[20]。目前不同的研究在抗体、阈值和判读标准方面都存在着差别，IHC 分型更多地是用作说明肿瘤生物学行为的指标，不能作为单独指导治疗的标准[17] [21]-[23]。IHC 分型可在一定程度上帮助评估 PDAC 的生物行为学及指导靶向治疗，但其在准确性及标准化判断上的欠缺性使得其难以应用于临床中独立作出治疗决策[11] [12]。

与此同时，随着多标志物联合检测策略不断完善，免疫组化正从对 PDAC 诊断准确性的“辅助工具”转变为“关键证据”[4] [11] [13]。

3. 预后相关免疫组化标志物

由于 PDAC 高度侵袭、高度异质，故接受根治性切除之后患者的生存结局差异极大[1] [24]-[26]。而目前传统的预后评估多依靠 TNM 分期、分化程度及淋巴结状态等指标，但这些指标不能可靠、充分地反映肿瘤内在的生物学行为[24]-[26]。因此，寻找可在常规石蜡标本中检测的预后标志物有十分明确的临床价值。

3.1. 增殖相关标志物

Ki-67 增殖标志物(Ki-67 antigen, Ki-67)是目前应用最广泛、最经典的增殖指标，高 Ki-67 指数一般与更高分级、复发风险增大、生存期缩短直接相关[27]。但是毋庸讳言，其阈值选择、计数方法(热点 vs 平均)及取样的异质性都影响其可重复性，因此更合理的做法是将其纳入综合模型中加以分析。

3.2. 抑癌通路异常与侵袭模式

有研究显示 SMAD4 (DPC4)参与调控 TGF-β 信号通路，SMAD4 表达缺失是 PDAC 最常见的组织学分子替代指标，同时具有更差预后及更高转移性，亦可作为 PDAC 经典研究的对象。需要注意的是，关于 SMAD4 状态和疾病进展模式的关系，不同的队列、不同的治疗方案都会导致不一样的结果，所以解释时应结合患者自身的临床分期以及接受的治疗方式进行解读。p53 异常的表达可能是发生了基因组不稳定性的一种预警，有个别文献报道表明了该指标可能跟不良的结局是相关的，但也有相反的结果出现，并不是所有的结果都是同一方向的，因此我们把 p53 单独作为一个标志物放入多参数体系中衡量是最科学的方法。

3.3. EMT、血管生成与微环境

上皮－间质转化(epithelial-mesenchymal transition, EMT)相关改变(即 E-钙黏蛋白(E-cadherin)下降、波形蛋白(vimentin)上调)与侵袭转移风险增加有十分清楚、明确的联系，故而 EMT 是 PDAC 预后研究中十分重要的方向[28]-[31]。但毋庸回避的是，EMT 实际上呈连续谱状态，且存在突出的空间异质性，因此对其分析时必须格外审慎[28]-[31]。更重要的是，血管内皮生长因子(vascular endothelial growth factor, VEGF)等血管生成指标与肿瘤进展相关的现有证据存在矛盾，而此种矛盾很自然地提示与 PDAC“低血供 + 高度纤维化”的特殊微环境有关[32] [33]。由此也自然地引出近年研究的新方向：从单一血管标志物转向“肿瘤间质－免疫－肿瘤细胞”多维评估[1] [34]-[36]。

3.4. 免疫相关预后指标

由于 PDAC 常呈免疫抑制性微环境，故免疫浸润及免疫检查点表达与预后的关系历来受到高度重视。[1] [34] [35]目前已有充分的文献及荟萃分析结果表明程序性死亡配体 1 (programmed death-ligand 1, PD-L1)高表达总体上与较差预后相关，但是毋庸讳言，不同研究中所用的阳性率及评分体系差异极大，因此其跨中心可比性仍有争议[11] [12] [37]-[40]。与此形成极好补充的是，免疫浸润(T 细胞、巨噬细胞亚群)与结局的关系在系统评价中已有明确讨论，提示“免疫表型”可能是更可靠、更稳定的风险分层维度[34]-[36]。

因此，由于今后预后评估模式要从传统的单指标判断转向利用多维生物学信息来建立综合模型，因此很自然就会更合理、更充分地反映肿瘤异质性。

4. 预测及治疗相关免疫组化标志物

由于精准医学发展迅猛，能预测治疗反应、指导个体化治疗的标志物已成为 PDAC 研究的热点[1]。而免疫组化检测简便可行，又成本相对可控，因此在治疗相关标志物筛查中有极好的应用前景[11] [12]。毋庸讳言，目前直接可用于治疗决策的 IHC 指标尚有限，但是已有若干方向展现了明确、扎实的临床意义[41]-[47]。

4.1. 免疫治疗相关标志物

PDAC 对免疫检查点抑制剂的反应十分有限，而其根本原因已十分清楚：即致密间质屏障、效应 T 细胞浸润不足及免疫抑制细胞富集[1]。与此形成极好对照的是，PD-L1 作为免疫逃逸相关指标在 PDAC 中的阳性率受多种评估标准的影响，故不宜单独作为可靠的预测指标使用[11] [12] [37]-[40]。与此形成完美补充的是，错配修复缺陷/高度微卫星不稳定(deficient mismatch repair/high microsatellite instability, dMMR/MSI-H)虽在 PDAC 中罕见，但是治疗意义明确，因此 MMR 蛋白 IHC 可自然、妥帖地用作识别潜在免疫治疗获益人群的初筛手段[41] [42]。

4.2. 靶向治疗相关标志物

虽然人表皮生长因子受体 2 (human epidermal growth factor receptor 2, HER2)扩增/过表达在 PDAC 中所占比例不高，但是属于明确的可行动靶点，因此 IHC (联合荧光原位杂交(fluorescence in situ hybridization, FISH))是识别此类亚群、指导抗 HER2 治疗最自然、最可靠的方法[43]-[47]。又正因其发生率低，常规全人群筛查的成本效益尚有争议，故目前更合理的做法是在难治/复发或临床指征明确的患者中进行策略性检测。需要强调的是，dMMR/MSI-H 在 PDAC 中的真实阳性率极低。系统综述与汇总数据显示，PDAC 中 MSI/dMMR 总体发生率约为 1%~2%，在采用更标准化/验证方法的研究中甚至更接近约 1%左右[48]。

多中心队列(n ≈ 445)基于 MMR 蛋白缺失的 IHC 筛查亦提示 dMMR 检出率约 1.6%，进一步印证其在 PDAC 中属于罕见事件[49]。因此，在资源与成本效益需权衡的真实世界场景中，更合理的策略是将 MMR IHC 纳入肿瘤分子病理检测流程中的“关键但低频”项目：对晚期/复发拟接受系统治疗患者应保持较低阈值检测，而在部分指南/实践中亦提出可在特定高获益亚群(如 KRAS 野生型或具有提示性组织学特征)中优先开展 MSI/MMR 评估，以提高检出效率[50]。

4.3. 化疗反应相关标志物

人平衡型核苷转运体 1 (human equilibrative nucleoside transporter 1, hENT1)是吉西他滨进入细胞所必需的主要转运体，现有文献十分清楚地提示 hENT1 高表达与更好的治疗反应相关[48] [49]。但是毋庸讳言，不同抗体克隆、染色平台及队列背景都会影响结果的一致性，故“是否可用于临床决策”的问题长期存在争议[11] [12] [50]-[54]。因此，化疗预测标志物必然需要严格的分析验证及充分的跨中心一致性研究支持。

4.4. 从单一指标到综合预测模型

由于 PDAC 治疗反应是由若干因素共同决定的，故把免疫表型、分子亚型及临床特征三者合理整合，有利于建立可靠、稳定的预测模型[8]-[23] [55] [56]。由于将预测性标志物从探索阶段推进到可操作的临床工具阶段是今后精确治疗体系构建中十分重要的一步，故宜予以充分重视[11] [12] [55] [56]。

4.5. 治疗相关新兴靶点在 IHC 检测中的现状与描述

在综合预测模型不断完善的同时，CLDN18.2、NTRK 融合等新兴可行动靶点正推动 PDAC 治疗相关检测从“模型分层”进一步走向“人群筛选–入组决策–用药管理”的闭环路径。就 CLDN18.2 而言，既往针对胰腺肿瘤的组织学研究已提示其在 PDAC 原发灶及转移灶中并非罕见，并可通过 IHC 建立相对标准化的强度与阳性比例评估框架，为 CLDN18.2 靶向治疗的潜在人群筛选提供病理学基础[57]-[62]。但在真实世界队列中，CLDN18/CLDN18.2 的阳性率受抗体克隆、染色平台及阳性阈值影响显著，导致不同研究间检出率存在跨度；例如部分切除队列采用较严格的“高表达”判定标准(如较高比例肿瘤细胞出现中/强膜染色)时，报告的阳性比例约为三成左右，从而提示该靶点虽具筛查价值，但更需要明确可复制的评分体系与报告要素以提升跨中心可比性[63] [64]。

然而，PDAC 常依赖穿刺/活检小标本完成诊断与分子病理检测，小标本代表性不足叠加肿瘤空间异质性，可能造成 CLDN18.2 IHC 的“低估/漏检”。近期研究专门评估了 CLDN18.2 在活检、切除与复发灶之间的一致性，显示活检与切除总体一致性虽可较高，但活检对 CLDN18.2 阳性病例的敏感性可能不足，提示仅凭活检结果用于治疗入组筛查时需谨慎，必要时应优化取材策略、阈值设定与复核流程[65]。

与 CLDN18.2 不同，NTRK1/2/3 融合在胰腺癌中总体发生率极低，更适合采用“IHC 筛查 + 分子确证”的策略嵌入临床路径。ESMO 关于 NTRK 融合检测的推荐明确指出：在融合罕见的肿瘤类型中，可选择 pan-TRK IHC 作为前线筛查，但 IHC 阳性病例应以测序(优先 RNA-NGS)进行确证；在资源允许且需兼顾广谱基因信息时，亦可考虑直接进行前线测序检测[61] [66]。需要强调的是，pan-TRK IHC 并非“阳性即融合”，其作为筛查工具存在一定的假阴性/假阳性风险，且对不同融合类型的敏感度并不完全一致；因此，阳性触发反射检测(reflex testing)与在关键临床场景下采用 RNA 层面确证策略，是将 NTRK 靶点检测从可行性走向可用性的核心环节[62] [63] [67]。

5. 免疫组化应用的局限性

尽管免疫组化在 PDAC 病理评估中具有重要价值，其临床应用仍面临多方面挑战[11] [12]。深入认

识这些局限，有助于规范检测流程并推动结果合理解读[11] [12] [57]-[60]。

5.1. 检测标准尚未统一

由于不同实验室在抗体克隆、染色平台、抗原修复及评分体系诸方面都存在差异，故其实验结果的一致性及可重复性必然受到影响[59] [60]。而 PD-L1、HER2 等有复杂评分体系的预测性标志物更需要严格验证及标准化流程。因此，建立统一质量控制及外部评估体系就是临床转化成功的先决条件。

5.2. 肿瘤异质性与取样偏倚

PDAC 存在显著空间/时间异质性，小活检或细针标本可能无法代表整体生物学特征，导致假阴性或解释偏差[2] [3] [11]。因此应结合标本类型与取样充分性，避免过度外推[11] [12]。

5.3. 半定量评估与观察者差异

传统 IHC 多为半定量判读，弱阳性与边界病例中主观差异明显。数字病理与图像分析有望降低观察者差异、提升定量一致性，但其在常规实践的普及仍需时间与证据积累[55] [56]。

5.4. 单一标志物的解释局限

由于肿瘤行为是由若干通路共同驱动的，单一蛋白不可能提供充分的决策信息，因此很自然、合理地要发展多指标整合模型[24]-[26]。而开展预后/预测研究时宜严格遵循规范报告原则(REMARK)，方能减少偏倚，提高结果的外推价值[57] [58]。

5.5. 与分子检测的关系仍需进一步明确

蛋白表达不像基因改变一样总是完全一致，免疫组化和分子检测更多的时候是相辅相成，而不能互相取代。故“形态学 - IHC - 分子检测 - 数字病理”的协同模式也许才是未来最有说服力的方向[55] [56]。

从现有的综合证据分析结果来看，免疫组化作为 PDAC 一种检测手段在从一种“辅助诊断工具”转变为一种“多维度临床评估手段”。尽管某个单独的标志物不能独立完成判断，在多种生物功能维度联合应用下，有望使免疫组化发挥更加整体的作用，在肿瘤异质性方面得到更多体现[23]。另外，任何形式的检测技术都很难将 PDAC 复杂的分子图谱进行描述，未来更有意义的评估或许是基于形态学、蛋白表达以及基因型相互之间存在联系来建立的检测评估体系，并达到更多的分级分层水平[55]。

6. 展望

随着分子肿瘤学研究的深入，PDAC 的生物学异质性也逐渐被揭开[8]-[10]，而免疫组化正是联系传统形态学和分子特征的一道桥梁[11] [12]。但目前还无法在广义上使精准医学落地生根开花结果，还需要从基础理论到检测技术乃至诊治策略等各个层面作出改进[11] [12] [57]-[60]。

首先，推动检测流程与判读标准规范化，为提升免疫组化临床价值的重要保障。虽然各实验室中，抗体以及评分方式存在一定差异，限制了多中心证据的整合及推广应用；同时，多标志物整合模型也可能成为风险评估的重要发展方向，基于 PDAC 属于多通路参与疾病的发生发展，把从不同角度出发获取的功能维度指标综合起来，将有助于形成更加稳定的分层体系[24]-[26]。

除上述外，将免疫组化联合分子检测也是未来方向，IHC 可用作高可及性的初筛手段，发现可能存在分子异常亚群进一步行检测[11] [12] [41] [42]。数字病理、人工智能等技术有助于 IHC 结果的客观判定以及复杂表型的判断，有助于观察者间差异减小以及复杂表型的发现[55] [56]，需注意未来还需要更多的

前瞻性临床证据证明对于这类阳性标志物的临床意义，即是否可以真实的通过这个标志物来给治疗带来获益，以体现临床价值，具体的不可仅从方案设计时便想当然认为只要加进代表阳性结果，就可以代表证明某种疾病的诊断金标准。

总体而言，免疫组化作为传统病理诊断的一部分，在多维评价中还可以架起梁桥，进一步丰富 PDAC 诊断的价值。持续完善检测技术，不断改进检测策略，并完善跨平台联合应用，或有助于形成准确、易及的综合性诊断系统，推进 PDAC 临床诊疗更加精细化、个体化、规范化的发展进程[55] [56]。

精准医学发展以来，免疫组化或将从传统辅助性检查手段转变成为整个多维的临床决策所用重要依据。

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