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# 黑色素瘤的诊断研究进展

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## 摘　要

**皮肤黑色素瘤是最严重的皮肤癌类型。深入理解黑色素瘤发生与发展的复杂生物学过程对推进患者诊疗至关重要。基于黑色素瘤较差的预后性，黑色素瘤诊断的新兴技术正在发生转变，旨在提升诊断准确性、预测疾病进展并改善预后。形态学临床病理分类预计将被更精确的分子分类所取代。随着经过验证、便捷且具有成本效益的分子检测方法的出现，分子诊断将在黑色素瘤的临床与组织学诊断中发挥更大作用。人工智能辅助的临床与组织学诊断预计将使这一过程更趋简化和高效。本文概述了黑色素瘤在诊断方面的最新进展。为深入理解当前治疗策略及新兴技术原理奠定基础，帮助临床医生把握黑色素瘤以提升临床决策水平。**

## 关键词

**黑色素瘤，组织诊断，人工智能，分子诊断**

# Advances in Melanoma Diagnosis Research

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## Abstract

**Cutaneous melanoma is the most aggressive type of skin cancer. An in-depth understanding of the complex biological processes underlying the occurrence and progression of melanoma is crucial for advancing the diagnosis and treatment of patients. Given the poor prognosis of melanoma, emerging technologies for melanoma diagnosis are undergoing transformations aimed at improving diagnostic accuracy, predicting disease progression, and enhancing prognosis. Morphological clinicopathological classification is expected to be replaced by more precise molecular classification. With the advent of validated, convenient, and cost-effective molecular detection methods, molecular diagnosis will play an increasingly important role in the clinical and histological diagnosis of**

**melanoma. Artificial intelligence-assisted clinical and histological diagnosis is anticipated to simplify and optimize this process. This review summarizes the latest advances in melanoma diagnosis, laying a foundation for in-depth comprehension of current therapeutic strategies and the principles of emerging technologies, and helping clinicians grasp the key points of melanoma to improve clinical decision-making.**

## Keywords

**Melanoma, Histological Diagnosis, Artificial Intelligence, Molecular Diagnostics**



## 1. 引言

黑色素瘤(Melanoma)是一种起源于黑色素细胞的恶性肿瘤，其特征是高度侵袭和多向转移，是皮肤癌中死亡率最高的一种[1]。近年来，受紫外线，家族史以及痣数量等风险因素影响，其发病率和死亡率在全球范围内不断提升[2]。因黑色素瘤的恶性程度较高和转移性扩散，预后效果较差，早期诊断是治愈的最佳方法[3]。随着对黑色素瘤基因组学基础的深入理解，其诊断与治疗领域取得了进步。如今黑色素瘤的诊断不再单纯依赖皮肤活检的组织学解读，而是涌现出更为精准的分子辅助检测技术，为病理医生提供了有力支持。

本文综述了黑色素瘤诊断研究的最新进展，内容涵盖临床、组织病理学、人工智能和分子诊断等方面，通过整合基础研究与临床数据，旨在为了解该疾病诊断技术和支持临床决策提供参考基础。

## 2. 临床诊断

黑色素细胞病变的分化依赖于黑色素细胞的特定标记，这些标记与其他细胞系中尚未表达的黑色素体相关[4]。准确的诊断对于提供最佳治疗至关重要。黑色素瘤的诊断需要临床检查或通过皮肤放大镜特征来提高诊断准确性，分类在很大程度上依赖于对组织病理学结果的解释，辨别病变需要多年的培训和经验，包括四种主要的不同临床病理亚型及其相应的原位病变：恶性黄斑、浅表扩散、肢端黄斑和结节，这种分类已经扩展到 9 种不同的亚型[5]。

临床上的病变通常是变化或生长的色素性皮损(也可能是无色素性) [6]。为了检测可疑病变，提出了 ABCDE 标准，已成为辅助黑色素瘤早期检测的重要工具，ABCDE 标准是指存在不对称，边缘不规则，颜色不均，病灶直径(>6 mm)，以及皮损演变或近期发生变化[7]。ABCDE 各标准的敏感性分别描述为 57%、57%、65%、90%和 84%，特异性分别为 72%、71%、59%、63%和 90% [8]。ABCDE 标准的挑战包括识别小病灶以及特定黑色素瘤亚型，如结节型、无色素性黑色素瘤和促结缔组织增生性黑色素瘤[9]。为提高诊断准确性，受过专业培训的医生使用皮肤镜技术区分黑色素瘤与非黑色素瘤可疑的皮肤病变。黑色素瘤的皮肤镜特征包括多种颜色分布不对称、不规则条纹、非典型色素网络、非典型球状结构、蓝白结构以及非典型血管模式等[10]。

## 3. 组织病理性诊断

组织病理学诊断黑色素瘤仍然是金标准，尽管有黑色素瘤明显符合特定亚型的临床和病理标准，但

许多黑色素瘤在同一病变中具有重叠的组织病理模式，病理学家通过切除或削取活检清除研究相关病灶，对于范围较大的皮损，则会在最可能发生浸润的区域进行部分取样，评估黑色素细胞和黑色素瘤细胞的数量、分布和形状、真皮中是否存在入侵以及组织反应等特征以确认临床诊断[11]。如果病变被归类为黑色素瘤，则使用 Breslow 厚度、溃疡、消退、刺激、免疫细胞的存在等特征来确定病变的严重性[12]。

在许多情况下，病理学家之间的观察者间差异较大。此外，需要受过培训的病理学家投入大量时间和精力。由于高估或低估了黑色素瘤的诊断，信息遗漏或错误的观察可能对患者造成不利影响。尽管试图改进诊断，但对色素病变和黑色素瘤的准确评估仍然困难。随着分子诊断技术的进步，病理学家正在转向更精确的基于分子的辅助诊断测试[13]。对于疑难病例，在组织病理学诊断基础上辅以免疫组织化学和分子检测可能具有重要价值，相关技术包括比较基因组杂交、荧光原位杂交(Fluorescence in situ hybridization, FISH)、靶向基因测序以及基因表达谱分析[14]。

## 4. 人工智能诊断

传统黑色素瘤的诊断依赖于病理学家在显微镜下观察苏木精－伊红(H&E)染色的组织切片，这种方法存在病理学家的诊断差异、耗费时间与精力和人眼提取信息有限等缺点[15]。人工智能，尤其是深度学习算法，能够自动、客观地从数字病理全切片图像中提取海量特征，包括人眼无法察觉的模式，从而有效应对上述挑战[16]。多项研究表明，深度学习模型能够鉴别黑色素瘤与良性痣，自动识别和分割肿瘤区域、表皮、真皮等，定位和量化异型黑色素细胞，自动评分肿瘤浸润淋巴细胞(Tumor infiltrating lymphocytes, TIL) [17]。卷积神经网络(Convolutional neural networks, CNN)是最常用的深度学习架构，将高分辨率的全切片图像分割成无数小图块，对每个图块进行特征提取和分析，最后根据所有图块的结果整合出对整个切片的诊断[18]。部分研究使用如 Grad-CAM 等方法生成“热力图”，直观显示模型做出判断所依据的图像区域，增强了模型的可信度和可解释性，并发现这些区域常与病理学家关注的区域吻合[19]。

人工智能诊断，特别是基于 H&E 染色数字病理图像的深度学习，已在黑色素瘤组织学诊断中展现出变革性的潜力，它能够以高精度完成核心鉴别诊断、自动化定量分析，并有望发现新的诊断特征。目前，FDA 批准 3 款黑色素瘤相关 AI 设备，均以非侵入性光谱分析搭配 AI 算法评估病变，避开图像类工具像素数据变异问题[20]。DermaSensor 用弹性散射光谱分析皮肤细胞；Nevisense 基于电阻抗光谱测组织阻抗；已退市的 MelaFind (因高假阳性退市)用多光谱成像捕捉病变特征，分析一维光谱数据降低算法过拟合风险，为获批关键。三款设备均高灵敏度、低特异性。可解释性(Explainability)是 AI 技术从实验室迈向临床应用的关键掣肘[21]。当下，黑色素瘤 AI 诊断模型多为“黑箱”算法，病理医生难以理解与验证其决策依据，这极大地限制了临床信任度与推广应用。最新研究指出，核心问题体现在三方面：技术与临床，AI 提取的特征超出传统病理诊断体系，难以对应标准指标；决策与逻辑，模型无法追溯判定恶性的依据，误差来源难查明且易受无关因素干扰；表达与理解，现有可解释性工具多为技术可视化，未转化为病理医生能理解的专业语言。未来，唯有融合规则与数据驱动、优化可视化工具、推动数据标准化与验证以及强化监管要求，才能实现破局[22]。人工智能诊断正稳步从一个研究概念发展为能够辅助病理学家、提升诊断质量和效率的实用临床工具，为实现更精准、个性化的黑色素瘤诊疗铺平了道路。

## 5. 分子诊断

黑色素瘤的分子诊断正朝着多技术整合、高特异性和非侵入性方向快速发展，核心依托基因组学、蛋白质组学及新型分子检测技术，弥补传统组织病理学诊断的主观性缺陷，为亚型分类、治疗指导和预后评估提供精准依据[23]。基因组学诊断通过检测基因突变、拷贝数异常等遗传特征，明确黑色素瘤的分子亚型和发病机制，是分子诊断的核心支柱[24]。核心检测技术包括下一代测序(Next-generation sequencing,

NGS)、荧光原位杂交以及比较基因组杂交(Comparative genomic hybridization, CGH) [25]。下一代测序可全面覆盖基因突变、拷贝数变异(Copy number variations, CNA)、染色体易位等多种遗传异常，用于黑色素瘤亚型分型(如 BRAF 突变型、NRAS 突变型、NF1 突变型)指导靶向治疗，其面对的局限性是早期黑色素瘤突变负荷较低，部分突变(如 TERT 启动子突变)的临床验证不足，尚未形成统一诊断标准[26]。荧光原位杂交通过特异性探针标记目标染色体片段，可视化检测基因扩增、缺失或易位，常用探针包括 6p25 (RREB1)、6q23 (MYB)、9p21 (CDKN2A)等，主要用于鉴别诊断模糊的病例(如 Spitz 痣)，但 Spitz 痣可能出现四倍体等假阳性情况，需结合其他技术验证[27]。比较基因组杂交分析全基因组拷贝数变化，可识别传统荧光原位杂交遗漏的染色体异常，95%以上的黑色素瘤存在染色体拷贝数异常，而仅 13%的良性痣有此特征，可有效区分良恶性病变[28]。

蛋白质组学通过检测差异表达蛋白，直接反映基因组突变、翻译后修饰及环境因素的综合影响，在早期诊断和表型区分中更具优势，核心检测技术包括免疫组织化学(Immunohistochemistry, IHC)、质谱技术、蛋白芯片与自身抗体检测[29]。免疫组织化学常用标志物黑色素瘤特异性抗原 PRAME、泛黑色素细胞标志物 S100 家族辅助确认肿瘤来源、CDKN2A 基因产物 p16 缺失提示恶性、黑色素细胞分化标志物 HMB45，其面对的局限是单一标志物诊断效能有限需组合使用[30]。部分标志物无法区分原位黑色素瘤与角化病[31]。质谱技术包括数据依赖采集(Data-dependent acquisition, DDA)、数据非依赖采集(Data-independent acquisition, DIA)、以及基质辅助激光解吸电离飞行时间质谱(Matrix assisted laser desorption ionization time of flight mass spectrometry, MALDI-TOF MS) [32]。数据非依赖采集技术可同时检测数千种蛋白，减少高丰度蛋白干扰[33]。MALDI 质谱成像可直接分析组织切片中蛋白空间分布，区分良性痣与黑色素瘤[34]。蛋白芯片与自身抗体检测通过检测血清中肿瘤相关自身抗体，如波形蛋白(Vimentin)在转移性黑色素瘤中高表达，膜联蛋白(Annexin)：调控炎症和凋亡与黑色素瘤进展相关，组蛋白 H4 (Histone H4)异常表达提示肿瘤增殖活跃，PRAME 在黑色素瘤中特异性高表达，可区分良恶性病变[35]-[38]。新型分子诊断技术包括色素病变检测(Pigmented lesion assay, PLA)、液体活检和基因表达谱(Gene expression profiling, GEP)检测[39]-[41]。

黑色素瘤的分子分型已成为精准治疗决策的核心依据，结合最新的临床指南(NCCN)及最新临床证据，基因组突变分型与肿瘤微环境(Tumor microenvironment, TME)功能分型对治疗具有一定的指导意义，黑色素瘤基因组突变检测聚焦 BRAF、NRAS、KIT、NF1 等核心驱动基因，检测时机与疾病分期挂钩，III 期术后辅助治疗前、IV 期初始治疗前检测以筛选靶向治疗人群[42]。不同突变分型指导价值有明确指南证据，BRAF 突变是关键靶点，NRAS 突变无明确获批靶向药，免疫治疗优先，部分靶向策略在探索；KIT 突变或扩增在特殊亚型高发，NF1 突变属免疫治疗优势人群，靶向治疗中 MEK 抑制剂联合免疫治疗有探索价值。肿瘤微环境功能分型结合 4 种保守 TME 亚型细化免疫治疗人群筛选，通过基因表达谱检测或免疫组化标志物综合判断，IE 亚型是免疫治疗最优响应人群，单药免疫治疗可达标，PD-L1 阳性者单药 ORR 更高；IE/F 亚型是双免疫联合适配人群，双免疫联合疗效优于单药，合并 VEGF 高表达者联合抗 VEGF 药物是临床研究优先推荐方向；F 亚型是免疫治疗低响应人群，需联合逆转微环境方案，有驱动突变者优先靶向联合治疗；D 亚型是免疫治疗难治人群，需采用免疫激活 + 靶点抑制联合策略，三药联合及个体化新抗原疫苗联合免疫治疗有相关研究推荐[43]。

当前的分子诊断技术主要运用于良恶性鉴别、亚型分类、治疗指导以及预后评估等，同时也面临着早期标志物验证不足、检测成本与可及性、异质性影响、假阳性与过度诊断等挑战[44]。未来趋势需多组学整合提高准确性、非侵入性技术优化、人工智能辅助提高诊断效率以及针对个体化标志物开发，实现精准诊断和治疗监测[45]。

## 6. 结语

黑色素瘤的诊断已从传统临床病理观察，逐步迈向“临床表型 + 分子特征 + 技术辅助”的多维度整合模式。当前，组织病理学仍是诊断的金标准(见表 1) [46]。但存在主观性强、良恶性中间型病变鉴别困难等局限，而基因组学、蛋白质组学技术的突破为解决这些痛点提供了关键支撑。同时，人工智能辅助诊断进一步提升了诊断的标准化与效率。然而，现有诊断体系仍面临早期分子标志物临床验证不足、检测成本较高、过度诊断争议等挑战[47]。未来通过多学科协作与技术创新，有望彻底改变当前诊断格局，实现早期精准识别、风险分层管理与治疗精准匹配的目标。

**Table 1.** Comparison of diagnostic techniques for melanoma
**表 1.** 黑色素瘤的诊断技术比较

| 诊断技术 | 临床诊断 | 皮肤镜检查 | 病理学诊断 | 人工智能辅助诊断 | 分子诊断 |
|---|---|---|---|---|---|
| 敏感性 | 约 70% | 75%~90% | 95%~98% | 85%~98% | 80%~95% |
| 特异性 | 约 75% | 70%~85% | 95%~99% | 80%~95% | 85%~98% |
| 成本 | 极低 | 低 | 中 | 中高 | 高 |
| 耗时 | 5~10 min | 10~15 min | 3~7 个工作日 | 5~30 min | 3~10 个工作日 |
| 核心优势 | 无创便捷<br>无额外费用 | 提升早期小病灶<br>识别率、无创 | 诊断金标准<br>提供预后指标 | 客观高效<br>减少人为误差 | 精准指导<br>个体化治疗 |
| 局限性 | 主观性强<br>特殊亚型易漏诊 | 无色素性病变<br>的敏感性低 | 有创<br>耗时较长 | 依赖高质量图像、<br>解释性不足 | 成本高、有创、<br>技术门槛高 |
| 适用场景 | 基层初步筛查<br>高危人群监测 | 可疑色素性<br>病变鉴别 | 明确诊断<br>肿瘤分期 | 病理图像初筛<br>基层诊断支持 | 亚型分型、靶向<br>或免疫治疗指导 |

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