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野生型胃肠间质瘤的临床病理特征及研究进展

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摘　要

本研究探讨野生型胃肠间质瘤(wt-GIST)的临床病理特征、分子分型、检测技术及治疗进展，为其精准诊疗提供参考。胃肠间质瘤(GIST)中10%~15%为无c-KIT/血小板源性生长因子受体α (PDGFRA)经典基因突变的wt-GIST，其分子机制、临床表型及治疗响应与突变型GIST差异显著。二代测序(NGS)推动了wt-GIST分子分型体系的完善，该肿瘤以SDHB免疫组化(IHC)为核心分为SDH缺陷型和SDH功能正常型，前者因SDH复合体功能丧失引发代谢重编程与表观遗传修饰异常，后者则以RAS-MAPK等经典信号通路异常激活为主要驱动机制。手术是局限性wt-GIST的根治核心，SDH缺陷型不推荐常规淋巴结清扫，传统酪氨酸激酶抑制剂(TKI)疗效有限，奥雷巴替尼等新型靶向药在SDH缺陷型中展现突破性疗效，免疫联合治疗及CD36代谢靶向治疗为新方向。目前wt-GIST仍存在诊疗策略不完善、部分亚型缺乏有效治疗手段等瓶颈，未来需依托多组学技术深化研究，完善精准诊疗体系。

关键词

野生型胃肠间质瘤，分子分型，分子诊断，靶向治疗，精准诊疗

Clinicopathological Features and Research Progress of Wild-Type Gastrointestinal Stromal Tumors

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Abstract

This study investigated the clinicopathological features, molecular subtyping, detection technologies

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and treatment progress of wild-type gastrointestinal stromal tumors (wt-GIST) to provide a reference for its precision diagnosis and treatment. Approximately 10% to 15% of gastrointestinal stromal tumors (GISTs) are wt-GISTs without classic c-KIT/platelet-derived growth factor receptor α (PDGFRA) gene mutations, which exhibit distinct molecular mechanisms, clinical phenotypes and treatment responses compared with mutant GISTs. Next-Generation Sequencing (NGS) has promoted the improvement of the molecular subtyping system for wt-GISTs. Based on succinate dehydrogenase B (SDHB) immunohistochemistry (IHC), wt-GISTs are classified into two major subtypes: SDH-deficient and SDH-proficient. The former is driven by metabolic reprogramming and aberrant epigenetic modifications caused by loss of SDH complex function, whereas the latter is mainly characterized by abnormal activation of classic signaling pathways such as RAS-MAPK. Surgical resection is the cornerstone of curative therapy for localized wt-GISTs, and routine lymph node dissection is not recommended for SDH-deficient subtypes. Conventional tyrosine kinase inhibitors (TKIs) show limited therapeutic efficacy, while novel targeted agents such as olverembatinib have demonstrated groundbreaking efficacy in the treatment of SDH-deficient wt-GISTs. Immune combination therapy and CD36-mediated metabolic targeted therapy have emerged as promising new therapeutic directions. At present, the clinical management of wt-GISTs still faces bottlenecks including incomplete diagnosis and treatment strategies and the lack of effective therapeutic approaches for some subtypes. In the future, it is necessary to conduct in-depth research relying on multi-omics technologies and further improve the precision diagnosis and treatment system for wt-GISTs.

Keywords

Wild-Type Gastrointestinal Stromal Tumor, Molecular Subtyping, Molecular Diagnosis, Targeted Therapy, Precision Diagnosis and Treatment

1. 引言

胃肠间质瘤(Gastrointestinal Stromal Tumor, GIST)是胃肠道最常见的间叶源性肿瘤，c-KIT 或 PDGFRA 基因功能获得性突变是其核心发病机制，其中 10%~15%因无上述经典突变被定义为野生型胃肠间质瘤(Wild-Type Gastrointestinal Stromal Tumor, wt-GIST) [1]。wt-GIST 的分子机制、临床表现及治疗反应与突变型 GIST 差异显著，是临床诊疗的重点与难点。随着二代测序(Next-Generation Sequencing, NGS)技术临床应用，wt-GIST 分子分型逐渐明确，主要包括琥珀酸脱氢酶(Succinate Dehydrogenase, SDH)缺陷型、RAS/BRAF 突变型、神经纤维瘤病 1 型(Neurofibromatosis Type 1, NF1)及四重野生型等亚型，各亚型具有独特的临床病理特征与生物学行为[2]。当前 wt-GIST 诊疗仍存在诸多问题：传统酪氨酸激酶抑制剂(Tyrosine Kinase Inhibitor, TKI)整体治疗响应率极低，仅部分 BRAF/RAS 突变亚型对特异性靶向抑制剂有效，SDH 缺陷型与四重野生型长期缺乏有效治疗手段[1]；个体化诊疗策略尚未建立，分子检测体系仍需完善，而 NGS 技术的普及为明确分型、挖掘潜在治疗靶点提供了关键支撑[2]。本文系统梳理 wt-GIST 的临床病理特征、分子分型、发病机制及检测技术进展，为其精准诊疗提供参考。

2. 野生型 GIST 的临床病理特征

wt-GIST 的临床病理特征具有显著亚型异质性，与突变型 GIST 差异明显，不同分子亚型的特征各有侧重，为临床鉴别诊断提供重要依据。

2.1. 流行病学特征

wt-GIST 流行病学特征受检测技术、年龄及地域因素影响，呈明显亚型特异性，与突变型 GIST 差异显著[3]。该肿瘤性别分布无明显差异，年龄呈双高峰特征，高发于青年女性与中老年群体[4]；发病部位以胃为主，其次为小肠，结直肠及食管发病占比不足 10% [5]。不同分子亚型的流行病学特征各具特异性[6] [7]：SDH 缺陷型是 wt-GIST 最常见亚型，好发于青年女性胃部，多呈多灶性惰性进展；BRAF 突变型以小肠发病多见，核分裂象相对较高；NF1 相关型 GIST 常为多灶性病变，与神经纤维瘤病密切相关[8]。全球 wt-GIST 发病率缓慢上升，主要归因于 NGS 技术发展及诊断标准完善，地域间的亚型分布差异仍需大样本队列研究验证。

2.2. 临床表现

wt-GIST 临床表现具有亚型异质性，疾病早期症状隐匿，多数患者出现特异性表现时已至中晚期，临床诊断需结合症状、影像学及分子检测结果[5]。多数患者以消化道出血为首发症状，长期慢性出血可继发中重度贫血，同时伴腹痛、腹胀等非特异性不适；小肠原发者腹痛更显著，部分可引发肠梗阻。SDH 缺陷型 GIST 进展偏惰性，但淋巴结及远处转移率更高，部分可合并 Carney 三联征或 Carney-Stratakis 综合征[9]。NF1 相关型 GIST 患者多伴随神经纤维瘤病典型体征，肿瘤多灶性且好发于小肠[10]。四重野生型 GIST 患者发病年龄偏大，病灶多见于胃部，高核分裂象病例进展快、转移风险高，术后辅助治疗获益有限[11]。

2.3. 病理形态特征

wt-GIST 与突变型 GIST 在大体结构、组织学表现及免疫表型方面存在明确差异[12]。大体上多为边界较清晰的结节状或多结节状肿块，部分呈浸润性生长，直径 2~15 cm 不等，较大肿瘤常伴发出血、坏死，SDH 缺陷型囊性变发生率显著更高[13]。组织学主要分为梭形细胞型、上皮样细胞型及混合型，SDH 缺陷型以上皮样细胞为主，易见淋巴管瘤栓[13]；NF1 相关性 GIST 绝大多数为梭形细胞型，间质常伴少量淋巴细胞浸润[14]；四重野生型以混合型多见[15]。免疫表型上，DOG1、CD117、CD34 为核心阳性标志物[15]；SDHB 蛋白表达完全缺失是 SDH 缺陷型的特征性标志，其敏感性及特异性均达 95%以上，为该亚型筛查金标准[16]。

3. 野生型 GIST 主要分子亚型及核心发病机制

wt-GIST 以 SDHB 免疫组化检测为核心筛查手段，结合基因测序等技术，可分为 SDH 缺陷型和 SDH 功能正常型两大类，各分子亚型具有独特的临床特征与发病机制，为精准靶向治疗提供了分子基础。

3.1. SDH 缺陷型 GIST

SDH 缺陷型 GIST 约占所有 wt-GIST 的 50%，也是野生型 GIST 中最具代表性的少见驱动亚型，其核心分子标志为 SDHB 蛋白表达缺失，由 SDH 复合体相关基因异常导致[17]，好发于青年及青少年人群，女性多见，好发部位以胃部为主，且具有易复发、易转移的特点，免疫组化表现为 SDHB 蛋白表达缺失[18] [19]。该亚型主要包括 SDHx 基因胚系突变型、SDHC 启动子甲基化型及其他 SDH 缺陷机制三类，其核心发病机制是 SDH 复合体功能丧失导致的代谢重编程和表观遗传修饰异常[17]：① 琥珀酸积累与 HIF1α 稳定：SDH 复合体功能缺失导致琥珀酸大量积累，进而抑制 α-酮戊二酸依赖的双加氧酶，使 HIF1α 稳定表达，激活下游靶基因促进肿瘤血管生成和细胞增殖[17] [20]；② 表观遗传调控异常：琥珀酸可抑制 DNA 和组蛋白去甲基化酶活性，导致基因组高甲基化，使肿瘤抑制基因沉默[20] [21]，与 SDHC 启动子甲基化形

成恶性循环，进一步加剧肿瘤进展[20]；③ IGF1R 信号通路激活：该通路在 89%的病例中表达上调[22]，通过 PI3K-AKT 和 MAPK 通路促进肿瘤增殖，且与 HIF1α 形成协同驱动机制[17]，是该亚型潜在的治疗靶点[22]。此外，SDH 基因功能缺陷还会导致细胞能量代谢紊乱、氧化应激异常及信号通路异常激活[23]。

3.2. SDH 功能正常型 GIST

SDH 功能正常型 GIST 即 SDHB 免疫组化阳性的 wt-GIST，分子机制主要涉及其他信号通路异常激活，各亚型相对罕见[24]：① NF1 相关型 GIST：核心发病机制是 NF1 基因功能丧失性突变导致 RAS-MAPK 通路持续激活[25]，部分病例还伴随 NOTCH 通路突变或染色体缺失，进一步增强肿瘤侵袭性[26]。临床中，该亚型肿瘤多为多中心性，好发于小肠，十二指肠发病者侵袭性更强[27]，部分散发性 wt-GIST 也可能存在体细胞 NF1 突变[28]，且患者传统 TKI 治疗疗效有限，治疗难度较高[29] [30]。② BRAF 突变型 GIST：以 V600E 为最常见突变类型[31] [32]，其核心发病机制是 BRAF V600E 突变使 BRAF 激酶持续激活，直接磷酸化 MEK 并激活 ERK，启动增殖相关基因转录，导致 RAS-RAF-MEK-ERK 信号通路持续活化，促进肿瘤细胞异常增殖[29] [33] [34]。该亚型与 KIT/PDGFRA 突变相互排斥[33]，MAPK 通路激活程度显著高于 KIT 突变型 GIST [31] [33]。③ 融合基因驱动型 GIST：已报道的融合基因包括 ETV6-NTRK3、FGFR1-TACC1 等[35] [36]，核心发病机制是融合基因编码的嵌合蛋白形成组成性激活的融合激酶，激活 PI3K-AKT 和 MAPK 通路，驱动肿瘤发生发展[35] [36]，部分病例对融合基因抑制剂治疗敏感，是该亚型重要的潜在治疗靶点[37]。④ 四重野生型 GIST：该亚型缺乏 KIT、PDGFRA、SDHx 及 RAS 通路基因突变，其分子驱动机制目前尚未明确[22]，临床中患者发病年龄偏大，病灶多见于胃部，高核分裂象病例进展快、转移风险高，术后辅助治疗获益有限[11]。

4. 野生型 GIST 的基因检测技术

wt-GIST 的分子诊断是精准诊疗的前提，检测流程需先排除经典 KIT/PDGFRA 突变，再进一步明确亚型。检测技术从传统的 Sanger 测序、ARMS-PCR 逐步发展为以 NGS 为核心，结合甲基化特异性 PCR、液体活检等新兴技术的多元化体系，检测效率与精准性不断提升。所有疑似 GIST 患者均需优先筛查 KIT 与 PDGFRA 基因热点区域，常规检测采用 Sanger 测序或 ARMS-PCR 技术，操作简便、成本可控，能快速覆盖 85%以上的突变型 GIST [38]；仅当常规检测阴性，且病理或临床特征提示 wt-GIST 时，进入亚型检测流程[39] [40]，2023 年 GEIS 指南明确推荐 CD117/DOG1 阴性的疑似病例必须通过分子检测确认 KIT/PDGFRA 状态[12]。Sanger 测序与 ARMS-PCR 是检测基础，但存在明显不足：Sanger 测序难以捕捉低丰度突变，假阴性率较高，且无法检测基因融合等复杂异常[12] [40] [41]；ARMS-PCR 仅能检测预设热点，无法发现新突变[30]。

NGS 技术凭借多基因并行检测、高灵敏度及广覆盖度，成为 wt-GIST 分子诊断的首选工具[42] [43]。定制化 panel 可一次性检测突变、拷贝数变异等，显著提升诊断效率[38]，也被指南推荐用于排查罕见分子异常[12] [44]，还能捕捉 KIT 继发性突变，为耐药患者提供治疗依据[45]。此外，甲基化特异性 PCR、焦磷酸测序是 SDH 缺陷型的重要补充检测手段[12]；液体活检适用于无法获取组织样本的晚期患者，目前灵敏度较低[38]；单细胞测序可解析肿瘤异质性，因成本较高尚未广泛应用[38]；[68Ga] NeoBPET/CT 分子成像可辅助 SDH 缺陷型的诊断与治疗筛选[42]。

5. 野生型 GIST 的治疗进展

5.1. 手术治疗

手术切除是可切除 wt-GIST 的根治性治疗核心，需在实现 R0 切除的同时兼顾器官功能保留[46] [47]。

胃来源 wt-GIST 根据肿瘤直径选择内镜手术、腹腔镜楔形切除术或胃部分切除术；小肠来源者恶性程度更高，推荐行肠段切除术联合区域淋巴结采样[46] [48]。SDH 缺陷型 GIST 淋巴结转移率高达 20%~30%，但多中心研究显示常规淋巴结清扫未显著改善患者预后，反而增加并发症发生率[49]。

目前国内外共识为：不推荐常规淋巴结清扫，术中发现可疑转移时应积极清扫；Carney 三联征相关病例需同时排查伴发病变，必要时多学科协同手术[50] [51]。术后辅助治疗时长需个体化调整[46] [47]：低危患者无需辅助治疗，中危患者胃来源者治疗 1 年、非胃来源者延长至 3 年，高危患者至少治疗 3 年，极高危者可延长至 5 年。辅助治疗药物首选伊马替尼，但 SDH 缺陷型对其疗效有限，客观缓解率仅 10%左右[23] [52] [53]，舒尼替尼等药物的应用尚缺乏高级别证据支持[23] [53]。

5.2. 靶向治疗

5.2.1. 以血管生成为核心靶点的酪氨酸激酶抑制剂

此类抗肿瘤药物以血管内皮生长因子受体(VEGFR)、血小板衍生生长因子受体(PDGFR)为核心作用靶点，通过抑制肿瘤新生血管的生成、阻断肿瘤细胞的营养供应，进而发挥显著的抗肿瘤作用，同时对 KIT、PDGFRA 等相关激酶也可产生一定的抑制效果，属于泛靶点、广谱性的抗肿瘤药物[54] [55]。舒尼替尼作为第一代广谱多靶点酪氨酸激酶抑制剂(TKI)，能够同时作用于 VEGFR1-3、PDGFRα/β、KIT、FLT3、RET 等多种激酶，主要应用于伊马替尼治疗后出现耐药或不耐受的晚期患者。瑞戈非尼的作用谱与舒尼替尼具有较高相似性，对 VEGFR、KIT、RET 以及 RAF 家族激酶均具备抑制活性，且其抗血管生成的作用更为显著，临床主要用于既往接受 TKI 治疗失败后的晚期 GIST 后线治疗[54] [55]。该类泛靶点抗肿瘤药物的应用无需依赖肿瘤细胞存在特定的驱动基因突变，其治疗核心目标在于有效控制疾病进展、延长患者的无进展生存期，但临床研究表明，其对非 KIT/PDGFRA 突变亚型的肿瘤患者，疗效通常较为有限，难以达到理想的治疗效果[55] [56]。

5.2.2. 针对特定驱动基因的精准靶向药物

随着分子分型体系的不断完善，针对 GIST 中 FGFR 融合、BRAF 突变、NF1 缺陷、SDH 缺陷等少见驱动亚型的特异性靶向药物逐步进入临床应用。

FGFR2/3 融合或重排的 GIST，FGFR 特异性抑制剂是核心治疗选择。该类药物通过竞争性结合 FGFR 激酶的 ATP 结合口袋，有效阻断下游 MAPK/PI3K 信号通路的异常激活，进而抑制肿瘤细胞增殖、侵袭及新生血管生成，对传统 TKI 疗效欠佳的该类耐药亚型展现出明确且稳定的抗肿瘤活性[56]。

BRAF 突变亚型 GIST，以 BRAF V600E 突变最为常见，该突变可导致 RAS-RAF-MEK-ERK 信号通路持续活化，促进肿瘤细胞异常增殖[29] [34]。以达拉非尼为代表的 BRAF 特异性抑制剂，可精准结合并抑制突变型 BRAF 激酶活性，阻断信号通路异常传导，从而发挥抗肿瘤作用；临床实践中，BRAF 抑制剂常与 MEK 抑制剂联合应用，可显著提升治疗疗效，同时有效延缓肿瘤耐药性的发生，进一步优化患者生存结局[29] [34]。此外，维莫非尼作为另一类 BRAF 抑制剂，单药或联合依维莫司、索拉非尼等药物的治疗策略，也已在 BRAF V600E 突变型肿瘤中证实具有显著疗效，为该亚型 GIST 患者提供了多元化治疗选择[34]。

NF1 缺陷型 GIST 是另一类重要的少见驱动亚型，NF1 基因功能缺失可导致 RAS 信号通路异常激活，推动肿瘤发生发展，该亚型患者传统 TKI 治疗疗效有限，治疗难度较高[29] [30]。目前，针对 NF1 缺陷型 GIST 的特异性靶向治疗研究持续深入，主要聚焦于 RAS 信号通路相关靶点的抑制剂研发，其中 MEK 抑制剂已展现出一定的治疗潜力，可通过抑制 MEK 激酶活性，阻断 RAS-RAF-MEK-ERK 信号通路活化，从而抑制肿瘤细胞增殖；同时，联合其他靶向药物的治疗方案也在探索中，有望进一步提升该亚型患者的治疗获益[29] [30]。

5.2.3. SDH 缺陷型 GIST 与奥雷巴替尼(HQP1351)的治疗突破

SDH 缺陷型 GIST 以 SDH 亚单位(SDHA, SDHB, SDHC, SDHD)突变或缺失为核心分子特征，可导致琥珀酸蓄积、HIF 通路激活及肿瘤代谢与微环境重塑，对伊马替尼、舒尼替尼等传统 TKI 呈原发性耐药，患者预后较差，是 GIST 临床治疗的重要难点[18] [23] [34]。奥雷巴替尼(Olverembatinib, HQP1351)作为新一代多靶点激酶抑制剂，其作用机制与传统 TKI 存在本质差异，通过多维度协同调控精准针对 SDH 缺陷致病核心，有效克服传统 TKI 局限，成为该亚型治疗的里程碑突破[23] [57] [58]，二者核心区别及奥雷巴替尼作用机制如下：① 传统 TKI 的靶点集中于 KIT、PDGFRA 或 VEGFR，核心作用是阻断上述激酶介导的肿瘤增殖信号，但 SDH 缺陷型 GIST 的发病机制不依赖此类突变，导致传统 TKI 无法触及该亚型的致病核心，进而产生原发性耐药[18] [55]。但奥雷巴替尼具备更广泛且针对性更强的靶点谱，不仅可强效抑制 VEGFR1-3、FGFR1-4 等经典激酶，更能直接作用于 SDH 缺陷驱动的核心致病分子 HIF-1α/2α，从源头阻断琥珀酸蓄积引发的缺氧信号通路异常激活，抑制肿瘤细胞在缺氧微环境中的异常增殖、代谢适应及转移能力；同时其可抑制 CSF1R、DDR1 等额外靶点，通过多靶点协同形成立体化抑瘤效应，区别于传统 TKI 的单一靶点作用模式[23] [56] [58]。② 传统 TKI 仅能阻断单一增殖或血管生成信号通路，无法纠正 SDH 缺陷引发的代谢紊乱与免疫微环境异常，难以实现全方位抑瘤效应[18] [55]。奥雷巴替尼则突破这一局限，构建“信号–代谢–免疫”三位一体的协同抑瘤体系：信号通路层面，同步阻断 VEGFR、FGFR 介导的血管生成信号及 KIT、PDGFRA 介导的增殖信号，双重遏制肿瘤细胞生长与血管新生、切断肿瘤营养供应；肿瘤代谢层面，特异性抑制脂质转运蛋白 CD36 的表达，纠正 SDH 缺陷导致的脂质代谢重编程，切断肿瘤细胞外源性脂质供给、抑制能量代谢，从代谢层面遏制肿瘤增殖；免疫微环境层面，通过抑制 CSF1R 调控肿瘤相关巨噬细胞(TAM)表型转化，减少 M2 型促瘤巨噬细胞浸润，逆转免疫抑制微环境，增强机体抗肿瘤免疫应答，实现“靶向治疗 + 免疫调控”双重效应，全方位提升抑瘤效果[19] [23] [56] [58]。③ 传统 TKI 围绕 KIT/PDGFRA 突变研发，作用靶点与 SDH 缺陷型 GIST 的致病机制无直接关联，无法针对琥珀酸蓄积、HIF 通路激活等核心致病环节发挥作用，难以有效控制疾病进展[18] [23]。奥雷巴替尼跳出传统 TKI 的研发局限，不再依赖 KIT/PDGFRA 靶点，而是直接靶向 SDH 缺陷下游关键致病环节，包括琥珀酸蓄积引发的 HIF 通路异常激活、脂质代谢重编程及免疫抑制微环境等，通过多靶点、多维度协同调控，从根源上阻断肿瘤发生发展的核心路径，有效克服该亚型对传统 TKI 的原发性耐药，成为难治性 SDH 缺陷型 GIST 的全新治疗策略，也为该领域精准治疗提供了新思路[23] [57] [58]。

5.3. 其他治疗策略探索

wt-GIST 肿瘤突变负荷较低，免疫检查点抑制剂单药疗效有限[53] [59]，但 SDH 缺陷型患者因琥珀酸蓄积激活肿瘤微环境免疫，伊匹木单抗联合纳武利尤单抗的临床获益率 40% [60]，PD-1 抗体联合抗血管生成药物也可为部分患者带来长期疾病稳定[61]，CD36 抑制剂与 PD-1 抗体联合治疗的预临床研究显示出协同作用[60]。SDH 缺陷型 wt-GIST 存在显著的脂质代谢紊乱，CD36 异常高表达导致肿瘤细胞对外源性脂质摄取高度依赖，这一特征已被国内外多项研究证实[59] [60]。针对这一独特代谢机制，脂肪酸合成酶(Fatty Acid Synthase, FASN)抑制剂(如奥利司他)、CD36 单克隆抗体在动物模型中显示出显著的肿瘤抑制效果。目前国际上正在开展 CD36 抑制剂治疗 SDH 缺陷型 wt-GIST 的 I 期临床试验，初步结果显示该类药物可有效抑制肿瘤脂质摄取，延缓肿瘤进展[60]。这一治疗方向为 SDH 缺陷型 wt-GIST 提供了全新的治疗思路，有望成为靶向治疗的重要补充。

6. 总结与展望

wt-GIST 作为特殊 GIST 亚型，具有高度亚型异质性，其临床病理特征及分子机制与突变型 GIST 差

异显著，各分子亚型的表型与致病通路迥然不同。SDHB 免疫组化结合 NGS 技术推动了 wt-GIST 分子分型体系的完善，检测已形成以 NGS 为核心、传统技术与新兴技术为补充的多元化体系；治疗上已形成以手术为核心、靶向治疗为主体、免疫与代谢靶向为补充的格局，手术策略的个体化制定及抗血管生成 TKI 的序贯使用显著改善了患者预后，奥雷巴替尼等新型靶向药在 SDH 缺陷型中展现突破性疗效，基于分子分型的个体化靶向策略也初步建立。

目前 wt-GIST 诊疗仍面临诸多瓶颈：四重野生型等亚型的分子驱动机制尚未明确，部分亚型缺乏有效治疗手段；传统 TKI 对多数 wt-GIST 疗效有限，新型药物的临床证据多为小样本研究或临床试验阶段；分子检测技术的临床普及性与标准化程度有待提升，肿瘤异质性也为诊断与治疗带来挑战。未来，需依托多组学技术深化各亚型分子机制研究，挖掘潜在治疗靶点；完善分子检测体系，推动检测技术标准化与临床应用；开展大样本、多中心临床试验，验证新型药物的疗效。

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