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# 微流控技术在疾病标志物检测中的应用与前景

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## 摘 要

**疾病生物标志物是指从生物样本中检测，与疾病发生、发展、预后密切相关的蛋白质、核酸、代谢物，在疾病的早期精准判断中发挥重要作用。微流控技术作为一种新兴技术，在疾病生物标志物检测中受到重视。本文通过综述微流控技术的设计、工作原理以及在疾病生物标志物检测中的应用，为微流控技术的进一步临床应用提供参考。**

## 关键词

**微流控，疾病生物标志物，医学检验技术**

# Applications and Prospects of Microfluidic Technology in Disease Biomarker Detection

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## Abstract

**Disease biomarkers refer to proteins, nucleic acids, and metabolites detected in biological samples that are closely associated with the onset, progression, and prognosis of diseases. They play a crucial role in early and precise diagnosis. As an emerging technology, microfluidics has garnered significant attention in the detection of disease biomarkers. By reviewing the design, working principles, and applications of microfluidic technology in disease biomarker detection, this paper aims to provide a reference for its further clinical application.**

## Keywords

**Microfluidics, Disease Biomarkers, Medical Laboratory Technology**

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## 1. 前言

疾病生物标志物以其“可测量性、与疾病发生发展高度关联、极高的临床评估价值”在预测疾病发生、发展及预后过程中发挥着重要作用[1]，对这些广泛存在于血清、血浆、尿液、脑脊液等生物流体及组织样本中的蛋白质、核酸、代谢物进行检测在疾病早期筛查、病程检测及疗效评估提供客观依据。传统的酶联免疫吸附实验(ELISA)和聚合式链式反应(PCR)是疾病生物标志物检测的经典方法，广泛应用于蛋白质类标志物的定量检测和核酸类标志物的扩增与检测，此外，化学发光免疫分析(CLIA)、放射免疫分析(RIA)等方法近年来广泛用于临床实验室检测。但目前常用的检测手段常面临操作流程复杂，需专业技术人员及大型仪器支持，常规检测方法灵敏度、特异性、快速性、便携性等方面难以平衡，对样本质量要求高，多重检测能力不足，难以实现单一平台同时检测多种生物标志物的要求，限制了其在临床的应用和普及[2] [3]。近年来，多种微流控检测芯片问世，在新型冠状病毒检测、肿瘤标志物检测、炎症相关疾病检测发挥了巨大作用。鉴于微流控技术在临床应用中逐步受到重视，本文对微流控技术的原理、设计、目前在临床疾病生物标志物检测中的应用以及未来发展趋势进行简要介绍。

## 2. 微流控平台的设计及工作原理

微流控技术是一种在微米尺度的微通道内操控流体并对其中的生物颗粒进行检测的新兴技术，该技术的概念最早可追溯至 20 世纪 90 年代初，Manz 和 Widmer 提出的微型全化学分析系统(miniaturized Total Chemical Analysis Systems, mTAS)理念[4]，核心是将传统实验室中的样品制备、生化反应、分离及检测等基本操作单元集成到微芯片上，实现“芯片实验室(lab-on-a-chip)”的功能，对微量样品进行高效、灵敏的分析[5]。与传统宏观流体系统不同，微流控的核心特征体现在“微尺度效应”，即当流体通道尺寸缩小至微尺度时，表面力(如毛细管力、表面张力)、粘性力等取代惯性力成为主导因素，从而呈现出独特的流体行为与传输特性[6]。微流控技术的发展为开发疾病标志物特异、灵敏、快速稳定、可负担工具提供了思路，有效提高检测效率，拓展了定量检测能力及普及性，满足了临床对于疾病标志物检测的多种需求[7]。

微流控芯片作为“芯片实验室”的核心载体，围绕“微型化、集成化、自动化”核心目标构成，结合材料特性与功能需求，形成多模块协同的复杂体系。其基本构成主要包括核心结构(微流控通道、功能腔室等)、材料基底、辅助功能组件三部分，通过调整各部分的设计与选材使其满足微流控流体操控的生物相容性、检测适配性等关键要求。

### 2.1. 核心结构

微通道是微流控芯片的“血管”，是流体流动与操控的核心通道，根据功能需求，微通道网络可分为直通道、Y 型通道、T 型通道、螺旋通道、交叉通道等多种结构，其中直通道结构最简单，是早期微流控芯片的基础通道形式，常用于血液中循环肿瘤细胞、蛋白质等无标记捕获[8]；Y 型通道常用于两种液体的混合或分流，例如 Roward 等设计的基于锯齿形电极的 Y 型微流控装置，通过低电压介电泳技术实现红细胞与血小板的连续高效分离[9]；T 型通道是目前液滴微流控的核心结构，通过剪切力形成分散的液滴[10]；螺旋通道利用 Dean 涡旋增强流体内粒子的分离，目前多用于细胞分选、血浆分离等应用[11]。

功能腔室是微流控芯片实现特定操作的“工作站”，经典的微流控功能腔室包括样品预处理腔、反应腔、检测腔等。核酸检测芯片中，样品预处理腔、PCR 反应腔、检测腔依次连通，实现从样品裂解、核酸扩增到信号检测的一体化[12]-[14]；而在器官芯片中，功能腔室模拟器官微环境，如肺芯片的腔室模拟肺泡结构，实现气体交换功能[15]

### 2.2. 基底材料

微流控芯片基底材料的选择基于成本、生物相容性等进行考量，目前常用的材料包括硅、玻璃、PDMS、纸基水凝胶等。无机基底材料以玻璃、硅片为代表，是微流控芯片发展初期的主流基材，也是实验室精密检测的核心选择。硅片依托成熟的光刻技术，可实现微纳级通道结构的精准制备，且导电性优异，与电化学检测技术高度适配，常被用于循环肿瘤细胞、核酸类标志物的微阵列捕获与检测[16]-[18]，玻璃则具备透光性佳、化学稳定性高、特异性生物吸附、生物相容性好的优势，玻璃基微流控芯片广泛应用于心肌肌钙蛋白[19]、肿瘤抗原等蛋白类标志物的高精准定量检测[20]，也可用于外泌体等胞外囊泡标志物的荧光成像分析。聚合物基底材料是当前微流控芯片临床转化的核心基材，兼具加工便捷性与检测适配性，成为疾病标志物检测中应用最广泛的材料。其中 PDMS 是实验室快速制备微流控芯片的首选，其柔性好、易模塑成型、透光性优异，可与玻璃/硅片实现不可逆键合，且表面易通过等离子体处理、接枝官能团完成改性，有效解决小分子吸附问题，适配免疫分析、微滴技术、荧光检测等多种方法[21] [22]。纸基基底材料以滤纸、纤维素膜、硝酸纤维素膜为核心，是微流控芯片在基层医疗与现场快速检测中的特色基材，也是低成本疾病标志物检测的重要选择[23] [24]。

### 2.3. 辅助功能组件

辅助功能组件是芯片实现检测的关键补充，包括检测模块、温控模块、表面修饰层等。检测模块作为微流控芯片的“信号读出终端”，其核心作用是将芯片内标志物与检测试剂的特异性相互作用转化为可量化、可识别的物理或化学信号，弥补了微流控芯片本体缺乏信号捕获与解析能力的短板[25]。光学检测核心是通过集成微型化光源、滤光元件、探测器等组件，实现对荧光、拉曼散射、比色信号的精准捕获与解析[26]-[28]。电化学检测模块则以微型化、低成本、易集成的优势，成为 POCT 领域的核心选择，其通过将电极集成于微流控芯片通道内，利用标志物与电极表面修饰物质的电化学相互作用，产生氧化还原电流、阻抗等，实现对标志物的定量检测[29] [30]。温控模块是微流控芯片保障检测反应特异性与高效性的关键补充，尤其针对核酸扩增、酶促反应等温度敏感型检测流程，确保检测反应在最优温度条件下高效进行，为疾病标志物的精准检测奠定基础[31] [32]。表面修饰层作为微流控芯片的“功能化外衣”，是提升检测特异性、灵敏度与稳定性的核心辅助组件。通过在芯片通道内壁、反应区域或检测电极表面修饰特定的生物分子(抗原、抗体、核酸探针)、纳米材料(石墨烯、金纳米颗粒)或功能聚合物，改善芯片表面的物理化学性质与生物相容性，疏水/亲水性能不佳等技术难题，实现对目标疾病标志物的精准捕获与分离[33] [34]。

微流控芯片的构成以核心结构模块为基础，材料基底为支撑，辅助功能组件为补充，形成多模块协同的复杂体系。各部位分工明确：微通道网络负责流体传输与操控，功能腔室实现样品预处理与生化反应，辅助功能组件优化检测性能。其检测过程遵循“样品预处理 → 流体操控与反应 → 信号检测 → 数据分析”的流程，通过微型化、集成化设计，实现了检测的高效化、低成本化与便携化，在炎症相关疾病、感染性疾病、病毒的快速检测中发挥重要作用。这三大领域均面临着从复杂生物基质(如外周血、尿液或组织液)中精准分离并检测极低丰度目标的共性技术挑战。为应对这一难题，微流控平台普遍采用了主动式物理场(如磁泳、介电泳)与被动式微通道流体力学相结合的通用样本富集策略。与此同时，不同领

域对该技术的核心需求侧重点存在着显著差异。

## 3. 微流控芯片用于炎症相关检测

在炎症与免疫功能评估中，例如对外周血中特定免疫调节因子的微量检测，临床更关注极高的检测灵敏度、细胞动态分泌信号的捕捉以及多重指标的平行分析能力。细胞因子是调控机体免疫应答、炎症反应及病理进展的重要分子，对其精准高效定量分析是疾病早期筛查、病情动态监测及治疗效果评估的重要临床支撑。酶联免疫吸附试验、流式细胞分析技术等传统检测手段普遍存在样本用量大、检测耗时久、灵敏度不足且难以捕捉动态分泌特性的问题。微流控技术依托微型化、集成化、高通量核心特性，结合创新驱动机制与信号放大方案研发的多款细胞因子检测系统，为多维度高精度解析生物标志物提供了多元技术路径[35] [36]。儿科患者血液等临床样本常因体积有限无法满足传统检测需求，微流控技术通过纳升至皮升级别的微腔室与微通道设计大幅减少样本消耗并提升利用效率。Zhang 团队构建的集成微流控反应腔电化学磁免疫传感系统可专门定量检测细胞因子 IL-6，依托微流控反应腔与磁珠富集技术的协同作用单次检测仅需纳升级血清样本，并且支持临床血清样本直接进样分析，结果验证与实验室仪器测定值高度一致[37]。Chen 等设计的局部表面等离子体共振微阵列芯片将单样本用量进一步降至 1μL，通过多通道阵列、编码微珠及多传感位点的整合设计可同步完成血清中 IL-2、IL-4、IL-6 等 6 种细胞因子的平行检测，样本利用效率较传统酶联免疫吸附试验提升近百倍[38]。Phillips 研发的微流控毛细管电泳–免疫亲和集成芯片实现了样本净化与分离功能的一体化，其内置多孔聚二甲基硅氧烷膜可有效去除血清中的白蛋白与免疫球蛋白IgG，经毛细管电泳技术分离目标细胞因子后结合激光诱导荧光检测模块，使 TNF-$\alpha$ 的检测干扰率降低 40%且耗时从传统方法的 8 小时缩短至 1.5 小时。传统细胞因子检测需离线分步完成样本净化、抗体孵育、洗涤等操作，易造成样本损耗与交叉污染，微流控芯片可将这些环节整合为自动化流程显著降低操作误差[39]。Portmann 等[40]人开发的微流控液滴分析平台将单个外周血单核细胞封装于独立液滴内，通过免疫夹心反应与荧光成像技术实现单位时间内 IL-6、TNF-$\alpha$ 等细胞因子分泌水平的动态监测。Cong 等[41]在液滴–表面增强拉曼散射平台上实现了细胞分泌特征与表型的关联分析，将表面增强拉曼散射探针锚定在细胞表面即可实时追踪单个细胞的血管内皮生长因子分泌过程，为探究细胞功能异质性提供了全新技术方向。微流控技术凭借样本用量微量化、操作流程集成化、单细胞功能解析、动态过程监测及多指标平行检测等优势，推动细胞因子检测技术革新，实现了微量样本检测中检测限、单细胞分泌行为捕获及短时高效检测的三重突破。

## 4. 微流控技术用于肿瘤生物标志物检测

肿瘤标志物作为肿瘤发生、发展过程中产生或释放的特异性生物分子，其精准检测对癌症的早期诊断、疗效评估及预后监测具有不可替代的价值。液体活检技术通过非侵入性方式从血液、唾液、尿液等体液中分离循环肿瘤细胞(CTCs)、循环肿瘤 DNA (ctDNA)、外泌体等肿瘤标志物，为癌症诊断提供了全新路径[42] [43]。当前肿瘤标志物检测依赖于分离富集与分析两大核心步骤，传统方法在实用性和效能上存在显著局限。分离富集方面，常用技术包括超速离心、沉淀法、尺寸排阻色谱及免疫亲和捕获等，分析检测方面，传统方法包括流式细胞术、ELISA、下一代测序(NGS)等，传统方法需多步骤手动操作，导致交叉污染风险增加、生物标志物降解及样本损失，且批量间一致性差，难以满足临床样本高通量、高灵敏度检测需求。由于循环肿瘤细胞或特征外泌体在血液中极度稀缺且容易受损，核心需求则全面高纯度、高通量以及维持靶标生物活性的无损分离，微流控技术通过微型化芯片集成样本处理、分离富集、检测分析等功能，凭借低试剂消耗、高灵敏度、高通量及集成化优势，成为突破传统检测瓶颈的关键技术，其应用涵盖 CTCs、ctDNA、外泌体等主要肿瘤标志物的检测[44]。在体液循环肿瘤细胞检测方面，

Abdulla 等开发的抗体功能化微流控芯片包含 3 个缓冲区和 4 个捕获区，捕获区内填充等边三角形柱体和周期性弯曲障碍物，增强了流体的混沌混合，延长了细胞在捕获区的停留时间，进一步提高了细胞与抗体的碰撞概率，提高捕获效率[45]。Zhao 等采用 HER2 适配体与 YAP1 抗体联合检测胃癌 CTC，适配体的使用提高了对低表达 HER2 CTC 的检出率。Li 等设计的 3D 多孔海绵微流控芯片，修饰 CD9 抗体后外泌体捕获效率达 90%，有效克服了 2D 芯片分离纯度低的缺陷[46]。在外泌体检测方面，由于外泌体含量较低，Mun 等开发了一种基于免疫磁泳技术的微流控芯片，通过磁分离技术实现了 HER2 过表达外泌体与普通外泌体的高效分离与特异性检测，为 HER2 阳性癌症的诊断与疗效评估提供了新途径[47]。Huang 等提出了一种基于表面增强拉曼散射频移的微流控芯片技术，用于胃癌核心生物标志物癌胚抗原(CEA)和血管内皮生长因子(VEGF)的同步检测，芯片采用毛细管泵设计并结合微通道亲水性处理，无需外部泵体即可实现流体自动流动，大幅提升了设备的便携性，为临床现场检测奠定了基础[48]。

## 5. 微流控技术在病毒检测中的应用

在病毒筛查与应对突发感染时，检测人员极度需要“样本进–结果出(Sample-in-Answer-out)”的极简自动化操作、低成本耗材以及极速的现场响应能力。近年来，微流控技术在病毒检测领域逐渐受到重视。近年来微流控技术在病毒检测领域为解决传统病毒检测周期长、灵敏度低的痛点提供了有效途径，在多种复杂环境中发挥出巨大优势。该技术通过在微米尺度的通道内精确操控流体，可实现样本前处理、扩增、分离、检测等流程的一体化集成，显著降低检测成本、缩短检测时间并提高检测性能。Witkowska 等提出了一种基于逆转录环介导等温扩增的纸基微流控检测平台用于检测 HCV 病毒，微流控装置采用纸基材料与聚甲基丙烯酸甲酯(PMMA)结合的低成本设计，集成扩增室和侧向流核酸检测条，扩增产物中的双链 DNA 通过毛细管作用与检测条上的链霉亲和素红色颗粒和抗 FITC 抗体结合，形成双带(阳性)或单带(阴性，仅控制带)的可视化结果，相比于现有的 POCT 产品，检测特异性、灵敏度、检测限都有明显提升[49]。Ji 等提出了一种融合纳米抗体技术、3D 打印微流控芯片与智能手机检测的一体化 POCT 平台，以 H7N9 病毒为模型验证了系统的实用性，这种“纳米材料–精密制造–智能终端”的交叉融合模式，为新发病毒的快速响应提供了高效解决方案[50]。Liu 等开发了整合巢式重组酶聚合酶扩增与 CRISPR/Cas12a 技术，实现了 SARS-CoV-2、呼吸道合胞病毒、流感 A/B 型等 8 种目标的同步检测。该微流控平台针对呼吸道病毒联合感染的临床需求，通过医工交叉设计突破了传统 CRISPR 检测的单一目标局限[51]。Hong 等设计了基于微珠编码技术的微流控芯片平台，实现 H1N1、H3N2、H7N3 三种流感病毒亚型的一步式同步检测[52]。

## 6. 总结与展望

微流控技术凭借高度集成化、检测特异性强、灵敏度高、极低样本消耗、检测设备简单便携在疾病标志物检测展现出无可比拟的应用价值。这项技术的持续迭代升级与临床转化有序推进有望有效打破目前传染性疾病、急诊检测、慢性病日常检测滞后的困局，为疾病早期预判精准调控优化开拓全新方向[53]-[55]。

微流控技术在疾病标志物检测中的核心优势完美适配了疾病标志物检测“早、快、准、便、廉”的临床需求。其一，低样本消耗与高利用率优势凸显，微流控芯片的微通道结构可将检测所需样本量降至微升甚至纳升级别，这在循环肿瘤细胞等珍贵样本检测中具有不可替代的价值，同时大幅降低了试剂消耗，有效控制检测成本[35] [56]。其二，检测灵敏度与特异性实现双重提升，微尺度下流体的层流特性、缩短的扩散距离及增强的表面积体积比，显著提升了生物分子的反应效率与信号强度[57]-[59]；其三，快速高效与集成化优势显著，微流控芯片可将样本前处理、分离、扩增、检测等多个步骤集成于方寸之间，将

传统数小时至数天的检测周期缩短至 30 分钟以内，部分核酸检测可在 20 分钟内完成，适配急诊抢救、疫情应急筛查等场景[60]-[62]，NGS 等生物信息学驱动的技术在基因组学信息的广度与深度上能够提供海量的突变与表达谱数据，微流控技术的核心竞争力并不在于全面替代这些重型深度分析工具，而是体现在其卓越的全流程微型化集成与时效性上。其四，便携化与普适性强，数字 PCR 凭借液滴或微孔的分隔物理屏障，在核酸绝对定量和极低频突变检测上展现出极高的精确度。然而，这些高精尖技术目前仍不可避免地存在设备极其昂贵、操作流程繁琐、高度依赖专业生物信息学分析且检测周期长等局限性，难以独立满足急诊筛查或现场即时检测(POCT)的迫切需求，微流控检测设备可实现手持式、小型化设计，无需专业实验室与复杂操作，适配基层医疗机构、偏远地区及居家检测场景，推动医疗检测资源的均等化，同时可实现多标志物同步检测，满足精准分型与个性化诊疗的需求[63]。此外，微流控技术还可实现活体单细胞的无损实时检测，通过模拟人体三维生理环境，动态监测细胞分泌的标志物变化，为疾病机制研究与药物筛选提供了全新工具[64]-[66]。

随着医工交叉融合的不断深化，微流控技术在疾病标志物检测领域将朝着智能化、集成化、低成本化、多元化的方向快速发展。在技术创新层面，提升芯片的生物相容性、稳定性与检测性能，降低生产成本；微流控技术正逐渐演变为多种技术的强大“前处理引擎”，通过基于液滴微流控的大规模单细胞多组学测序等前沿手段，大幅剔除复杂样本的背景干扰并提升信噪比，微流控技术与 CRISPR 基因编辑、质谱分析、液晶传感等前沿技术深度融合，进一步提升检测灵敏度与特异性，拓展检测范围，实现从单一标志物检测向多组学联合检测的跨越，推动无损实时检测、单细胞动态监测等高端功能的普及化[67]。在智能化与便携化层面，人工智能与微流控检测系统深度融合，通过智能数据分析算法实现检测信号的自动判读、异常结果预警与诊疗建议生成，推动居家检测、远程医疗的发展。同时，微流控技术也会在标志物筛选、药物筛选、肿瘤耐药机制[68]研究等领域发挥重要作用，通过模拟人体生理微环境，特别是妊娠状态等难以进行临床试验的生理病理过程，实现药物疗效的快速评估与个性化给药方案的制定，推动精准治疗模式的普及[69] [70]。综上所述，微流控技术不仅填补了高端实验室深度测序与临床现场快速决策之间的关键技术空白，更作为不可或缺的底层平台赋能了其他新兴技术的发展。

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