

## PERSPECTIVE ARTICLE

# The role of exosomes in the diagnosis of hematological cancers

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## Abstract

Exosomes, nanoscale extracellular vesicles secreted by various cell types, have emerged as pivotal players in the diagnosis and monitoring of hematological cancers, including lymphomas, leukemia's, and multiple myeloma. These vesicles encapsulate a diverse array of biomolecules, reflecting the physiological and pathological states of their origin cells, thus providing valuable insights into tumor biology. This article discusses the unique molecular signatures carried by exosomes, particularly focusing on microRNAs and proteins that serve as biomarkers for early detection, disease progression, and treatment response. The integration of artificial intelligence (AI) into exosomal research is highlighted as a transformative approach for identifying novel biomarkers, enhancing the precision of diagnostic assays, and facilitating personalized treatment strategies. Despite the promising potential of exosome-based diagnostics, challenges such as the standardization of isolation techniques and ethical considerations surrounding AI implementation remain. Future research directions should aim to overcome these obstacles, with an emphasis on improving exosome characterization methods and exploring novel biomarkers, ultimately enhancing patient outcomes through tailored therapeutic approaches.

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## 1. Introduction

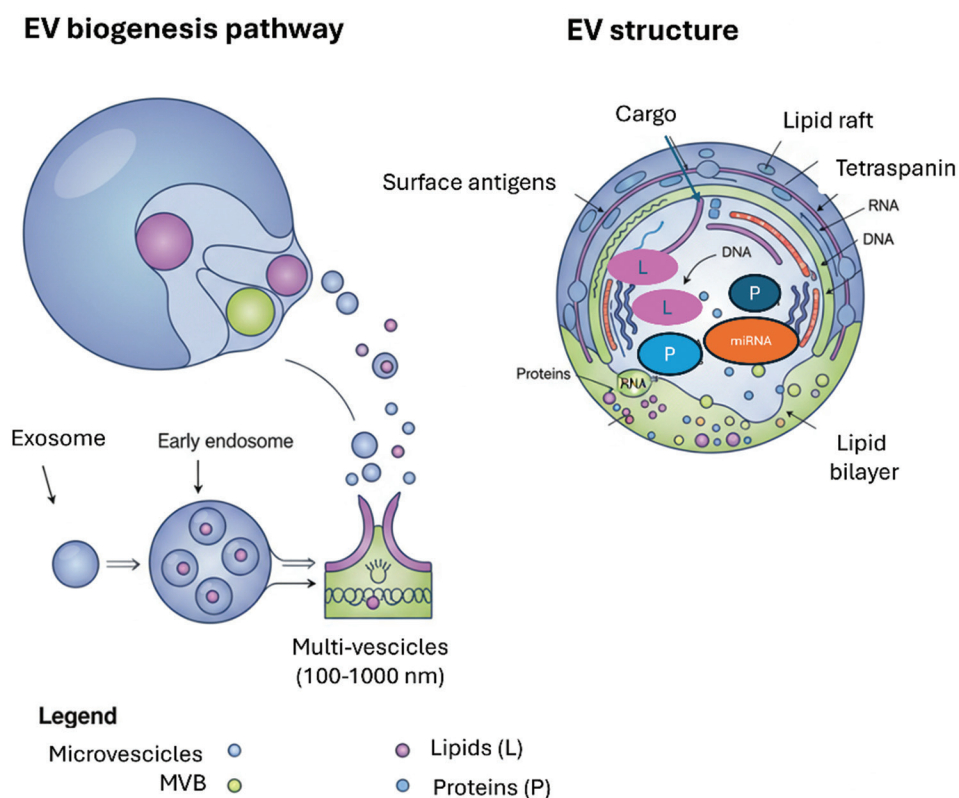
Exosomes are nanoscale extracellular vesicles, typically ranging from 30 to 150 nm in diameter, that play a crucial role in cell-to-cell communication ([Figure 1](#)). They are secreted by a wide array of cell types, encapsulating a diverse set of biomolecules, including proteins, lipids, DNA, and various forms of RNA such as messenger RNA and microRNA. These vesicles originate from the endosomal compartment of cells and are released into the extracellular space, where they can travel through biological fluids such as blood, urine, and saliva ([Figure 2](#)). The content of exosomes often mirrors the physiological or pathological state of their cells of origin, making them invaluable for understanding cellular processes and disease states.<sup>1,2</sup>

Exosomes have emerged as critical players in cancer diagnostics due to their ability to carry tumor-specific markers.<sup>3,4</sup> They offer a non-invasive means of accessing tumor-derived molecular information, which can be crucial for facilitating early diagnosis, monitoring disease progression, and evaluating treatment responses. Unlike traditional biopsies, which are invasive and provide only a static snapshot of the tumor, exosomes can be repeatedly sampled from bodily fluids, offering a dynamic view of the tumor's molecular landscape over time. This capability is particularly beneficial in identifying early-stage cancers, predicting disease outcomes, and tailoring personalized treatment strategies.

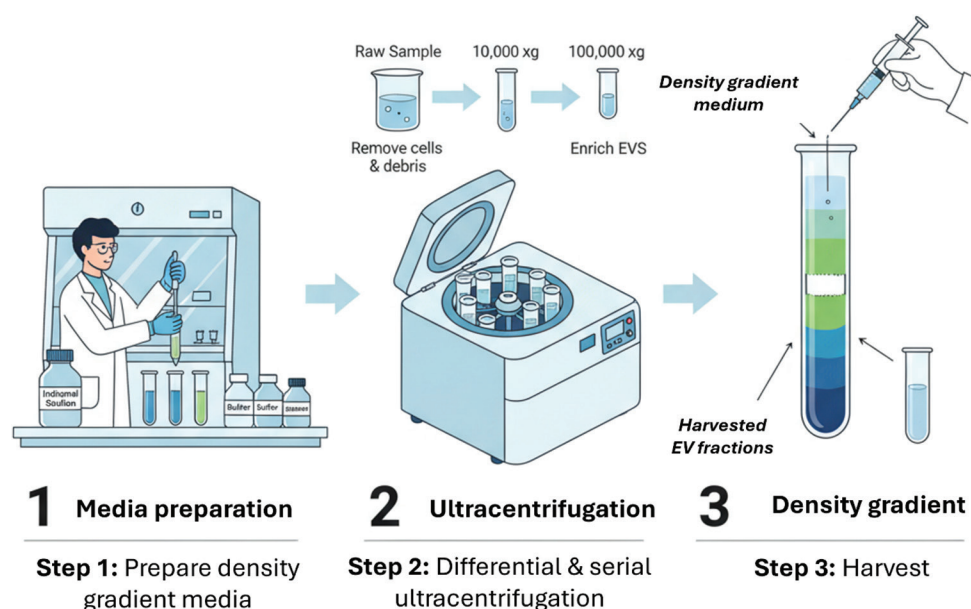
Hematological cancers, including lymphomas, leukemia's, and multiple myeloma, pose significant diagnostic challenges due to their heterogeneous nature and often subtle early symptoms. Exosomes derived from these cancer cells carry distinct molecular signatures that

can aid in their diagnosis and monitoring. For example, lymphoma-derived exosomes may contain specific microRNAs linked to oncogenesis, while exosomes from leukemia patients can reflect the genetic aberrations driving the disease. In multiple myeloma, exosomal content can reveal insights into the interactions between tumor cells and the bone marrow microenvironment, providing clues for early detection and disease monitoring.

However, the complexity of the information provided by exosome profiling remains a challenge. The integration of artificial intelligence (AI) into exosome research has the potential to revolutionize the field of cancer diagnostics. AI technologies, particularly machine learning and deep learning algorithms, can handle the complexity and high-dimensionality of exosomal data, identifying patterns and biomarkers that conventional analytical methods might overlook. AI can accelerate the development of diagnostic assays by sifting through vast datasets to pinpoint the



**Figure 1.** Extracellular vesicle biogenesis pathways and structure. The left EV biogenesis pathways panel illustrates the distinct processes leading to the formation of exosomes and microvesicles. Exosome biogenesis begins with the inward budding of the plasma membrane, forming an early endosome. This matures into a multivesicular body (MVB), characterized by intraluminal vesicles (ILVs) formed by further membrane invaginations. MVBs can then fuse with the plasma membrane, releasing the ILVs as exosomes (typically 30–150 nm) into the extracellular space. In contrast, microvesicles (or ectosomes) are formed by the direct outward budding and scission of the plasma membrane, generally resulting in larger vesicles (100–1,000 nm, potentially up to 1,500 nm). The right EV structure panel provides a magnified view of a generic EV, highlighting its key components. It is enclosed by a lipid bilayer membrane, which can contain various embedded and associated proteins (e.g., CD9, a common EV marker). The internal space, or lumen, carries a diverse cargo derived from the parent cell, including various forms of nucleic acids (DNA, RNA, such as mRNA, lncRNA, and microRNA), lipids (e.g., cholesterol), and metabolites. This diverse cargo underscores the role of EVs in intercellular communication and biomarker potential. Created in Gemini, Google, United States of America.



**Figure 2.** Extracellular vesicle (EV) separation by density gradient ultracentrifugation. The first step is the preparation of appropriate media for exosome collection, such as iodixanol, various buffers, and other reagents necessary for creating density gradients and washing steps. This preparation ensures the optimal conditions for EV integrity and separation. Followed by the second step, ultracentrifugation. A raw sample (e.g., plasma, cell culture supernatant) first undergoes low-speed centrifugation (e.g.  $10,000 \times g$ ) to remove cells and debris. The supernatant from this step is then subjected to high-speed ultracentrifugation (e.g.  $100,000 \times g$ ) to enrich EVs, pelleting a crude EV fraction. This differential centrifugation significantly reduces contaminating larger particles and macromolecules. The third step involves centrifugation on density gradient, and harvest involves applying the enriched EV pellet onto a pre-formed or self-forming density gradient medium in an ultracentrifuge tube. During subsequent ultracentrifugation, EVs migrate to and band at specific density layers that match their buoyant density. Different EV populations (e.g., exosomes, microvesicles) will settle at distinct layers due to their differing densities and compositions. Finally, an operator carefully aspirates the specific density layers to obtain EV fractions, representing highly purified EV populations suitable for downstream analysis. Created in Gemini, Google, United States of America.

most relevant exosomal indicators for specific cancers. Moreover, AI-driven tools can enhance the interpretation of clinical data by integrating exosomal profiles with other clinical parameters, leading to more accurate and personalized treatment strategies. This synergy between AI and exosome research is poised to advance the precision and efficacy of hematological cancer diagnostics, paving the way for novel insights and therapeutic approaches.

## 2. Exosomes in hematological malignancies

### 2.1. Lymphomas

Lymphomas are a diverse group of malignancies originating from lymphocytes. The exosomes secreted by lymphoma cells carry unique molecular signatures that can be exploited for diagnostic purposes. In particular, lymphoma-derived exosomes are enriched with proteins and RNA molecules that reflect the oncogenic processes occurring within the tumor.<sup>5-8</sup> These exosomes can be isolated from the blood and other bodily fluids, providing a non-invasive means to assess the disease state.

One of the most studied exosomal biomarkers in lymphomas is miR-155.<sup>9-11</sup> This microRNA plays a crucial

role in lymphocyte development and has been implicated in the pathogenesis of several lymphoma subtypes, including diffuse large B-cell lymphoma (DLBCL), peripheral T-cell lymphomas, and Hodgkin lymphoma.<sup>10,12-14</sup> Elevated levels of miR-155 in exosomes are correlated with disease progression and poor prognosis. In addition, in cases of Epstein-Barr virus (EBV)-associated lymphomas, exosomes may contain EBV-encoded RNAs, which can serve as specific biomarkers for early diagnosis and monitoring, replacing or integrating the analysis of circulating EBV DNA.<sup>13,15-19</sup>

Of note, lymphoma-derived exosomes are not merely diagnostic tools; they actively participate in shaping the tumor microenvironment.<sup>20,21</sup> They facilitate immune evasion by suppressing T-cell activity and promoting the expansion of regulatory T-cells and myeloid-derived suppressor cells.<sup>4</sup> These exosomes also carry molecules that inhibit natural killer cell function, further dampening the antitumor immune response.<sup>22,23</sup> Understanding these mechanisms could lead to the development of novel therapeutic strategies targeting exosome-mediated pathways.<sup>24</sup>

## 2.2. Leukemias

Leukemias are characterized by the presence of neoplastic cells in the peripheral blood, making the assessment of genetic information relatively easier than in solid malignancies. However, exosomes still retain a wide range of utility, as they can provide additional information. For example, in acute myeloid leukemia (AML), exosomes are rich in oncogenic miRNAs, such as miR-29a and miR-125b.<sup>4,20,25-28</sup> These miRNAs contribute to leukemogenesis by targeting tumor suppressor genes and promoting cell survival. Chronic lymphocytic leukemia-derived exosomes, on the other hand, often contain miRNAs such as miR-150 and miR-29c, which are associated with disease progression and chemoresistance.<sup>12,29-31</sup>

The presence of specific miRNAs and proteins in exosomes can serve as early detection markers, particularly in high-risk populations. For example, the detection of miR-125b in AML-derived exosomes can indicate impending disease transformation in patients with myelodysplastic neoplasms.<sup>32</sup> These exosomal markers also provide prognostic information, helping to stratify patients based on their risk and guide treatment decisions.

Remarkably, leukemic exosomes play a role in disrupting normal hematopoiesis by transferring oncogenic proteins and RNAs to healthy hematopoietic cells. This transfer can alter the function and fate of these cells, promoting a leukemia-favorable microenvironment. In addition, exosomes from leukemic cells can modulate the bone marrow niche, enhancing the survival and proliferation of malignant cells.

## 2.3. Multiple myeloma

As discussed for leukemias and lymphomas, exosomes from neoplastic plasma cells of multiple myeloma patients carry distinct molecular signatures that can aid in diagnosis and monitoring. In particular, they exhibit a unique proteomic and transcriptomic profile, reflecting the genetic and epigenetic abnormalities of the tumor.<sup>33,34</sup> Proteins such as cluster of differentiation (CD)138, a marker of plasma cells, are commonly found in these exosomes. In addition, oncogenic miRNAs within these exosomes can provide insights into the disease's molecular underpinnings, including miR-15a and miR-16-1.<sup>33,34</sup> The ability to detect myeloma-derived exosomes in the blood offers a promising approach for early diagnosis, especially in asymptomatic patients or those with monoclonal gammopathy of undetermined significance (MGUS). In this regard, monitoring changes in exosomal content over time can also provide real-time insights into treatment response and disease progression.<sup>33-35</sup>

Similar to those derived from AML cells, exosomes in multiple myeloma actively participate in modulating the bone marrow microenvironment. They promote osteoclastogenesis and inhibit osteoblast activity, leading to the characteristic bone lesions seen in the disease.<sup>36-38</sup> These exosomes also facilitate angiogenesis and immune evasion, supporting tumor growth and survival.<sup>33,36</sup> Understanding these interactions may facilitate the development of novel therapeutic approaches aimed at disrupting the exosome-mediated crosstalk in the bone marrow niche.

## 3. Exosomes as tools for early diagnosis

Exosomal biomarkers offer several advantages over traditional diagnostic methods, including those examining tissue biopsies and serum protein markers. One of the primary benefits is their ability to provide a comprehensive molecular snapshot of the tumor. Traditional biopsies are invasive and provide only a static view of the tumor at a single point in time, whereas exosomes constantly circulate in the bloodstream, reflecting the dynamic state of the disease. Exosomes encapsulate a variety of biomolecules, including proteins, lipids, and nucleic acids, which can offer insights into the genetic and epigenetic landscape of the cancer. This breadth of information can help identify specific mutations, oncogenic pathways, and potential therapeutic targets. In addition, because exosomes are stable in bodily fluids, they preserve the integrity of their cargo, allowing for reliable and reproducible analysis.

The non-invasive nature of exosome sampling is another significant advantage, especially in hematological cancers. Blood, urine, and other body fluid samples can be used to isolate exosomes, reducing the need for invasive procedures such as bone marrow biopsies. This ease of access allows for repeated sampling over time, facilitating real-time monitoring of disease progression and treatment response. Such real-time monitoring is particularly crucial in managing hematological malignancies, where rapid changes in disease state can occur, and the study of minimal residual disease has long been demonstrated to be clinically meaningful.

Several studies have demonstrated the potential of exosomal biomarkers in the early diagnosis of hematological cancers. In one study, elevated levels of exosomal miR-155 were detected in the plasma of patients with DLBCL before clinical symptoms emerged<sup>39,40</sup> and were also associated with the early identification of chemotherapy resistance.<sup>11,41</sup> Another example involves AML, where specific exosomal miRNAs, such as miR-29a, have been identified as early biomarkers in patients with pre-leukemic conditions like myelodysplastic neoplasms. The ability to detect these markers before overt leukemia



development highlights the potential of exosomes in early diagnosis and risk stratification.

In multiple myeloma, exosomal proteins, such as CD138, have been used to distinguish between patients with active disease and those with smoldering myeloma or MGUS. This differentiation is critical for initiating treatment at the appropriate time and avoiding unnecessary interventions in low-risk patients.

Together, these case studies underscore the transformative potential of exosomal biomarkers in revolutionizing the early detection and management of hematological cancers, paving the way for the development of more precise and targeted therapeutic approaches.

#### 4. Disease monitoring and prognostication

Exosomes offer a dynamic means to monitor treatment response in patients with hematological cancers. As exosomal content reflects the ongoing biological processes within tumors, changes in their molecular cargo can indicate how the disease is responding to therapy. For example, a decrease in specific oncogenic microRNAs or proteins in exosomes can signify effective treatment and tumor regression. Conversely, the persistence or increase of such markers suggests treatment resistance or incomplete response. By regularly analyzing exosomal profiles during treatment, clinicians may obtain real-time feedback on therapeutic efficacy. This information allows for timely adjustments to treatment regimens, such as switching to alternative therapies or modifying dosages, thus optimizing patient outcomes. It would be notable to correlate exosome profiling with conventional MRD assessments, including positron emission tomography scanning in lymphomas and gene fusions/mutation assessment in leukemias and lymphomas.

In this regard, it has been shown that exosomes also play a crucial role in predicting relapse and resistance in several hematological malignancies. The re-emergence of specific biomarkers in exosomes, even when clinical remission is achieved, can serve as an early warning sign of relapse. For example, in chronic lymphocytic leukemia, the reappearance of certain exosomal miRNAs associated with disease progression can indicate an impending relapse before clinical symptoms become apparent.<sup>42</sup> Moreover, exosomal analysis can reveal mechanisms of therapeutic resistance. In multiple myeloma, exosomes may carry mutations or altered signaling pathway components that confer resistance to standard treatments. Identifying these changes early can guide the development of targeted interventions to overcome resistance and improve long-term disease control.

The integration of exosomal data with traditional clinical parameters may enhance the precision of disease monitoring and prognostication. Combining exosomal biomarkers with clinical factors such as patient age, genetic mutations, and responses to previous treatments can lead to more accurate risk stratification and individualized treatment plans.

The increased complexity of the analyzed data will therefore need an adequate bioinformatic support. Advanced computational tools, including machine learning algorithms, can process and integrate these diverse datasets to generate predictive models. These models can help clinicians identify patients at high risk of relapse or those who may benefit from more aggressive treatment approaches. By providing a comprehensive view of the disease, this integrative approach may facilitate more informed clinical decision-making and personalized patient care. The main molecules relevant to our analysis are summarized in [Tables 1 and 2](#).

### 5. Role of AI in exosome-based diagnostics

#### 5.1. Development of diagnostic assays

First, AI has become an invaluable tool in the discovery of novel exosomal biomarkers. Machine learning algorithms can process vast amounts of high-dimensional data generated from exosomal analyses, identifying patterns and correlations that may be missed using traditional methods. These algorithms can sift through complex datasets to pinpoint specific RNA, protein, or lipid signatures that are characteristic of particular hematological cancers. This capability accelerates the discovery process, leading to the identification of new biomarkers that can improve the accuracy and reliability of diagnostic assays.<sup>44</sup>

Furthermore, AI-driven approaches can enhance the sensitivity and specificity of exosome-based diagnostic assays.<sup>44</sup> By optimizing the selection and combination of biomarkers, AI can help develop assays that are more precise in distinguishing between malignant and non-malignant conditions. In addition, AI can aid in refining the protocols for exosome isolation and analysis, ensuring that assays are both robust and reproducible. This optimization is crucial for translating exosome-based diagnostics from research settings to clinical practices, where accuracy and consistency are paramount.<sup>45</sup>

To reduce bias in AI models, it is important to collect data from a wide range of sources that represent different demographics, such as age, gender, ethnicity, socioeconomic position, and geographic location.<sup>46,47</sup> This is commonly done in partnership with community organizations and health institutions. Tools for evaluating

**Table 1. Clinical characteristics and associated molecules in hematological cancers**

Tumor subtype	Clinical characteristics	Molecules with reported roles	References
Lymphomas	Diverse malignancies originating from lymphocytes	MiR-155 (disease progression, poor prognosis)	2,4,5,7-22,43
	Often presents with lymphadenopathy, fever, night sweats, and weight loss	EBERs (biomarkers for EBV-associated lymphomas)	
	Heterogeneous nature; can be aggressive	Proteins and RNA molecules linked to oncogenesis	
Leukemias	Presence of neoplastic cells in peripheral blood	MiR-29a (oncogenic role in AML)	1,10,18,23-30
	Symptoms include fatigue, bleeding, infections, and anemia	MiR-125b (associated with leukemogenesis and chemoresistance)	
	Acute and chronic forms with varying prognoses	MiR-150 and miR-29c (associated with CLL progression)	
Multiple myeloma	Characterized by neoplastic plasma cells in the bone marrow	CD138 (marker of disease)	31-34
	Symptoms include bone pain, anemia, renal dysfunction, and infections	MiR-15a and miR-16-1 (insights into disease's molecular underpinnings)	
	Associated with osteolytic lesions and immune evasion	Proteins and RNAs involved in osteoclastogenesis and angiogenesis	

Abbreviations: AML: Acute myeloid leukemia; CD: Cluster of differentiation; CLL: Chronic lymphocytic leukemia; EBER: Epstein-Barr virus encoded RNA; EBV: Epstein-Barr virus.

**Table 2. Key exosomal biomarkers in hematological cancers**

Cancer type	Biomarker (miRNA/protein)	Source/origin	Implications for diagnosis	Implications for monitoring/treatment
Lymphoma	MiR-155	Lymphoma-derived exosomes	Early detection	Disease progression, chemotherapy resistance
	EBERs	EBV-associated lymphomas	Specific biomarker for diagnosis	Monitors EBV load
Leukemia	MiR-29a	AML-derived exosomes	Early detection of myelodysplastic neoplasms	Prognostic marker for treatment response
	MiR-150	CLL-derived exosomes	Associated with disease progression	Predicts chemoresistance
Multiple myeloma	CD138	Myeloma-derived exosomes	Distinguishes active versus smoldering disease	Monitors treatment response
	MiR-15a	Myeloma-derived exosomes	Diagnostic potential	Insights into disease progression

Abbreviations: AML: Acute myeloid leukemia; CD: Cluster of differentiation; CLL: Chronic lymphocytic leukemia; EBER: Epstein-Barr virus encoded RNA; EBV: Epstein-Barr virus.

bias are important for assessing how data is represented and identifying imbalances. Re-weighting, adversarial debiasing, and regularization are some examples of algorithmic fairness strategies that help lower bias during model training and evaluation. After the model is deployed, it needs to be analyzed and evaluated to see how well it works for different demographic groups. If biases appear, there should be feedback loops for retraining.<sup>46,47</sup> Being open about the model creation process, including how the datasets are described, how bias is reduced, and how performance is measured, is therefore necessary.

## 5.2. Interpretation of clinical data and data integration

The integration of exosomal data with other clinical parameters is a complex task that benefits significantly from AI-driven models. These models can combine exosomal

profiles with patient demographics, genetic information, and clinical history to generate comprehensive insights into the disease state. Machine learning algorithms can analyze these integrated datasets to develop predictive models that assess disease risk, track disease progression, and evaluate treatment efficacy. This holistic approach provides clinicians with a more comprehensive understanding of the patient's condition, facilitating more informed decision-making.<sup>44,45</sup>

Therefore, AI is expected to facilitate the development of personalized treatment strategies by analyzing exosomal profiles to identify patient-specific therapeutic targets. By understanding the unique molecular landscape of each patient's cancer, AI can suggest tailored interventions that are more likely to be effective. For example, if exosomal analysis reveals a particular pathway driving tumor growth, AI can recommend targeted therapies that specifically

inhibit that pathway, enabling real-time adaptation of targeted strategies. This personalized approach can enhance treatment efficacy, minimize adverse effects, and reduce the overall treatment cost by optimizing the available resources.<sup>44,45</sup>

There are several technical challenges in developing exosome-based diagnostics. Current techniques for isolating and analyzing exosomes are not standardized yet (Figure 2), making results inconsistent and lowering reproducibility.<sup>43</sup> Obtaining regulatory approval is also difficult due to the limited number of analyzed cases, technical complexity, and overall heterogeneity. Moreover, the high expenses of sophisticated technologies and specialized equipment limit accessibility, especially in countries with limited resources. Nonetheless, approaches that eventually standardize diagnostic workflows will be especially valuable for low-resource settings.<sup>48</sup> Integrating AI into the processing of exosomal data raises ethical concerns about data privacy and algorithmic bias. Therefore, researchers, regulatory agencies, and industry partners must collaborate to standardize methodologies, demonstrate clinical utility, and improve the accessibility of these diagnostic tools.<sup>48,49</sup>

## 6. Challenges and future directions

One of the primary challenges in exosome research is the efficient and reliable isolation of exosomes from biological fluids. Current methods, such as ultracentrifugation, size-exclusion chromatography, and immunoaffinity capture, each have limitations in terms of yield, purity, and scalability. The heterogeneity of exosomes, which can originate from various cell types, further complicates their characterization. Distinguishing between exosomes derived from cancer cells and those from normal cells remains a significant hurdle. Advancements in isolation techniques and characterization tools are essential to enhance the precision and applicability of exosome-based diagnostics. A major limitation in this regard is the lack of standardized protocols for exosome isolation and analysis, posing a barrier to the widespread adoption of exosome-based diagnostics. Variability in protocols can lead to inconsistent results, hampering the reproducibility and comparability of studies. Establishing standardized methodologies and validation criteria is crucial for ensuring that exosome-based assays are reliable and can be integrated into clinical practice. Collaborative efforts among researchers, clinicians, and regulatory bodies are needed to develop and implement these standards.

### 6.1. Ethical considerations of AI in diagnostics

The integration of AI into exosome-based diagnostics brings ethical considerations that must be addressed.

Issues such as data privacy, algorithmic transparency, and potential biases in AI models are critical concerns. Ensuring that patient data is securely handled and that AI algorithms are transparent and interpretable is essential for building trust in AI-driven diagnostic tools. In addition, addressing potential biases in AI models, which may arise from imbalanced training datasets, is crucial to prevent disparities in healthcare outcomes. Developing ethical guidelines and regulatory frameworks will be key to navigating these challenges. Recognized biobanks should play a primary role in standardizing processes of exosome isolation and analysis.

### 6.2. Future research directions and potential breakthroughs

Future research in exosome-based diagnostics is likely to focus on several key areas. Improving isolation and characterization techniques will be a priority, with advances in microfluidics and nanotechnology offering promising solutions. The exploration of novel biomarkers within exosomes, including long non-coding RNAs and metabolites, can expand the diagnostic potential of exosomes beyond current capabilities. In addition, the integration of multi-omics approaches, combining proteomics, genomics, and metabolomics, will provide a more comprehensive understanding of exosomal content and its implications for disease diagnosis and treatment. The development of AI-driven platforms for real-time data analysis and interpretation will further enhance the precision and utility of exosome-based diagnostics.

Major potential breakthroughs may also arise from the application of exosome-based therapies, where engineered exosomes are used to deliver therapeutic agents directly to tumor cells. This approach can complement diagnostic applications, offering a dual strategy for managing hematological cancers.

## 7. Conclusion

While challenges remain, the future of exosome-based diagnostics and AI integration holds immense promise. Overall, the use of exosomes in disease detection, monitoring, and prognostication represents a significant advancement in the management of hematological cancers, offering the potential for improved patient outcomes through tailored therapeutic strategies. Continued research and collaboration across disciplines will be essential to unlocking the full potential of exosomes in transforming the diagnosis and treatment of hematological cancers.

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## Conflict of interest

Pier Paolo Piccaluga is an Associate Editor of this journal, but was not in any way involved in the editorial and peer-review process conducted for this paper, directly or indirectly. Separately, other authors declared that they have no known competing financial interests or personal relationships that could have influenced the work reported in this paper.

## Author contributions

*Conceptualization:* Pier Paolo Piccaluga

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## Ethics approval and consent to participate

Not applicable.

## Consent for publication

Not applicable.

## Availability of data

Not applicable.

## Further disclosure

Pier Paolo Piccaluga is currently affiliated to the University of Nairobi (Nairobi, Kenya) and the University of Botswana (Gaborone, Botswana).

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