Histiocyte Society blueprint for non-Langerhans cell histiocytosis research: unraveling complex diseases through collaboration

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Abstract

Histiocytic neoplasms are rare hematologic disorders characterized by pathological infiltration of myeloid-derived cells in various organs, resulting in diverse manifestations. Traditionally, histiocytic neoplasms were classified into Langerhans cell histiocytosis (LCH) and non-LCH, the latter comprising a heterogeneous group of diseases including Erdheim-Chester disease, xanthogranuloma family of lesions, Rosai-Dorfman disease, indeterminate cell histiocytosis, and malignant histiocytic neoplasms. Over the past decade, the discovery of recurrent somatic alterations in the MAPK pathway has revolutionized the diagnosis and management of these disorders, enabling the use of targeted therapies and significantly improving patients' outcomes. Despite these advances, critical gaps remain in our understanding and treatment of non-LCH. Challenges include adverse effects from prolonged use of targeted therapies, insufficient data on the natural history of these diseases, outdated nomenclature and classification systems that fail to account for emerging insights, and limited availability of clinical trials due to the rarity of the conditions. In this article, we synthesize key advancements in the field and propose a blueprint for future research to address these unmet needs. We emphasize the importance of collaborative efforts, such as large, multi-institutional registries and novel clinical trials, to generate robust, high-quality data that can guide diagnostic, management, and prognostic strategies.

Introduction

Histiocytic neoplasms are rare hematologic disorders characterized by infiltration of myeloid-derived monocytes, macrophages, and dendritic cells in various organs. Conventionally, histiocytic neoplasms were divided into two broad categories, Langerhans cell histiocytosis (LCH) and 'non-LCH', the latter group representing nearly 20 different subtypes of histiocytic neoplasms including Erdheim-Chester disease (ECD), anaplastic lymphoma kinase (ALK)-positive histiocytosis, indeterminate cell histiocytosis (ICH), the xanthogranuloma (XG) family of lesions, Rosai-Dorfman disease (RDD), and malignant histiocytic neoplasms (MHN). ICH is synonymous with indeterminate dendritic cell tumor as well as indeterminate dendritic cell histiocytosis[1,2] as recognized by the World Health Organization (WHO) and International Consensus Classification (ICC) classifications of hematopoietic tumors. MHN is an umbrella term encompassing four subtypes: histiocytic sarcoma, interdigitating dendritic cell sarcoma, indeterminate cell sarcoma, and Langerhans cell sarcoma. All subtypes of MHN except indeterminate cell sarcoma are included under histiocytic neoplasms by the WHO and ICC classifications.[1,2] Indeterminate cell sarcoma is recognized exclusively by the Histiocyte Society classification and, in clinical practice, this may be synonymous with 'dendritic cell sarcoma, not otherwise specified'.[1,3,4] Historically, MHN were categorized as distinct from 'non-LCH' in the initial Histiocyte Society classification in 1987, but recent efforts by the Histiocyte Society have incorporated these conditions within the broader umbrella of non-LCH for the purposes of committee structure, research prioritization,

and education, recognizing the practical overlap in clinical and scientific domains. A recently described entity, ALK-positive histiocytosis, was recognized as a distinct histiocytic neoplasm by the WHO and is characterized by *ALK* gene rearrangements.[5,6]

Historically, most of the research efforts were directed toward LCH given its recognition as a clonal neoplastic disorder in 2008;[7,8] however, over the last decade, the discovery of recurrent somatic alterations in the mitogen-activated protein kinase (MAPK)-extracellular signal-regulated kinase (ERK) pathway in non-LCH lesions[9,10] has led to the recognition that entities such as ECD and RDD are also neoplastic,[2] leading to regulatory approvals of targeted therapies. These discoveries have also highlighted new challenges that need to be addressed to improve outcomes of patients with non-LCH. The goal of this article is to synthesize current knowledge, highlight gaps, and propose a roadmap for future research for the various non-LCH entities.

Epidemiology and clinical manifestations

The incidence of non-LCH is unknown but estimated at 3-4 cases/million, based on extrapolation of data from MHN and ECD.[11-13] ECD typically affects adults aged 50-60 years old,[13] although rare pediatric cases exist.[14] Current estimates suggest ~1,500 ECD cases worldwide.[15] Nearly 1,200 cases of RDD have been described in the literature.[16] RDD is more common in children and young adults (mean age ~20 years), although it can occur at any age. To date, there are no studies that specifically compare the incidence of RDD between pediatric and adult populations.[17]

The clinical spectrum of non-LCH can vary from entities with a relatively indolent or chronic course (e.g., ECD, ALK-positive histiocytosis, ICH, RDD, XG family disorders) to those that are more aggressive (MHN). However, the morbidity burden from indolent entities can be substantial and often correlates with the degree of organ involvement. ECD is the most notorious for involving multiple organ systems and having non-specific manifestations mimicking other disorders.[9]

The classic feature of ECD that can lead to the diagnosis in nearly 90% cases is symmetric osteosclerosis of distal femur and proximal tibia/fibula (knee bones). ECD can also involve other vital organs, such as the posterior fossa of the central nervous system, cardiovascular system, and retroperitoneum (aka 'hairy kidney').[9] ECD can lead to involvement of the hypothalamic/pituitary axis causing arginine vasopressin deficiency, a manifestation shared with LCH. RDD, on the other hand, has more diverse phenotypes, ranging from single organ involvement (mostly skin or lymph node) to multiple organs, but rarely affects the central nervous system or other vital structures.[18] ICH predominantly involves cutaneous sites and rarely extra-cutaneous sites with nodal involvement, the latter associated with a poor prognosis.[19] The XG family of disorders include juvenile xanthogranuloma (JXG), which primarily appears as asymptomatic and self-limiting cutaneous nodules, although systemic involvement can occur,[20] and adult XG (AXG), which is thought to present mostly as a solitary skin lesion. ALK-positive histiocytosis can involve single or multiple systems in both children and adults, with frequent neurological involvement.[5,6] MHN tend to exhibit a more aggressive clinical course than other non-LCH, especially in cases with multi-organ involvement, including the liver, spleen, bone marrow, and lymph nodes.[3,21]

Diagnosis

The diagnosis of non-LCH subtypes relies on histopathological evaluation (Table 1), combined with clinical, radiographic, and molecular features. While diagnosing RDD and ALK-positive histiocytosis can be relatively straightforward based on immunohistochemistry and molecular findings, other subtypes, such as ECD, non-cutaneous XG lesions, and MHN present diagnostic challenges.[3,22,23] ECD and XG lesions are indistinguishable and characterized by foamy histiocytes with frequent admixed Touton-type giant cells, with some patients harboring *BRAF*^{V600E} mutations (Table 1). *BRAF*^{V600E} immunohistochemistry can aid in the diagnosis of ECD, but clinical and radiographic studies are crucial, especially in mutation-negative cases, in which distinction from reactive histiocytic proliferation is difficult. Recent evidence suggests strong expression of cyclin D1 (CCND1) and p-ERK in neoplastic histiocytes as a surrogate to distinguish them from reactive histiocytic infiltrates.[3,22,24] For classic lesions of JXG with cutaneous involvement, dermoscopy (a non-invasive skin imaging tool) can aid in diagnosis, revealing a "setting sun" appearance with a red-yellow center and an erythematous halo.[25] RDD features accumulation of macrophages with frequent emperipolesis (i.e., engulfment of lymphocytes, plasma cells, and occasionally neutrophils), although the latter is not pathognomonic. ALK-positive histiocytosis shares histopathological features with RDD, ECD, and the XG family of lesions[6] but is distinguished by *ALK* gene rearrangements resulting in cytoplasmic/membranous ALK immunoreactivity on tissue biopsies. ICH has similar morphological features to those of LCH along with intact CD1a expression by immunohistochemistry but, unlike LCH, it lacks langerin expression.[4,19] MHN are characterized by overtly malignant cytology with nuclear pleomorphism associated with monocyte-macrophage/dendritic cell phenotypes.[3,4] The diagnosis of MHN requires distinction from carcinoma, soft tissue sarcoma, anaplastic lymphomas, and melanomas, which can be achieved by comprehensive immunohistochemistry.[3]

Table 1. Immunophenotypic characterization of histiocytic neoplasms: diagnostic immunophenotypes for distinguishing various subtypes of histiocytic neoplasms.

IHC	LCH	XG family of lesions (including ECD)	RDD	ALK-positive histiocytosis	ICH	Malignant histiocytic neoplasms			
						Histiocytic sarcoma	Interdigitating dendritic cell sarcoma	Indeterminate cell sarcoma/ dendritic cell sarcoma, NOS	Langerhans cell sarcoma
CD68	+ (occ.dot-like Golgi)	+	+	+	+ (occ. dot-like Golgi)	+	+ (occ. dot-like Golgi)	+ (occ. dot-like Golgi)	+
CyclinD1	+	+/-	+	+	+	+	+	+	+
CD163	-/+	+	+/-	+	-/+	+	+/-	-/+	+/-
FXIIIa	-	+	+/-	+	-	+/-	-/+	-	-/+
S100	+	-/+	+	+/-	+	+ (patchy)/-	+ (diffuse)	+	+
OCT2	-/+	-/+	+	+/-	-/+	+/-	+/-	-/+	-/+
CD1a	+	-	-	-	+	-	-	+	+
Langerin	+	-	-	-	-	-	-	-	+
ALK	-	-	-	+ (cytoplasmic; rarely dot-like Golgi or membranous)	-	-	-	-	-

(+) Indicates positive staining; (-) indicates negative staining; (+/-) positive in a majority of cases (>50% cases); (-/+) negative in a majority of cases/positive in a minority (<50% cases). IHC: immunohistochemistry; LCH: Langerhans cell histiocytosis; XG: xanthogranuloma; ECD: Erdheim-Chester disease; RDD: Rosai-Dorfman disease; ALK: anaplastic lymphoma kinase; ICH: indeterminate cell histiocytosis; NOS: not otherwise specified; occ: occasional; FXIIIa: activated factor XIII.

Workup and staging studies

Evaluation of non-LCH includes assessment of organ involvement, equivalent to 'staging' studies in other cancers. At baseline, we conduct a full-body fluorodeoxyglucose positron emission tomography (PET)/computed tomography (CT) (from vertex to toes) in all adults, which is especially important for ECD to capture the classic bone lesions affecting the knees.[9] In children, the staging practices can vary based on the disease, with some clinicians utilizing PET/CT or magnetic resonance-based imaging studies if there is a clinical suspicion of systemic involvement. For infants with localized cutaneous lesions and no systemic symptoms, a basic laboratory panel and ophthalmologic examination may suffice. However, patients with multiple lesions, systemic symptoms, or laboratory abnormalities require imaging for systemic assessment. Bone marrow evaluation is necessary in cases of abnormal peripheral blood cell counts.[15]

Tissue-based next generation sequencing (NGS) is usually recommended for mutational testing, including the detection of gene fusions. However, a step-wise approach to look for *BRAF*^{V600E} mutations followed by broader NGS studies is also a reasonable option. Challenges in molecular evaluation include limited quantities of DNA due to small biopsy samples, decalcified bone tissue, and low tumor content in the lesional tissue. As some neoplasms harbor low variant allele frequencies (i.e. <5%), below the assay sensitivity for commercial NGS, reviewing the raw data can be helpful to identify clinically relevant mutations. In some cases, targeted digital droplet polymerase chain reaction of lesional DNA may be helpful because of its high sensitivity; however, this method is not yet widely available in all clinical laboratories and has not been evaluated for non-*BRAF*^{V600E} alterations. Finally, in cases in which tissue mutational testing is not feasible, circulating mononuclear or urine cell-free DNA analysis can represent a specific test,[26] although sometimes not as sensitive due to false negative results.[27]

Treatment approaches

Treatment decisions in indolent or chronic non-LCH depend on organ involvement and symptoms. Asymptomatic patients with limited, non-critical organ involvement may be monitored closely. Treatment options are divided into 'targeted' or 'conventional' treatments, including chemotherapy, interferon, and anti-cytokine agents. In children, there is often a reticence to use targeted therapies due to the need for prolonged administration, and systemic therapies are borrowed from LCH protocols. Internation-

al guidelines exist for ECD and RDD;[9,10] however, optimal treatment remains elusive. In ECD, targeted therapies are preferred based on mutational status. Recent data suggest that upfront targeted therapy may benefit RDD patients with MAPK-ERK mutations.[28] In other subtypes of non-LCH, however, treatment guidance is lacking due to their rarity and heterogeneity. XG family of disorders are usually limited to the skin but may require systemic therapy, similar to ECD, if internal organs are involved. For ALK-positive histiocytosis, limited data suggest generally favorable outcomes, especially with the use of ALK inhibitors such as crizotinib and alectinib.[6] The treatment of ICH is similar to that of LCH; however, there is a high prevalence of concomitant hematologic neoplasms that may warrant specific treatments.[19] The optimum treatment for MHN is unknown, and the prognosis seems to be strongly tied to the extent of disease.[11] Patients with localized/solitary resectable MHN have an excellent prognosis with surgery alone or in combination with radiation therapy. However, the response to systemic therapies, including targeted inhibitors, in multifocal MHN appears to be dismal.[21,29]

Advances in molecular biology

Inflammatory milieu

The histiocytic neoplasms are characterized histologically by proliferation of mature histiocytes in a background of inflammatory stroma.[30] Studies have shown that a cytokine and chemokine network exists in ECD lesions. Secretion of interleukin (IL)-6 and cysteine-X-cysteine (CXC) chemokine ligand 8/IL-8 (CXCL8/IL8) has a role in the recruitment and activation of histiocytes and inflammatory cells.[31,32] This process is regulated by tumor necrosis factor (TNF), activating additional downstream inflammatory factors, further worsening tissue damage.[33] While LCH lesions are characterized by a T helper-2-skewed immune response, ECD appears to be driven primarily by T helper-1 lymphocytes expressing chemokine receptors, which in turn promote histiocyte activation and chemokine production,[34] further emphasizing the distinct immunological profiles of these entities. Before *BRAF*^{V600E} was discovered, ECD was considered an autoimmune disorder due to the presence of inflammatory cytokines, prompting the use of anti-cytokine therapies such as anakinra.[35,36]

RDD lesions exhibit moderate expression of IL-6, which may be associated with polyclonal plasmacytosis and hypergammaglobulinemia. Additionally, the lesions express IL-1β and TNF-α. Systemic symptoms in RDD might be linked to the elevated production of these cytokines.[37] The exact cytokine profile in JXG is not as well-defined and warrants further investigation.

Mutational landscape

Somatic mutations, particularly in the MAPK pathway, have revolutionized our understanding of the pathogenesis of histiocytic neoplasms. In 2010, a recurrent *BRAF*^{V600E} mutation was identified in 57% of LCH lesions (Figure 1),[38] establishing its role in constitutive MAPK activation, which drives both proliferation and inflammation.[39,40] Subsequently, in 2012, clonal *BRAF*^{V600E} mutations were discovered in ECD lesions[41] (Figures 1 and 2). A landmark study showed that the *BRAF*^{V600E} mutations could be traced to classical monocytes, nonclassical monocytes, and CD1c^{+} myeloid dendritic cells in the blood as well as myeloid precursors in the bone marrow, raising a question of multiple cells of origin for LCH and ECD.[42] Moreover, *BRAF*^{V600E} mutations were also detected in CD34^{+} hematopoietic progenitors,[43,44] suggesting shared origins for LCH and ECD, such as infiltration of myeloid cells that carry a mutation in genes involved in the MAPK pathway, and presence of the same mutation at the progenitor level. When mouse hematopoietic stem cells expressing *BRAF*^{V600E} were transplanted into immunodeficient mice, they developed an LCH-like, but not ECD-like, phenotype, suggesting that additional factors may drive ECD pathogenesis.[45,46]

Subsequent studies identified other clonal somatic activating mutations in *MAP2K1*, *ARAF*, *NRAS* and *KRAS*, and PI3K-AKT pathway genes, including *PIK3CA*, in LCH and ECD[47-53] (Figure 2). Additionally, mTOR pathway activation has been demonstrated in ECD,[54] suggesting a potential novel treatment target[55,56] (Figure 3). In 2017, recurrent *KRAS* and *MAP2K1* mutations were also reported in about 30% cases of RDD[57] (Figure 2), prompting the recognition of this disease as a histiocytic neoplasm by the WHO. Recent data identified *BRAF*^{V600E} and *KRAS* mutations, as well as recurrent *ETV3::NCOA2* fusions in ICH.[19,58] XG family diseases tend to exhibit more *BRAF* fusions than *BRAF* point mutations.[59] Large-scale sequencing has revealed novel alterations including *CSF1R* mutations, and *NTRK*, *ALK*, and *RET* fusions (Figure 2).[60-62] ALK-positive histiocytosis is the first histiocytic neoplasm defined by a specific molecular rearrangement. While indolent non-LCH tend to have low tumor mutational burden and single gene mutations,[63] MHN display a complex genome with multiple somatic alterations,[21] rendering them less likely to be oncogene-addicted and to respond to targeted therapies. While the discovery of novel alterations opens the door to targeted therapies, it also raises several questions. The cell-of-origin for non-*BRAF*^{V600E} histiocytic neoplasms is still unknown, and recent data have suggested distinct clinical features compared with *BRAF*^{V600E}-harboring disease entities[23] as well as differences in frequencies of mutations within disease subtypes,[64] which needs further investigation.

Epigenetic alterations

Recently, epigenetic changes have been studied in the context of disease pathogenesis. In ECD, patients exhibit a distinct microRNA (miRNA) profile compared to that in healthy controls, contributing to the inflammatory and

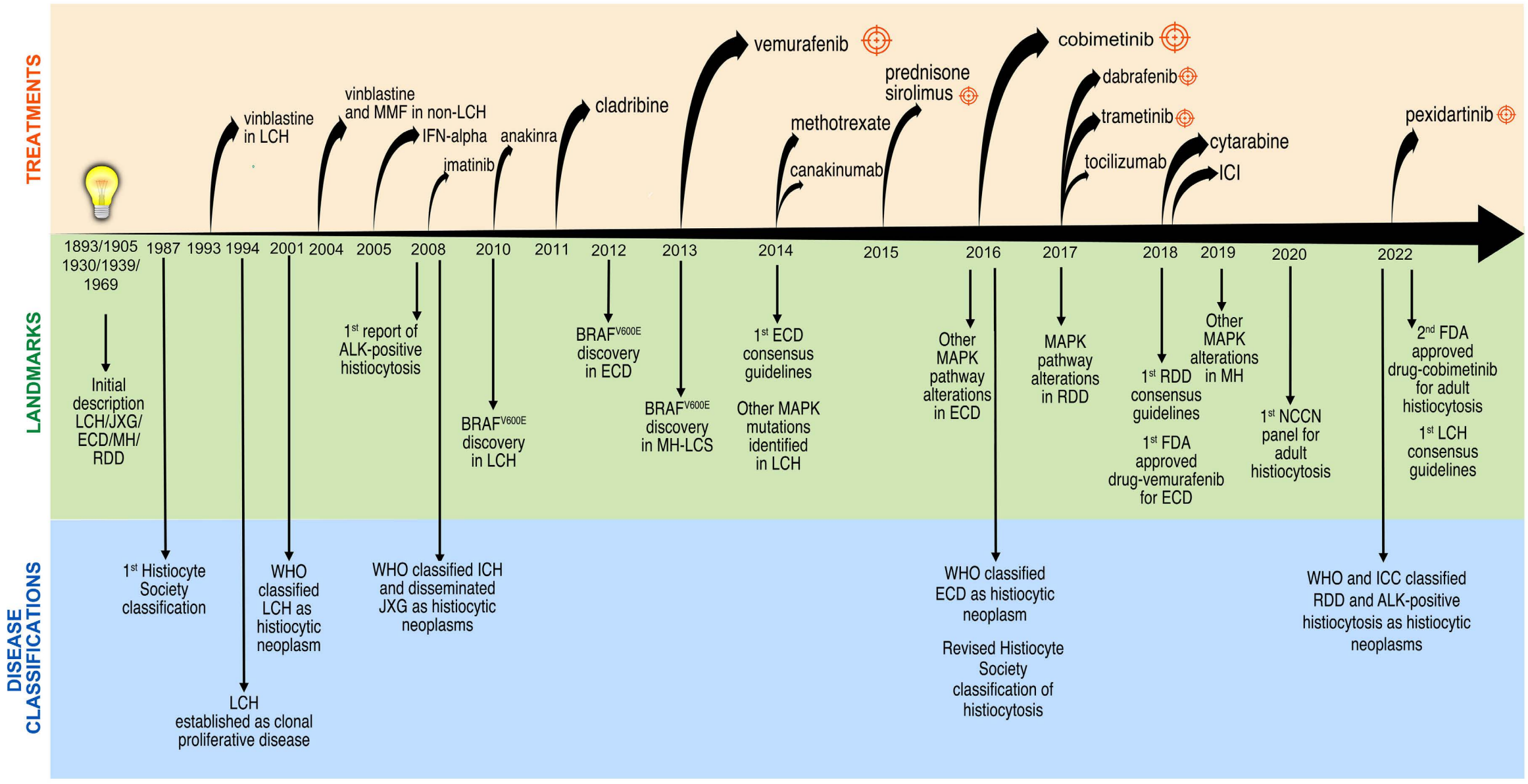

Figure 1. Timeline of advances in histiocytic neoplasms. The figure illustrates the initial descriptions of the disease entities, their recognition as clonal neoplasms, and significant milestones during the course of disease evaluation. LCH: Langerhans cell histiocytosis; JXG: juvenile xanthogranuloma; ECD: Erdheim-Chester disease; MH: malignant histiocytosis; RDD: Rosai-Dorfman disease; WHO: World Health Organization Classification of Hematopoietic Tumors; MMF: mycophenolate mofetil; IFN: interferon; ALK: anaplastic lymphoma kinase; ICH: indeterminate cell histiocytosis; LCS: Langerhans cell sarcoma; FDA: Food and Drug Administration; ICI: immune checkpoint inhibitor; NCCN: National Comprehensive Cancer Network; ICC: International Consensus Classification of Hematopoietic Tumors.

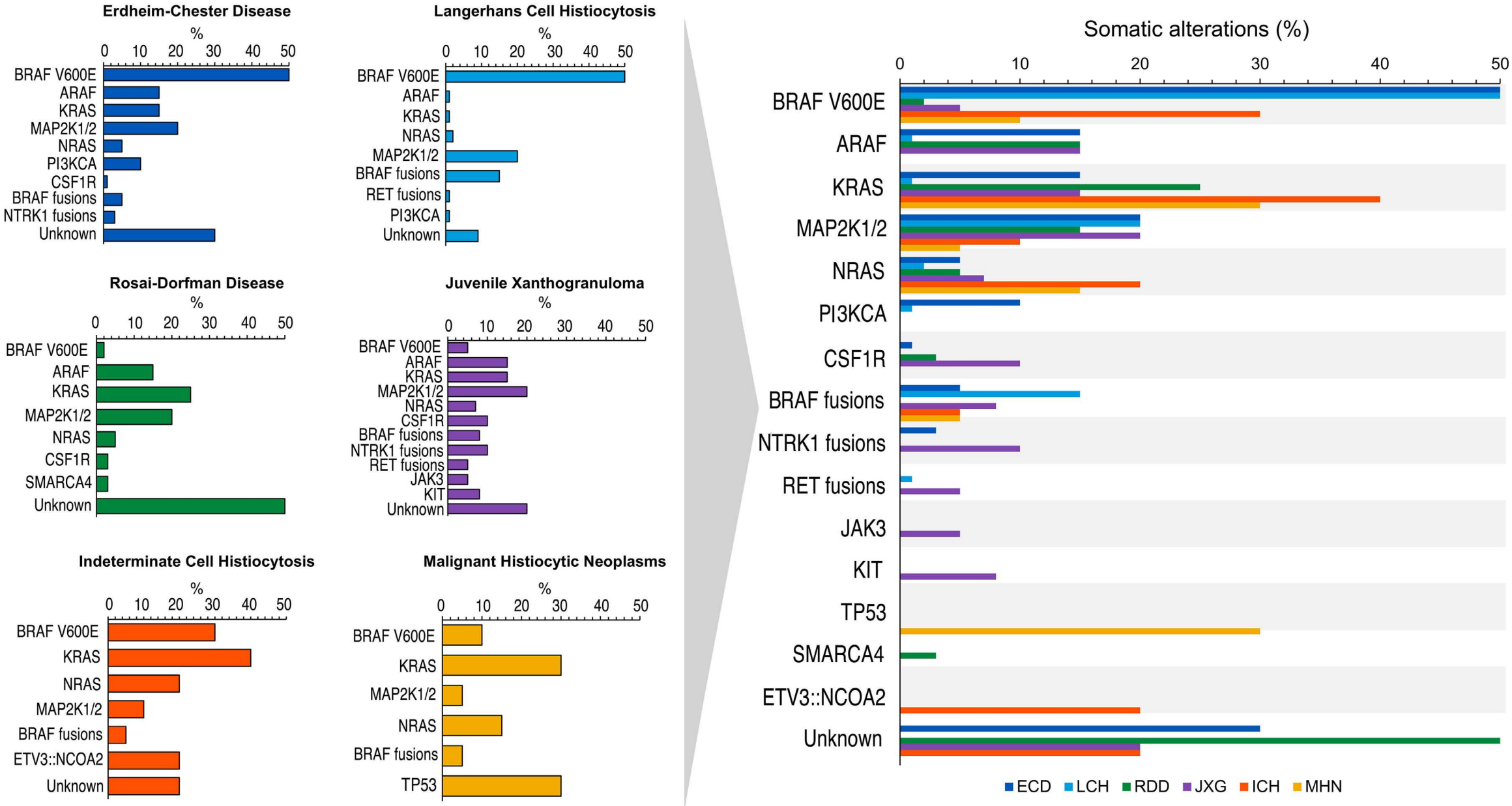

Figure 2. Diverse genetic alterations across histiocytic neoplasms. The left panel presents the frequency of known driver alterations observed across patients with Erdheim-Chester disease, Langerhans cell histiocytosis, Rosai-Dorfman disease, juvenile xanthogranuloma, indeterminate cell histiocytosis, and malignant histiocytic neoplasms, highlighting distinct mutational patterns characteristic of each entity. The right panel summarizes the frequency of known driver alterations observed across all diseases. The figure does not include ALK-positive histiocytosis as this is characterized by 100% prevalence of *ALK*-rearrangements. ECD: Erdheim-Chester disease; LCH: Langerhans cell histiocytosis; RDD: Rosai-Dorfman disease; JXG: juvenile xanthogranuloma; ICH: indeterminate cell histiocytosis; MHN: malignant histiocytic neoplasms.

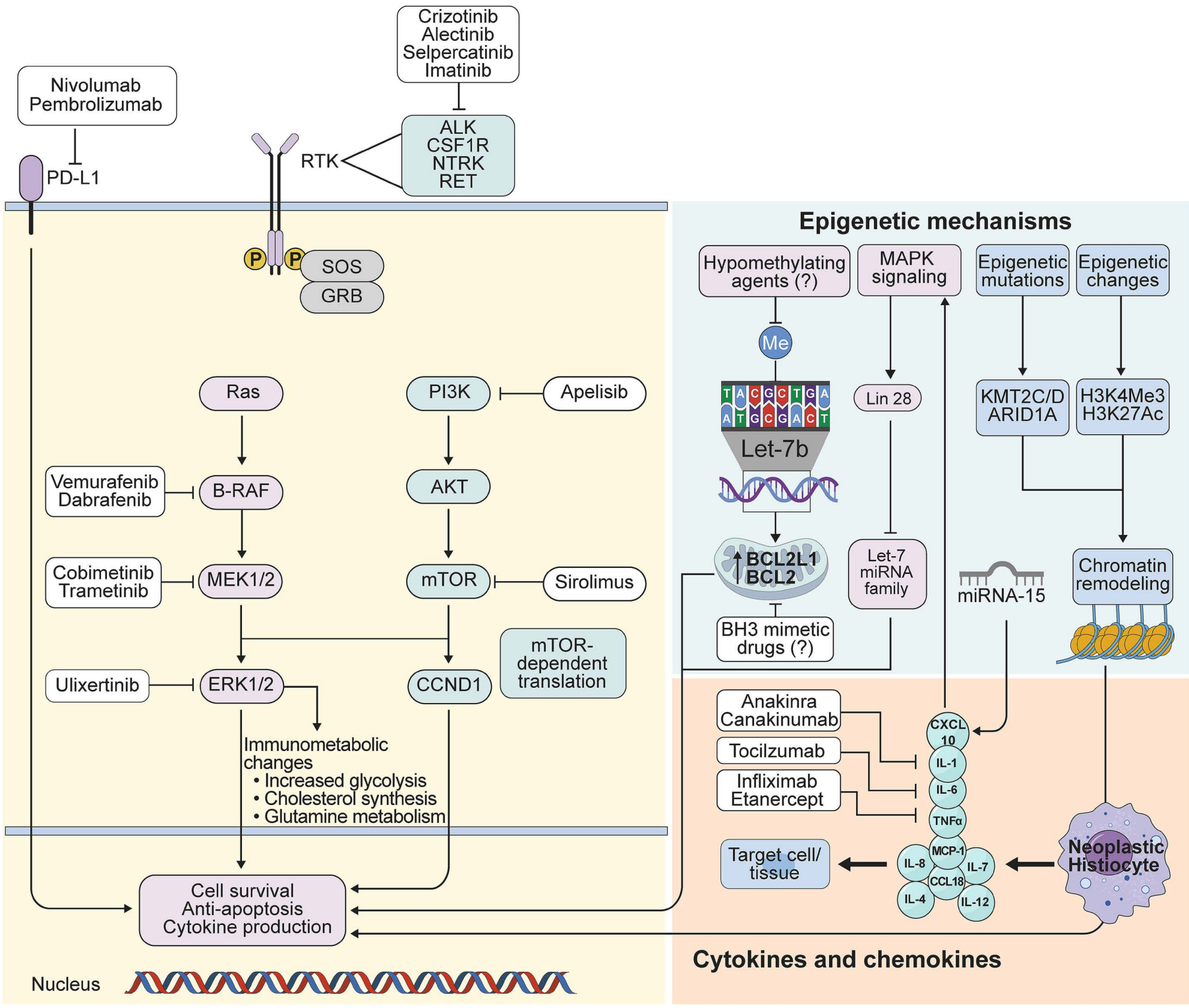

Figure 3. Molecular mechanisms and potential therapeutic targets in histiocytic neoplasms. This figure illustrates the role of genetic and epigenetic alterations, cytokines, and chemokines in the pathophysiology of histiocytic neoplasms along with existing and potential therapeutic targets. The left panel highlights somatic alterations activating the mitogen-activated protein kinase (MAPK)/extracellular signal-regulated kinase and phosphoinositide 3-kinase/protein kinase B/mammalian target of rapamycin pathways, leading to cell survival and secretion of cytokines and chemokines. Rare alterations in the receptor tyrosine kinases (e.g., anaplastic lymphoma kinase, colony-stimulating factor 1 receptor, neurotrophic receptor tyrosine kinase, rearranged during transfection) may also drive these pathways, offering additional targets for therapy. Overexpression of programmed death-ligand 1 enables immune evasion, and can be targeted by nivolumab and pembrolizumab. The upper-right panel demonstrates epigenetic alterations affecting gene expression. Hypermethylation of the let-7b promoter results in a lack of regulation of B-cell lymphoma 2 family members, leading to an anti-apoptotic effect. Additional epigenetic modifications such as trimethylation of histone H3 at lysine 4, acetylation of histone H3 at lysine 27, and mutations in lysine methyltransferase 2C/D, and AT-rich interaction domain 1A influence chromatin remodeling. Moreover, downregulation of microRNA-15 increases C-X-C motif chemokine ligand 10 and MAPK signaling, further enhancing oncogenic Lin28 expression and reducing let-7 family regulation. The lower-right panel illustrates the role of cytokines and chemokines in the microenvironment of histiocytic neoplasms. Pro-inflammatory cytokines and chemokines recruit histiocytic and immune cells, perpetuating inflammation. PD-L1: programmed death-ligand 1; RTK: receptor tyrosine kinases; ALK: anaplastic lymphoma kinase; CSF1R: colony-stimulating factor 1 receptor; NTRK: neurotrophic receptor tyrosine kinase; RET: rearranged during transfection; SOS: son of sevenless; GRB: growth factor receptor-bound protein; Ras: rat sarcoma; MEK: MAPK kinase; ERK: extracellular signal-regulated kinase; PI3K: phosphoinositide 3-kinase; AKT: protein kinase B; mTOR: mammalian target of rapamycin; CCND1: cyclin D1; BCL2: B-cell lymphoma 2; BH3: Bcl-2 homology 3; miRNA: microRNA; KMT2C/D: lysine methyltransferase 2C/D; ARID1A: AT-rich interaction domain 1A; H3K4Me3: trimethylation of histone H3 at lysine 4; H3K27Ac: acetylation of histone H3 at lysine 27; CXCL10: C-X-C motif chemokine ligand 10; IL: interleukin; TNF: tumor necrosis factor; MCP-1: monocyte chemoattractant protein-1; CCL18: C-C motif chemokine ligand 18.

neoplastic characteristics of histiocytic neoplasms.[65] In particular, members of the let-7 miRNA family are significantly downregulated in ECD. Since the let-7 family regulates the MAPK pathway, its reduced expression can activate this pathway even in the absence of canonical mutations.[66] A follow-up study showed that downregulation of miR-15a-5p in ECD led to CXCL10 upregulation, which in turn activated the MAPK pathway, thereby increasing Lin28a expression – a known repressor of the let-7 family. Consequently, let-7 family members were downregulated, promoting aberrant cell survival (Figure 3).[67] These findings suggest that MAPK inhibitors may be effective in patients with no detectable mutations in the pathway but with epigenetically driven activation, thus broadening the potential therapeutic relevance of targeted therapies. Additionally, distinct DNA methylation patterns have been observed in ECD, RDD, and LCH compared to controls.[68] Specifically, hypermethylation in the region encoding let-7b miRNA has been found in these neoplasms, resulting in downregulation of the mature miRNA. This, in turn, leads to aberrant regulation of its target gene *BCL2L1*, resulting in its overexpression and further contributing to cell survival (Figure 3). Another study[69] found a high prevalence of epigenetic mutations in histiocytic neoplasms (in ECD and RDD patients among others). The most common epigenetic mutations include *KMT2C*, *KMT2D*, and *ARID1A*, which are involved in chromatin remodeling and may contribute to disease pathogenesis (Figure 3). A different study demonstrated that the *BRAF* oncogene can contribute to maladaptive activation of trained immunity in ECD.[70] Trained immunity is a proinflammatory program in monocyte/macrophages induced by pathogens and characterized by immunometabolic and epigenetic changes that enhance cytokine production. When maladaptively activated (i.e., in the absence of infection), trained immunity can contribute to pathological inflammation and disease progression. While ECD is clearly a clonal myeloid neoplasm driven by MAPK pathway mutations, *BRAF*^{V600E}-expressing myeloid cells also exhibit key molecular features of trained immunity, including activation of the AKT/mTOR signaling pathway, increased glycolysis, glutaminolysis, and cholesterol synthesis, as well as epigenetic modifications (*H3K4Me3* and *H3K27Ac*). This results in enhanced cytokine production and a hyperinflammatory state. Pharmacological inhibition of immunometabolism pathways, such as glycolysis, effectively reduces cytokine production in myeloid cells, presenting a potential therapeutic strategy to reduce inflammation.

Clonal hematopoiesis of indeterminate potential

Clonal hematopoiesis of indeterminate potential (CHIP) refers to the presence of somatic mutations in genes commonly associated with myeloid malignancies, detected in individuals without overt hematologic disease.[71] CHIP becomes increasingly prevalent with age and has been linked to elevated risks of hematologic malignancies, cardiovascular disease, and death. A high frequency of CHIP has been identified in ECD patients, with mutations in *TET2*, *DNMT3A*, and *ASXL1* detected in bone marrow CD34^{+}CD38^{-} progenitors and peripheral blood monocytes. It was found that CHIP-positive ECD patients were older, more likely to harbor *BRAF*^{V600E} mutations, and exhibited increased vascular and retroperitoneal involvement.[72] In some cases, ECD co-occurred with overt myeloid malignancies such as myelodysplastic syndrome, chronic myelomonocytic leukemia, or secondary acute myeloid leukemia.[73,74] The role of CHIP mutations in the prognosis of ECD and other histiocytic neoplasms, as well as in the development of second myeloid malignancies, requires further investigation.[75]

Heterogeneity in nomenclature and classification

One of the most significant advances in the field of histiocytosis has been the recognition of its vast clinical, pathological, and molecular heterogeneity. At the same time, these advances have highlighted significant overlaps between LCH and non-LCH entities, such as activating mutations in the MAPK pathway (e.g., *BRAF*^{V600E}) (Figure 2) and co-occurrence of lesions (mixed histiocytosis), making the categorization of 'non-LCH' questionable and inappropriate. Furthermore, the existing nomenclature and classification systems for these disorders are inaccurate. The current WHO/ICC classification lumps histiocytic neoplasms into the category 'histiocytic and dendritic cell neoplasms' including entities with distinct biology from other histiocytic neoplasms (such as blastic plasmacytoid dendritic cell neoplasm and follicular dendritic cell sarcoma). A more appropriate terminology might be 'neoplasia of the histiocytic system' (i.e., tissue cell encompassing macrophage-, monocyte-, or dendritic cell-related neoplasms).

Inconsistencies in the methodologies used to define individual disease entities further exacerbate diagnostic confusion. For example, lesions with xanthogranulomatous morphology - typically associated with JXG, AXG, or ECD - are not pathognomonic of a single disease. Rather, they require integration of clinical, radiographic, and molecular findings. Traditionally, ECD is thought of as a systemic disease, with its diagnosis typically reliant on characteristic radiographic findings (e.g., osteosclerosis of leg bones, retroperitoneal infiltration, or posterior fossa tumors), whereas a diagnosis of JXG/AXG is supported by a primary cutaneous involvement.[9,76] However, "systemic" (i.e., extracutaneous) and more aggressive JXG/AXG can present with a variety of visceral,[77] osseous/craniofacial,[78,79] ocular,[80] and neurological[61] forms, resembling ECD but lacking its hallmark features. Additionally, while ECD was historically seen as an adult-only disease, pediatric-onset classic ECD has been identified as well,[14] further blurring the lines between these subtypes. Whether all JXG/AXG

in extracutaneous sites or with more than one skin lesion need to be reclassified as atypical phenotypes of ECD or presumptive evidence/precursor lesions of ECD requires further exploration.[23] Mutational profiling alone cannot differentiate ECD from other XG family diseases, since MAPK mutations have been reported in isolated JXG/AXG as well.[59,61,81]

The lack of a unified classification system creates barriers to advancing both research and clinical care. From a research perspective, it limits the ability to pool data across subtypes, which is critical given the rarity of these conditions. Clinically, the lack of standardization complicates diagnosis, often leading to delays or inappropriate management. For instance, adults diagnosed with "JXG" may be incorrectly reassured that the disease is benign and self-limiting, with no staging studies performed. Simply appending "-histiocytosis" to disease names (e.g., XG family histiocytosis) could serve as a reminder for clinicians, especially those outside hematology/oncology, to pursue appropriate staging assessments. To address this gap, we propose a provisional framework (Figure 4) that better integrates morphological, clinical, and molecular features, and we advocate for a collaborative effort – led by the Histiocyte Society and supported by large, multi-institutional datasets – to establish a new, consensus-based classification system. The revised framework should also consider instances in which definitive categorization of histiocytosis cannot be made. It is essential for the Histiocyte Society to establish clear nomenclature guidelines - whether based on clinical phenotype (i.e., the name of the disease should suggest systemic spread such as ECD *vs*. the more benign XG), histopathology, regardless of the clinical phenotype (like LCH and RDD), or molecular findings (e.g., ALK-positive histiocytosis regardless of pathological features). Two recent series described *NTRK*-rearranged histiocytosis with XG morphology.[82,83] As NGS use expands, more molecular groups may emerge, warranting evaluation of whether they represent distinct entities or reflect the molecular diversity within XG family disorders. The classification systems have implications for the pathologists too, as in reality most non-histiocytosis focused clinicians rely on the pathology report for making management decisions. By moving beyond traditional, morphology- or clinical phenotype-based classification and adopting a data-driven, integrative approach, the field can pave the way for precision medicine in these rare, complex disorders.

Therapeutic advances and challenges

The identification of recurrent MAPK pathway mutations in non-LCH (Figure 1) has revolutionized the treatment landscape, leading to the introduction of small molecule inhibitors that have led to high response rates.[28,57,83-85] Therapies approved by the Food and Drug Administration in the USA include vemurafenib for *BRAF*^{V600E} ECD (2017) and cobimetinib for adult histiocytoses (2022). Vemurafenib showed nearly 100% efficacy in *BRAF*^{V600E} ECD by PET-based criteria in a phase II trial,[86] while cobimetinib, a MEK inhibitor, was approved based on a phase II trial of a mixed histiocytosis cohort in which the response rate was 89%.[87] However, real-world data have dampened the initial enthusiasm, especially in patients without detectable MAPK mutations, in whom response rates are significantly lower.[28,88] Moreover, not all MAPK mutations confer equal sensitivity to inhibition. *BRAF* and *MEK* mutations are classified into three classes.[89] Class I *BRAF* mutations (e.g., V600E) are RAS-independent and highly active as monomers. Class II mutations also signal independently of *RAS* but require dimerization and have lower activity. Class III mutations are kinase-impaired and depend on upstream *RAS* activation via *BRAF-CRAF* dimers. *MEK* mutations follow a similar pattern: class I mutations are RAF-independent and activate *ERK* through autophosphorylation, leading to strong feedback inhibition of *RAS*. Class II mutations retain kinase activity that is enhanced by activated *RAF*, with moderate signaling. Class III are *RAF*-dependent and signal only in the presence of *RAF* binding, resulting in weak pathway activation and minimal feedback. A recent study[90] showed that cobimetinib was effective in patients with class I and class II *BRAF* mutations, but not in those with class III mutations, highlighting the need to match therapies to specific mutation classes. Despite the advances with targeted kinase inhibitors, key challenges remain. Targeted therapies require prolonged administration due to the high risk of relapse at drug discontinuation. In two institutional studies, one prospective and another retrospective, the relapse rate was nearly 75% after interruption of targeted therapies.[91,92] The adverse event profile of these drugs becomes especially pertinent in the setting of chronic administration, resulting in high rates of discontinuation. In a recent study, we found that 60% of patients with ECD discontinued BRAF inhibitors at a median follow-up of 4 years due to adverse events.[93] Mutational analysis on peripheral blood can potentially offer a tool for minimal residual disease detection, as has been undertaken in children with LCH using mononuclear cell or circulating cell-free *BRAF*^{V600E}.[94,95] However, a recent study examining mononuclear cell and cell-free DNA was unable to identify mutations in most of the ECD cases studied with known driver mutations in the tumor.[27] Furthermore, access to targeted agents can be limited globally, especially in resource-limited settings.

Fixed-duration chemotherapy (e.g., cladribine or cytarabine) offers an alternative with potentially high response rates and durable remissions in some cases, although these approaches have not been compared directly with targeted therapies. A retrospective case series reported an overall response rate of 52% with a median clinical response duration of 9 months in ECD patients treated with cladribine.[96] Another study involving nine ECD patients and five RDD pa-

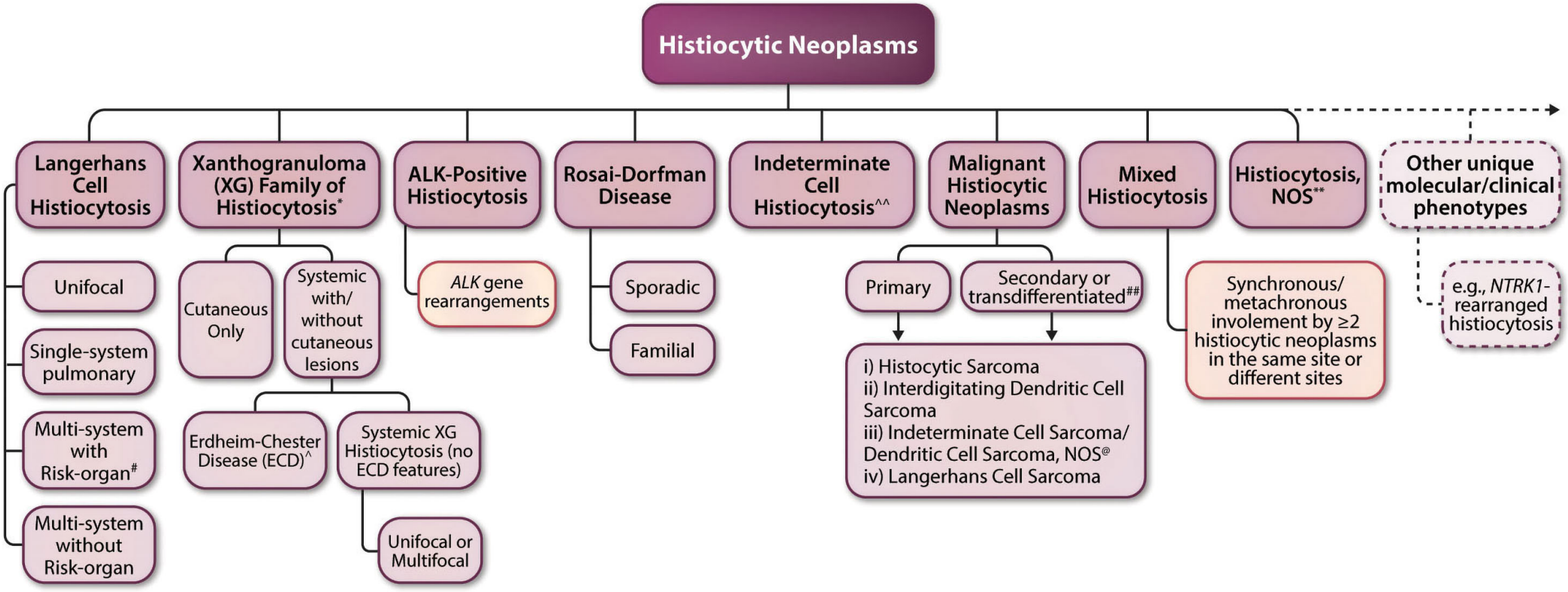

Figure 4. Proposed classification of histiocytic neoplasms with integration of clinical and pathological characteristics. #Risk organs include liver, spleen and bone marrow. *Encompasses the previously known subtypes 'juvenile xanthogranuloma' and 'adult xanthogranuloma'. ^The classic phenotype of Erdheim-Chester disease is characterized by symmetric osteosclerosis of the distal femur and/or proximal tibia/fibula. Other features include perinephric or periaortic infiltration ('hairy' kidney and 'coated' aorta), posterior fossa tumors, and right atrial pseudotumor. ^^Indeterminate cell histiocytosis is also known as indeterminate dendritic cell tumor or indeterminate dendritic cell histiocytosis according to the World Health Organization (WHO)/International Consensus Classification (ICC) classifications (2022) of hematopoietic tumors. ##Secondary/transdifferentiated malignant histiocytic neoplasm indicates association with a hematologic neoplasm. @Indeterminate cell sarcoma is an entity recognized by the revised 2016 Histiocyte Society Classification of Histiocytosis; the WHO and ICC classifications (2022) do not recognize this entity as a subcategory and therefore the terminology of 'dendritic cell sarcoma, not otherwise specified' could be utilized as appropriate (reference: Ravindran *et al.*[3] **Provisional category: represents entities that could not be categorized into the other existing subtypes. ALK: anaplastic lymphoma kinase; NOS: not otherwise specified; NTRK: neurotrophic receptor tyrosine kinase.

tients treated with cytarabine reported an overall response rate of 87.5%, with a 2-year progression-free survival rate of 85.6% and an overall survival rate of 92.3%.[97] A phase II clinical trial utilizing lenalidomide and dexamethasone in patients with RDD yielded an 87% overall response rate, with 30% achieving complete responses, and a 2-year progression-free survival of 69%, and offers a low-cost yet efficacious treatment option.[98]

There is a need to develop practical treatment guidelines that allow for personalized care of patients in varied resource settings as well as investigate treatments that are affordable and offer long-term remissions. Furthermore, systematic studies are warranted to examine discontinuation of BRAF- and MEK-inhibitors after a pre-specified period of remission to identify patients who are best suited for treatment interruption, correlating responses with circulating mutational burden. Investigation of combination therapies incorporating sequential or concomitant targeted and non-targeted agents (chemotherapy) to achieve cure should also be considered, as is being undertaken in LCH.[99]

Emerging therapies

Multiple novel treatment strategies and targets are being investigated or are worth investigating in histiocytic neoplasms. Due to the challenges associated with resistance to MEK inhibition for class II and III *MEK/MAP2K* mutations, it seems logical to block the MAPK pathway further downstream by using an ERK inhibitor. A phase II clinical trial (NCT06411821) is investigating ulixertinib, an ERK 1/2 inhibitor, and is showing early promise for overcoming resistance in patients harboring *MEK1* E102I103_del and class III *MEK* alterations.[100] Chimeric antigen receptor (CAR) T-cell and bispecific antibody therapies, proven effective in various hematologic malignancies, are particularly attractive in non-LCH because of their potential to induce sustained remissions. While LCH has a specific CAR T-cell target (CD207) under evaluation (NCT05477446), identifying specific targets for non-LCH remains crucial. Overexpression of CCND1[24,101] suggests a role for CDK4/6 inhibitors, such as palbociclib or abemaciclib,[102,103] although these agents have yet to be clinically evaluated in histiocytoses.

There are emerging case reports of successful treatment of ECD using pexidartinib, a CSF1R (chromosome region maintenance 1) inhibitor.[104] The efficacy of targeting *CSF1R* may not be limited to patients with a *CSF1R* mutation as CSF1R signaling is essential for monocyte and macrophage maturation.[105,106] *CRM1*, also known as exportin 1 (*XPO1*), serves as the primary molecular exporter of macromolecules from the nucleus to the cytoplasm and is often overexpressed in hematologic malignancies,[107] including histiocytic neoplasms (ECDGA annual meeting 2024, *unpublished data*). This overexpression can be exploited for therapeutic benefit through the use of small molecular CRM1 inhibitors and is being evaluated in a clinical trial (NCT04640779).[108]

There are emerging data on the potential efficacy of nivolumab and pembrolizumab, anti-PD1 checkpoint inhibitors, in MHN especially with high lesional PDL1 expression.[21,109] The role of epigenetic regulators, including hypomethylating agents like azacitidine and decitabine, and the upregulation of anti-apoptotic proteins such as BCL2L1 and BCL2, highlight the potential of combining these agents with BH3 mimetics for therapeutic synergy.[68] Currently active clinical trials investigating different drugs as single-agent treatments and as combination treatments are listed in the Table 2. Together, these strategies underscore the expanding horizon of treatment possibilities for histiocytic neoplasms.

Lack of information on incidence, natural history and long-term outcomes

Despite numerous advances in deciphering the biology and treatments of non-LCH, their true incidence is unknown. There is a need to determine the global incidence and prevalence of these disorders to aid with targeted resource allocation and educational efforts. There is also a lack of understanding of the natural history and long-term outcomes to inform treatment choices. While there is some sense of predictors of 'high-risk' disease (liver, spleen, bone marrow involvement) in LCH, such data are very sparse in non-LCH. Conversely, the predictors of 'low-risk' disease are equally important as patients with such disease may not warrant systemic treatments. Indeed, existing cohorts have reported spontaneous[73,110] remissions in all non-LCH subtypes, even within MHN.[21,111] Furthermore, with improvement in treatments, there is a growing population of non-LCH survivors who are at risk of late complications as a result of the disease and/or its treatments. Recent studies have demonstrated the occurrence of clonally related myeloid neoplasms in ECD and ECD/LCH overlap, leading to near universal mortality.[73,110] The delayed diagnosis further complicates the morbidity burden, leading to organ dysfunction that may not be reversible. There is a need for large studies to address these unresolved issues.

Roadmap for future research

Establishing large, collaborative patient registries

The rarity and heterogeneity of non-LCH demand large-scale collaboration. A global network of clinicians and researchers through scientific organizations (e.g., the Histiocyte Society) and patient advocacy groups (e.g., the Histiocytosis Association and ECD Global Alliance) can facilitate data-sharing, standardize diagnostic crite-

Table 2. Overview of clinical trials investigating therapies for histiocytic neoplasms as of December 2024. Studies involving only Langerhans cell histiocytosis are excluded.

Phase	Treatment	Institutions	Comments	Status as of December 2024
I	Anakinra or denosumab + everolimus (mTOR inhibitor)	MD Anderson (Houston)	NCT01624766; previously treated	Completed
I	DCC-2618 (c-Kit inhibitor)	Multiple	NCT02571036; previously treated	Completed
I	Ulixertinib or BVD-523 (ERK inhibitor)	Multiple	NCT01781429; newly diagnosed or previously treated	Completed
I	Selinexor + choline salicylate	Mayo Clinic, MN	NCT04640779; previously treated	Recruiting
I	Virotherapy	Mayo Clinic, MN	NCT03017820; previously treated	Recruiting
I	CSF1R inhibitor	Mayo Clinic, MN	NCT06712810; previously treated or untreated patients in whom the 1st line therapy was deemed ineffective, or unaffordable	Not recruiting
I/II	PLX8394 (BRAF inhibitor)	Multiple (11 sites)	NCT02428712; previously treated *BRAF* mutated	Active, not recruiting
I/II	HH2710 (ERK1/2 inhibitor)	Multiple	NCT04198818; previously treated *MAPK* mutated	Terminated
II	Lenalidomide (immunomodulatory agent)	Dana Farber (Boston)	NCT02523040; newly diagnosed or previously treated	Active, not recruiting
II	HLX208 (BRAF inhibitor)	China	NCT05092815; newly diagnosed or previously treated; *BRAF* mutated	Recruiting
II	Cobimetinib	NACHO (Baltimore, Dallas, DC, Houston, Madison, Memphis, Orange)	NCT04079179; previously treated	Recruiting
II	Dabrafenib (BRAF inhibitor) or trametinib (MEK inhibitor)	National Institute of Health (Bethesda)	NCT02281760; newly diagnosed or previously treated; *BRAF* mutated; study suspended	Completed
II	Nivolumab (PD1 antibody)	Multiple (52 sites)	NCT02832167; previously treated	Completed
II	LY3023414, selumetinib, ensartinib, olaparib, palbociclib, ulixertinib, selpercatinib	Children's Oncology Group: Pediatric MATCH trial; multiple US sites	NCT03155620; previously treated	Recruiting
II	Ulixertinib	Memorial Sloan Kettering	NCT06411821; previously treated	Recruiting
II/III	Vemurafenib and cobimetinib	Multiple (UK)	NCT05768178; newly diagnosed; *BRAF* mutated	Recruiting

ria, and improve patients' access to specialized care. It is critical to develop and expand international registries and biobanks to collect longitudinal clinical, genetic, and treatment data from patients across the spectrum of non-LCH. A centralized pathology repository using digital images may be a novel mechanism to develop uniform and systematic definitions for diagnostic criteria. Such resources will enable robust large-scale studies integrating genomic, transcriptomic, proteomic, and epigenomic data, leading to a clinically and biologically informed classification system that supports precision diagnostics and therapy selection (Figure 5). In the long-term, such collaborative registries can inform the natural history of histiocytoses, which can in turn lead to risk stratification for clinical trials and practice.

Molecular studies and biological models for pathogenesis and drug development

Critical areas for further investigation include proteomics, a deeper exploration of epigenetic regulation, and metabolic reprogramming (Figure 5). Proteomics may reveal protein interactions driving disease progression, while epigenetic studies might uncover mechanisms influencing treatment resistance and disease heterogeneity. Metabolic profiling could elucidate altered pathways supporting non-LCH cell survival, offering new therapeutic targets. Additionally, non-invasive biomarkers, such as cell-free DNA and non-coding RNA, offer potential for monitoring response and early resistance.

Developing suitable research models remains a challenge. While several cell lines align with certain disease char-

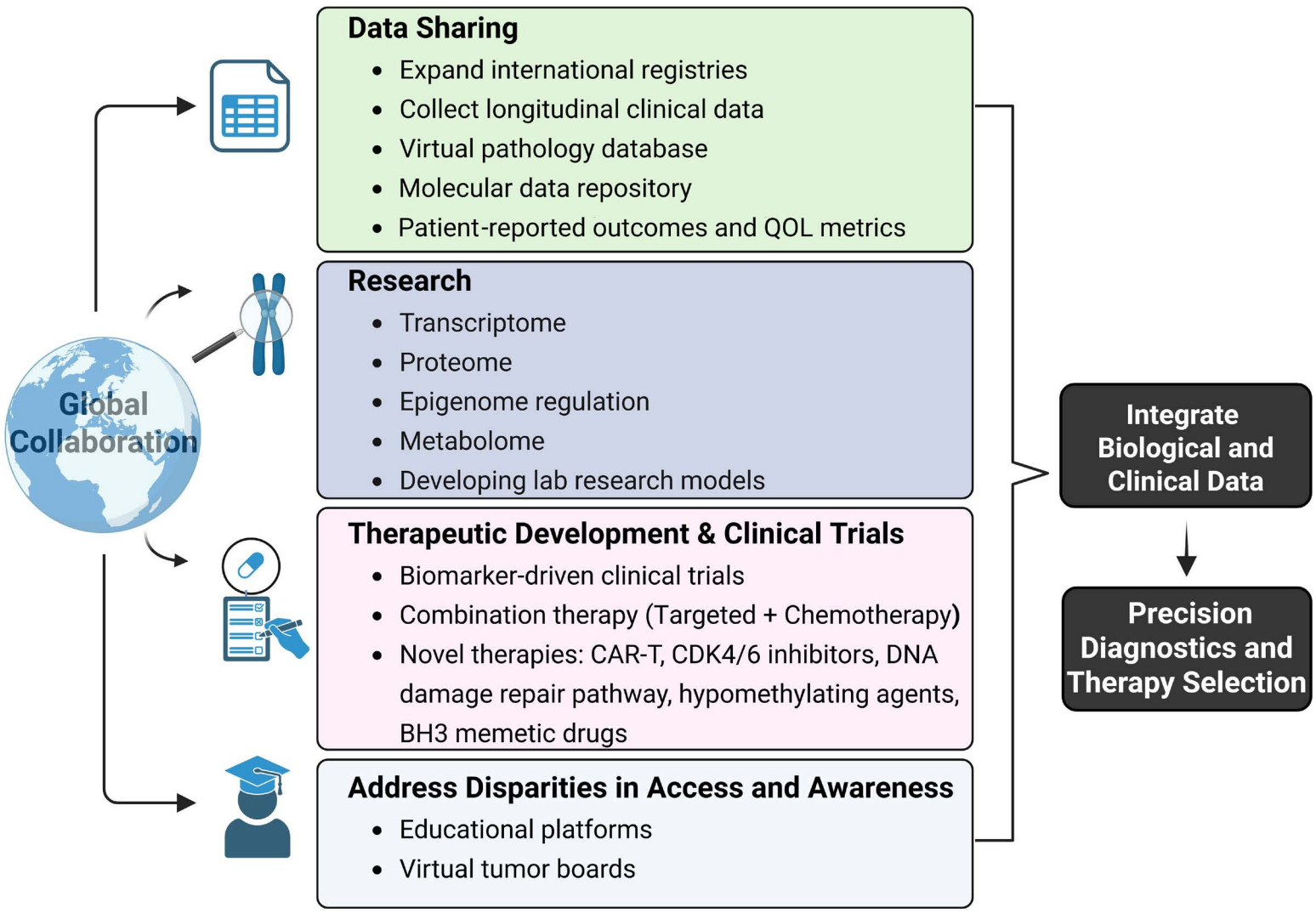

Figure 5. Roadmap for future research in histiocytic neoplasms. Framework for advancing the management of histiocytic disorders through global collaboration. The diagram outlines four areas of focus: (i) data sharing, (ii) research, (iii) therapeutic development and clinical trials, and (iv) addressing disparities in access and awareness. The integration of these four areas will enable precision diagnostics and therapy selection. QOL: quality of life; CAR-T: chimeric antigen receptor T cells.

acteristics, they do not fully replicate histiocytosis. The human myeloid progenitor-derived cell lines OCI-AML3, KG-1a, and THP-1 may mimic the hematopoietic origin of histiocytic cells and exhibit constitutive kinase activity with MAPK pathway overexpression.[67,112,113] However, their use in modeling histiocytic biology is limited and primarily based on shared signaling pathways. Therefore, there is a need to develop more representative cellular models. Additionally, Ba/F3 cells, a murine pro-B cell line engineered to overexpress the *BRAF*^{V600E} mutation,[67,114] provide a tool for functional assays. These cells are cytokine-dependent under normal conditions but acquire growth independence upon oncogenic transformation by *BRAF*^{V600E}, thereby modeling key aspects of histiocytic pathogenesis. A promising direction involves culturing tumor cells directly from patients' tissues, although slow proliferation limits their utility in long-term studies. A potential solution could involve the use of induced pluripotent stem cells, as recently applied in LCH.[115] Differentiating induced pluripotent stem cells into the myeloid lineage and using CRISPR-Cas9 to introduce MAPK pathway mutations could establish versatile models. This strategy could advance understanding of histiocytoses and support therapeutic discoveries.

Optimizing clinical trial strategies

The rarity of histiocytic neoplasms necessitates careful clinical trial design and execution. Opening multiple trials investigating similar therapies across different locations can lead to fragmented data and prolonged recruitment periods. For instance, five investigational molecules each requiring 30 patients, would need a total of 150 participants – a challenging task for a rare disease. A "lumping" approach, which groups histiocytoses with shared molecular or clinical features, can address this challenge more effectively than "splitting" them into narrowly defined subtypes. This strategy was successfully employed in the case of the cobimetinib trial, facilitating drug approval by broadening the eligible population of patients.[87] Such an approach may accelerate the approval of new treatments, especially for the rare subtypes, such as MHN, in which it is unlikely that a specific trial would be undertaken.

Another solution to overcome the rarity challenge is to utilize existing trial machinery through various cooperative groups, as recently done for LCH through the Children's Oncology Group (NCT05828069). Platform studies further streamline drug development by using master agreements between sites, enabling the evaluation of multiple therapies under a unified protocol. This design allows for the seam-

less introduction of new investigational agents, reducing regulatory delays and resource burdens.
Sample size determination in rare disease trials also demands innovative approaches. Traditional approaches often fail due to the limited number of patients. Bayesian methods and adaptive trial designs offer alternative frameworks, enabling robust evaluations of novel therapies. These methodologies allow for adjustments based on interim data, enhancing trial efficiency while maintaining ethical integrity.

Addressing disparities in access and awareness

Rare diseases such as non-LCH are often under-recognized, and access to specialized care remains inequitable. There is a need to increase awareness among healthcare providers about these rare disorders and advocate for policies that improve access to expert care and clinical studies. This could be achieved by creating open-access education platforms, virtual conferences, and partnerships between specialized centers and regional healthcare providers. Such efforts can ensure equitable treatment opportunities and reduce diagnostic delays. There is also a need to recognize that most existing diagnostic and management guidelines are based on studies from developed countries, which may not be applicable to low-resource settings.

Incorporating patient-reported outcomes in research and care

In non-LCH research, integrating patient-reported outcomes (PRO) remains underdeveloped. Future studies should integrate standardized PRO tools to assess symptom burden, fatigue, physical and mental health, and treatment side effects. Metrics such as time to diagnosis, diagnostic burden, and communication clarity are equally important. These data can refine diagnostic algorithms, support shared decision-making, and personalize care. Longitudinal PRO collection in trials and registries will help to define meaningful clinical benefits beyond imaging or laboratory results. For example, a therapy that improves fatigue or cognition – despite causing only limited radiographic changes – may be of significant value to the patient. Incorporating PRO measures into registries also enables real-world benchmarking and cross-study comparisons. Ultimately, elevating the patients' voice helps align medical advances with outcomes that matter most, making care truly person-centered.

Conclusion

The future of non-LCH research lies in embracing interdisciplinary collaboration, leveraging technological advances, and prioritizing patient-centered approaches. By addressing these key areas, the field can move closer to delivering precision medicine and improving outcomes for individuals affected by a histiocytic neoplasm. This roadmap serves as a call to action for the community to work together toward these ambitious yet achievable goals.

Disclosures

GG has received consulting fees from Recordati and Pharmassentia, and served on advisory boards for Seagen, Opna Bio, Electra and Sobi.

Contributions

OH-R created the initial draft with support from JPA and AR. GG reviewed and revised the final draft. All authors have read and approved the final version.

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