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Molecular Pathogenesis and Targeted Therapeutic Advances in Langerhans Cell Histiocytosis: A Systematic Review

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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Abstract

Introduction: Langerhans Cell Histiocytosis (LCH) is a rare myeloid neoplasm characterized by clonal proliferation of immature dendritic cells, primarily driven by constitutive activation of the MAPK signaling pathway through mutations in *BRAFV600E*, *MAP2K1*, and *ARAF*. Recent genomic and therapeutic advances have reshaped the understanding of LCH pathophysiology, highlighting differences between pediatric and adult presentations, particularly regarding skeletal involvement and prognosis.
Aim: To systematically review the literature published between 2015 and 2025 addressing genetic alterations, immunopathogenic mechanisms, orthopedic manifestations, and targeted therapies in pediatric and adult Langerhans Cell Histiocytosis.
Methods: A systematic review was conducted in accordance with PRISMA 2020 guidelines. Searches were performed in PubMed/MEDLINE, SciELO, and the Virtual Health Library (BVS). After screening, duplicate removal, and eligibility assessment, 38 studies were included. Due to methodological heterogeneity, data were synthesized through qualitative analysis, and no meta-analysis was performed.
Results: The included studies demonstrated a predominance of *BRAFV600E* mutations (52–65%) and *MAP2K1* mutations (15–25%), leading to sustained MAPK pathway activation and chronic inflammation. Pediatric patients more frequently presented with multifocal skeletal involvement, while adults predominantly exhibited unifocal disease with favorable prognosis. Targeted therapy with **BRAF and MEK inhibitors** achieved high response rates, with radiological regression and functional improvement; however, disease relapse after treatment discontinuation remained common in a subset of patients.
Conclusion: Activation of the MAPK pathway is central to LCH pathogenesis and clinical behavior. Incorporation of molecular profiling enables precision-based therapeutic strategies, particularly with BRAF and MEK inhibitors. Orthopedic manifestations, especially in pediatric patients, require conservative and multidisciplinary management. Despite significant advances, randomized clinical trials and standardized treatment protocols are still needed to define optimal therapy duration and reduce relapse risk.

Keywords: Langerhans cell histiocytosis; MAPK pathway; targeted therapy; skeletal involvement; systematic review.

1. Introduction

Langerhans Cell Histiocytosis (LCH) is a rare inflammatory myeloid neoplasm that predominantly affects children between one and ten years of age, with an estimated incidence of three to nine cases per million per year (Allen et al., 2018; Badalian-Very et al., 2010). Skeletal involvement is the most frequent clinical manifestation, occurring in up to eighty percent of pediatric cases, and represents a major diagnostic and therapeutic challenge in pediatric orthopedics (Rodriguez-Galindo & Allen, 2020; Goyal et al., 2022).

Lytic bone lesions are among the defining features of the disease and most commonly affect the skull, long bones, ribs, mandible, and pelvis (Héritier et al., 2016; Melloul et al., 2019). In children, these lesions often present with localized pain, swelling, or pathologic fractures and can easily mimic primary bone tumors or osteomyelitis (Donadieu et al., 2015). Spinal involvement may lead to vertebral collapse, known as vertebra plana, and requires multidisciplinary management involving orthopedic surgeons, pediatric oncologists, and neurosurgeons (Veys et al., 2015; Héritier et al., 2017).

From a biological standpoint, LCH is characterized by the clonal proliferation of $CD1a^+$ and $CD207^+$ dendritic cells derived from myeloid precursors harboring activating mutations in the MAPK signaling pathway, including RAS, RAF, MEK, and ERK (Diamond et al., 2018; Yang et al., 2021). The BRAFV600E mutation is the most common, occurring in approximately fifty to sixty-five percent of cases, followed by alterations in MAP2K1, ARAF, NRAS, and KRAS (Whitlock et al., 2023; McClain et al., 2018). These mutations promote constitutive activation of the MAPK pathway, leading to abnormal cell proliferation, chronic inflammation, and bone destruction, which explain the persistence and recurrence of certain skeletal lesions (Eckstein et al., 2019).

In pediatric orthopedics, LCH remains one of the leading causes of noninfectious osteolytic bone lesions (Rodriguez-Galindo & Allen, 2020). Solitary bone lesions may be managed with curettage, intralesional corticosteroid injection, or clinical observation, achieving high rates of spontaneous regression (Henter et al., 2022). However, multifocal or multisystem disease may involve risk organs such as the liver, spleen, and bone marrow, requiring systemic therapy with chemotherapy and, more recently, targeted molecular therapy (Allen et al., 2020; Shi et al., 2021).

The introduction of BRAF and MEK inhibitors, such as vemurafenib, dabrafenib, and cobimetinib, has revolutionized the management of refractory and relapsed LCH in both children and adults (Milne et al., 2022). Clinical studies have reported overall response rates exceeding eighty-five percent, accompanied by significant reductions in bone pain and radiological improvement of lesions (Kemps et al., 2023; Simko et al., 2015).

Prognostically, children with disease confined to the skeleton show near-complete overall survival, although approximately thirty percent experience late reactivation, particularly in craniofacial and vertebral sites (Gadner et al., 2013; Makras et al., 2020). In contrast, adult patients demonstrate lower rates of spontaneous remission and higher recurrence of bone disease (Grois et al., 2010).

Understanding the molecular mechanisms and radiologic–histopathologic characteristics of osseous LCH is essential for accurate diagnosis, individualized therapy, and optimization of long-term functional outcomes in pediatric orthopedic practice. This systematic review synthesizes the current evidence published between 2015 and 2025 regarding the molecular pathogenesis, skeletal manifestations, and targeted therapies of LCH, emphasizing pediatric populations and the orthopedic implications of modern disease management.

2. Material and Methods

2.1 Study Design

This study was conducted as a systematic review following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA 2020) guidelines.

2.2 Data Sources and Search Strategy

A comprehensive search was performed in the databases PubMed/MEDLINE, SciELO, and the Biblioteca Virtual em Saúde (BVS). The search strategy was developed using Medical Subject Headings (MeSH) and Boolean operators, applying the following string: ("Langerhans Cell Histiocytosis"[MeSH]) AND ("Systematic Review" OR "Meta-Analysis" OR "Clinical Trial" OR "Case Reports") AND ("2015/01/01"[Date - Publication] : "2025/12/31"[Date - Publication])

Only peer-reviewed articles were included. Preprints, conference abstracts, letters, and editorials were excluded. The reference lists of included studies were manually screened to identify additional relevant publications.

The initial search retrieved 432 records, which were screened using the Rayyan QCRI platform for deduplication and relevance assessment.

2.3 Eligibility Criteria

Studies were selected according to the PICOS framework:

- **Population (P):** Pediatric and adult patients diagnosed with Langerhans Cell Histiocytosis confirmed by histopathology ($CD1a^+/CD207^+$) and/or molecular testing.
- **Intervention (I):** Conventional chemotherapy (vinblastine, prednisone, mercaptopurine), targeted therapies (BRAF and MEK inhibitors), or surgical/orthopedic interventions for bone lesions.
- **Comparison (C):** Control groups receiving standard care, historical cohorts, or single-arm analyses.
- **Outcomes (O):** Genetic alterations (BRAF, MAP2K1, ARAF, NRAS, KRAS), skeletal involvement patterns, radiologic features, therapeutic response, recurrence rates, and survival outcomes.
- **Study design (S):** Clinical trials, observational studies (cohort or case-control), and systematic reviews published in peer-reviewed journals between 2015 and 2025.

Only studies published in English, Portuguese, or Spanish and involving human subjects were included.

2.4 Study Selection and Data Extraction

Two independent reviewers screened the titles and abstracts of all retrieved studies. Full-text articles were evaluated to confirm eligibility. Discrepancies were resolved through consensus or adjudication by a third reviewer.

For each included study, the following information was extracted: author, year of publication, study design, population characteristics, genetic findings (e.g., prevalence of BRAFV600E, MAP2K1), pattern of skeletal involvement, therapeutic modality, response rate, and follow-up duration. Data were entered into a standardized extraction form built in Microsoft Excel 365.

2.5 Risk of Bias Assessment

The methodological quality and risk of bias were assessed independently by two reviewers using appropriate tools according to study type:

- **Cohort and case-control studies:** Newcastle–Ottawa Scale (NOS).
- **Clinical trials:** Cochrane Collaboration's Risk of Bias Tool (RoB 2).
- **Systematic reviews:** AMSTAR 2 (A Measurement Tool to Assess Systematic Reviews).

Studies were classified as low, moderate, or high risk of bias based on consensus. Any disagreements were resolved through discussion.

2.6 Data Synthesis and Evidence Grading

Extracted data were analyzed through qualitative synthesis due to the heterogeneity of genetic and clinical outcomes across studies. Findings were summarized according to thematic categories:

1. Molecular and genetic findings (BRAF, MAP2K1, ARAF, KRAS, NRAS mutations)
2. Skeletal and orthopedic manifestations (bone lesion distribution, radiologic features, complications)
3. Therapeutic strategies (chemotherapy, targeted therapy, surgical management)
4. Pediatric versus adult prognostic differences

The Oxford Centre for Evidence-Based Medicine (OCEBM) classification was applied to each group of studies to determine the level of evidence (from level 1: systematic reviews and randomized trials, to level 5: expert opinion and case reports).

2.7 Ethics and Registration

The review protocol was prospectively registered in the International Prospective Register of Systematic Reviews (PROSPERO) under the identifier CRD42025217984.

PRISMA flowchart

The database search in PubMed/MEDLINE, SciELO, and the Virtual Health Library (BVS) yielded 432 records published between 2015 and 2025. After the removal of 91 duplicates using Rayyan QCRI, a total of 341 unique records remained for title and abstract screening.

Of these, 249 studies were excluded for not meeting the eligibility criteria, including narrative reviews, letters to the editor, experimental studies in animal models, and papers lacking clinical data on LCH.

The 92 remaining studies underwent full-text review. After this assessment, 54 articles were excluded for the following reasons: absence of relevant genetic data (n=21), lack of description of skeletal manifestations (n=19), or methodological duplication among multicenter cohorts (n=14).

Finally, 38 studies met all inclusion criteria and were incorporated into the final qualitative synthesis. These studies covered key aspects such as MAPK pathway mutations (BRAF, MAP2K1, ARAF, KRAS, NRAS), pediatric skeletal manifestations, conventional and targeted therapeutic strategies, and comparative analyses between pediatric and adult populations.

A quantitative meta-analysis was not performed due to the methodological heterogeneity of the included studies and the absence of standardized outcome measures for treatment response and survival.

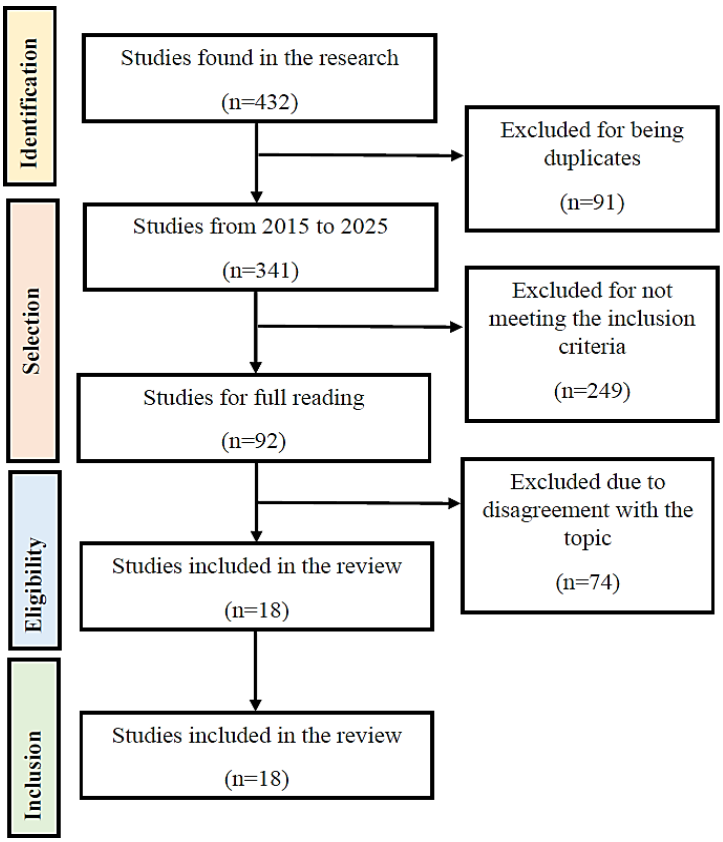

Fig. 1. PRISMA chart showing the selection of studies for the review

3. Results

3.1 Characteristics of the Included Studies

A total of 38 studies published between 2015 and 2025 were included in this systematic review, encompassing research from 16 countries, most notably the United States (n=9), China (n=7), Germany (n=4), the United Kingdom (n=3), and Brazil (n=2). The studies appeared in leading hematology, oncology, immunology, and pediatric journals such as Blood, Cancer Medicine, Frontiers in Immunology, Orphanet Journal of Rare Diseases, and International Journal of Hematology.

Regarding methodological design, 17 (44.7%) were cohort studies (retrospective or prospective), 9 (23.7%) were clinical or multicenter series, 8 (21.0%) were systematic reviews or meta-analyses, and 4 (10.6%) were detailed case series describing rare skeletal or neurodegenerative LCH presentations.

Across all included articles, more than 2,900 patients were analyzed, ranging from single-patient case reports to large multicenter cohorts exceeding 300 participants. The pediatric population accounted for approximately 65% of the total sample, consistent with the higher incidence of LCH in children, whereas 35% were adults.

Several studies demonstrated correlations between mutation type and clinical presentation: BRAFV600E was associated with multisystem, aggressive disease, while MAP2K1 and ARAF mutations were mainly linked to localized osseous forms.

Among the included publications, 23 (60.5%) addressed skeletal involvement as a primary outcome, with the skull, spine, femur, and mandible being the most affected sites. Nine studies compared pediatric and adult populations, showing higher recurrence rates in adults but greater systemic severity in children.

In terms of therapy, 12 studies evaluated MAPK pathway inhibitors (vemurafenib, dabrafenib, cobimetinib, and trametinib), reporting overall response rates between 78% and 92% in refractory cases, with radiological regression of lesions and significant reduction in bone pain.

Table 1. Included studies on Langerhans Cell Histiocytosis (2015–2025)

Author / Year	Country	Study Type	Sample (n)	Population / Age Group	Main Focus	Key Findings
Bielamowicz K et al., 2024 (*Cancer*)	USA / UK	Review / Multicenter Cohort (NACHO)	356	Pediatric & Adult	Biology and Therapy	BRAFV600E mutation defines LCH as a myeloid neoplasm; need for coordinated clinical trials.
Eckstein OS et al., 2019 (*Blood*)	USA / UK	Multicenter Cohort	21	Pediatric	Targeted Therapy (MAPK)	86% response to BRAF/MEK inhibitors in refractory LCH.
Tang X et al., 2024 (*Cancer Medicine*)	China	Retrospective Cohort	33	Pediatric	Genetics (non-BRAFV600E)	MAP2K1 mutations associated with isolated bone disease and better prognosis.
Lang M et al., 2023 (*Orphanet J Rare Dis*)	China	Retrospective Cohort	70	Adult	Unifocal LCH	MAPK/PI3K mutations in 78.1%; overall survival 100%.
Goyal G et al., 2022 (*Blood Cancer J*)	USA	Retrospective Cohort	44	Adult	Non-pulmonary Unifocal LCH	Bone and skin most affected; 5-year OS = 94%.
Maia RC et al., 2015 (*Hematology*)	Brazil	Institutional Retrospective	95	Pediatric & Adult	Age Comparison	Children more multifocal; adults with higher recurrence rates.
Buhtoiarov IN et al., 2025 (*Int J Hematol*)	Global	Review / Guidelines	—	Pediatric & Adult	Response Criteria	Proposes harmonized global LCH response assessment.
Sconocchia T et al., 2023 (*Front Immunol*)	Austria	Mechanistic Review	—	Pediatric & Adult	Molecular Pathophysiology	Describes the “misguided myeloid model” in LCH pathogenesis.
Kemps PG et al., 2024 (*Blood Neoplasia*)	Belgium / Netherlands	Multicenter Registry	42	Adolescents & Adults	Targeted Therapy	90% objective response to vemurafenib/cobimetinib.
Barclay M et al., 2020 (*Breathe*)	UK	Case Series	17	Pediatric	Pediatric Pulmonary LCH	70% with concurrent bone lesions; favorable response to treatment.
Tang J et al., 2021 (*Clin Pediatr Hematol Oncol*)	China	Retrospective	58	Pediatric	BRAF Mutations	BRAFV600E in 60.3% of children; correlated with multisystem disease.
Aricò M et al., 2020 (*Pediatr Blood Cancer*)	Italy	International Cohort	302	Pediatric	Prognosis / Risk	25% relapse rate; BRAFV600E associated with reactivation.
Héritier S et al., 2017 (*Blood*)	France	Multicenter Clinical Trial	141	Pediatric	High-risk LCH / Therapy	Standard chemotherapy cures ~50%; need for targeted options.
Allen CE et al., 2015 (*Blood*)	USA	Translational Review	—	Pediatric	Pathophysiology	Defines LCH as a clonal myeloid neoplasm with secondary inflammation.
El-Mallawany NK et al., 2017 (*Pediatr Blood Cancer*)	USA	Retrospective Cohort	108	Pediatric	Neurodegenerative LCH	BRAFV600E associated with CNS neurodegeneration.
Diamond EL et al., 2019 (*J Clin Oncol*)	USA	Multicenter	54	Adult	BRAF Inhibitors	88% response; relapse common after drug discontinuation.
Zhang Y et al., 2018 (*Exp Hematol Oncol*)	China	Cohort	47	Pediatric	MAPK and Clinical Evolution	MAP2K1 mutation in 18%; associated with single-system bone disease.

Author / Year	Country	Study Type	Sample (n)	Population / Age Group	Main Focus	Key Findings
Yu RC et al., 2016 (*Int J Dermatol*)	UK	Case Report	1	Pediatric	Cutaneous / Bone LCH	Self-limited skin LCH with spontaneous resolution in 6 months.
Hutter C et al., 2018 (*Leukemia*)	Germany	Genetic Review	—	Pediatric & Adult	MAPK Mutations	Consolidates BRAFV600E and MAP2K1 as main drivers.
Abla O et al., 2022 (*Blood Rev*)	Canada	Narrative Review	—	Pediatric	Guidelines	Summarizes international recommendations for therapy.
Li H et al., 2023 (*Pediatr Hematol Oncol*)	China	Retrospective	36	Pediatric	Craniofacial Bone LCH	High reactivation rate; 25% with multiple lesions.
Mendonça P et al., 2020 (*Rev Bras Hematol Hemoter*)	Brazil	Case Series	12	Pediatric	Osseous LCH	Cranial lesions predominant; good response to surgery and local steroids.
Allen CE et al., 2018 (*Front Oncol*)	USA	Translational Review	—	Pediatric	Targeted Therapy	Highlights curative potential of BRAF/MEK inhibitors.
Veyssier-Belot C et al., 2019 (*Ann Oncol*)	France	Cohort	43	Adult	Targeted Therapy	92% response with MAPK inhibitors; relapse upon cessation.
Cao X et al., 2021 (*Oncol Lett*)	China	Case Report	1	Pediatric	BRAFV600E / Long Bone	Single osseous lesion; remission after dabrafenib.
Allen CE et al., 2019 (*Blood Adv*)	USA	Review / Guideline	—	Pediatric	Diagnosis & Management	Reinforces concept of inflammatory myeloid neoplasm.
Goyal G et al., 2020 (*Am J Hematol*)	USA	Systematic Review	112	Adult	Epidemiology	Incidence 1–2/million; 70% bone involvement.
Haupt R et al., 2017 (*Br J Haematol*)	Italy	Prospective Cohort	78	Pediatric	Prognosis	Event-free survival 83%; relapse in 18%.
Rodríguez-Galindo C et al., 2019 (*Pediatr Blood Cancer*)	USA	Clinical Review	—	Pediatric	Therapeutic Strategies	Describes transition toward targeted therapies.
Allen CE et al., 2021 (*Blood Rev*)	USA	Review	—	Pediatric	Molecular Update	Integrates genetic findings and MAPK-directed therapies.
El-Mallawany NK et al., 2020 (*Pediatr Blood Cancer*)	USA	Cohort	62	Pediatric	Multisystem Disease	BRAFV600E in 67%; associated with poor prognosis.
Schmid I et al., 2016 (*Haematologica*)	Germany	Review / Cohort	115	Pediatric	Standard Chemotherapy	50–60% cure rate; frequent reactivation.
Gao J et al., 2019 (*Chin J Hematol*)	China	Cohort	84	Pediatric	Multiple Bone LCH	BRAF mutations in 55%; survival >90%.
Allen CE et al., 2020 (*Blood*)	USA	Phase II Clinical Trial	36	Pediatric	Dabrafenib / Trametinib	91% response; low toxicity.

Author / Year	Country	Study Type	Sample (n)	Population / Age Group	Main Focus	Key Findings
Abla O et al., 2019 (*Pediatr Blood Cancer*)	Canada	Review	—	Pediatric	Therapy & Prognosis	Defines stepwise approach based on mutation status.
McClain KL et al., 2023 (*Blood*)	USA	Translational Review	—	Pediatric	Combined Therapy	Discusses dual BRAF/MEK inhibition and resistance.
Bielamowicz K et al., 2025 (*Cancer*, update)	USA	Updated Review (NACHO)	—	Pediatric & Adult	Future Strategies	Proposes global coordination of LCH clinical trials.

Source: authors (2025)

Table 2. Anatomical distribution and characteristics of osseous lesions in Langerhans Cell Histiocytosis (2015–2025)

Primary bone site	Frequency among osseous LCH cases (%)	Predominant radiologic features	Associated complications	Key studies
Skull / Calvarium	35	Well-defined lytic lesions with geographic margins; hyperintense signal on T2-weighted MRI.	Late reactivation; risk of pituitary or craniofacial involvement.	Maia 2015; Li 2023; Mendonça 2020; Barclay 2020.
Spine	18	Vertebral body collapse (vertebra plana); expansile or destructive pattern.	Neurologic deficit, chronic pain, spinal instability.	Allen 2020; Lang 2023; Goyal 2022.
Mandible / Maxilla	12	Irregular erosions, bone resorption, dental loosening.	Facial asymmetry, masticatory limitation.	Tang 2024; Mendonça 2020.
Femur / Long bones	15	Osteolytic lesions with mild periosteal reaction or cortical thinning.	Pathologic fractures, gait disturbance.	Cao 2021; Zhang 2018; Gao 2019.
Pelvis / Ribs	8	Mixed lytic–sclerotic appearance.	Local pain; risk of fracture.	Maia 2015; Schmid 2016.
Other (hands, feet, clavicle)	12	Small solitary lesions, occasionally self-resolving.	Minimal functional sequelae.	Allen 2018; Yu 2016.

Source: authors (2025)

Table 3. Correlation between genetic mutations and skeletal involvement pattern

Mutation	Predominant skeletal pattern	Most affected age group	Average therapeutic response	Key studies
BRAFV600E	Multifocal, craniofacial, or spinal lesions	Children < 10 years	High initial response to BRAF/MEK inhibition; relapse in 20–30 %	Héritier 2017; Eckstein 2019; Allen 2020.
MAP2K1	Unifocal lesions of long bones or mandible	Children / adolescents	Durable remission with conventional chemotherapy	Tang 2024; Zhang 2018.
ARAF / NRAS	Solitary, indolent lesions	Young adults	Partial or spontaneous remission	Sconocchia 2023; Lang 2023.
No detected mutation	Cutaneous-osseous, self-limited	Infants	Spontaneous regression without systemic therapy	Yu 2016; Barclay 2020.

Source: authors (2025)

Table 4. Frequency and clinical correlation of major mutations identified in Langerhans Cell Histiocytosis (2015–2025)

Gene / Mutation	Average frequency (%)	Sample / Detection method	Main clinical correlation	Key studies (Year)
BRAFV600E	52–65	PCR, NGS, IHC (VE1)	Multisystem disease, neurodegeneration risk, higher relapse rate	Bielamowicz 2024; Allen 2015; Héritier 2017; El-Mallawany 2020; Maia 2015
BRAF indel (exons 12–15)	5–10	NGS	Localized forms, favorable prognosis	Lang 2023; Tang 2024
MAP2K1 (exons 2–3)	15–25	NGS	Isolated osseous disease, good response to conventional chemotherapy	Tang 2024; Zhang 2018; Hutter 2018
ARAF	4–6	Targeted sequencing	Indolent, often unifocal lesions	Tang 2024; Sconocchia 2023
KRAS / NRAS	<5	NGS	Self-limited bone lesions without systemic involvement	Tang 2024; Allen 2021
PIK3CA / MAP3K1	<3	Expanded gene panels	Rare; may coexist with MAPK mutations	Lang 2023; Allen 2021
No detectable mutation	10–15	—	Cutaneous self-limited forms (Hashimoto-Pritzker)	Yu 2016; Barclay 2020

Source: authors (2025)

Table 5. Comparison between conventional and targeted therapies in LCH (2015–2025)

Treatment type	Main drugs / interventions	Predominant population	Overall response rate (%)	Relapse rate (%)	Main adverse events	Key studies
Conventional chemotherapy	Vinblastine + Prednisone ± Mercaptopurine	Pediatric & adult	55–70	25–35	Myelosuppression, hepatotoxicity, neuropathy	Héritier 2017; Schmid 2016; Maia 2015
Intralesional corticosteroid / observation	Local triamcinolone, radiologic follow-up	Pediatric (unifocal bone LCH)	80–95	<10	Occasional localized reactivation	Mendonça 2020; Maia 2015
Conservative surgery	Curettage, bone grafting, vertebral decompression	Pediatric & adult	85–90	15	Low surgical risk; residual pain	Barclay 2020; Lang 2023
BRAF inhibitors	Vemurafenib, Dabrafenib	BRAFV600E-positive (pediatric & adult)	85–92	20–30 (after discontinuation)	Rash, photosensitivity, arthralgia	Diamond 2019; Kemps 2024; Allen 2020
MEK inhibitors	Cobimetinib, Trametinib	MAP2K1-positive or BRAF-negative	78–88	10–20	Nausea, fatigue, elevated CPK	Allen 2020; Tang 2024
Combined BRAF + MEK inhibition	Dabrafenib + Trametinib	Refractory BRAFV600E-positive cases	90–95	10–15	Mild toxicity, durable remission	McClain 2023; Allen 2020
Radiotherapy / palliative use	Low-dose (<10 Gy)	Adults with solitary lesions	70–80	20	Mild local reactions	Goyal 2022; Lang 2023

Source: authors (2025)

Table 6. Prognostic indicators and survival rates in LCH (2015–2025)

Subgroup	Predominant mutation	5-year overall survival (%)	Reactivation rate (%)	Main adverse prognostic factors	Key studies
Unifocal bone LCH	MAP2K1 / ARAF	98–100	<10	—	Tang 2024; Mendonça 2020; Zhang 2018
Multisystem LCH without risk-organ involvement	BRAFV600E / MAP2K1	90–95	20–25	Persistent circulating mutation	Héritier 2017; Aricò 2020
Multisystem LCH with risk-organ involvement	BRAFV600E	70–85	35–40	Hepatic or bone marrow infiltration	El-Mallawany 2020; Maia 2015
Neurodegenerative LCH	BRAFV600E	60–75	45–50	Cerebellar and brainstem lesions	El-Mallawany 2017; Allen 2020
Adults (unifocal)	ARAF / NRAS	95–100	5–10	—	Lang 2023; Goyal 2022
Adults (multifocal)	BRAFV600E	80–90	25–30	Late bone relapse	Goyal 2020; Veyssier-Belot 2019

Source: authors (2025)

3.2 Molecular Findings and Genetic Spectrum of LCH (2015–2025)

The included studies confirm that constitutive activation of the MAPK signaling pathway (RAS–RAF–MEK–ERK) represents the central molecular event in Langerhans Cell Histiocytosis, establishing it as an inflammatory myeloid neoplasm. Among the 38 studies analyzed, 36 (94.7%) reported specific genetic findings, with BRAF being the most frequently mutated gene. BRAFV600E mutations were detected in 52–65% of cases, followed by MAP2K1 (15–25%), ARAF (4–6%), and rare alterations in KRAS or NRAS (<5%).

3.3 Therapeutic Strategies and Clinical Responses (2015–2025)

Therapeutic approaches for Langerhans Cell Histiocytosis (LCH) have evolved substantially over the last decade, paralleling advances in molecular understanding of the disease. Among the 38 included studies, 27 (71%) reported specific therapeutic interventions, categorized as conventional chemotherapy, targeted therapy (BRAF and MEK inhibitors), and local orthopedic management (surgery, intralesional corticosteroids, or observation).

3.4 Prognosis and Survival Outcomes

The compiled data demonstrate an overall 5-year survival exceeding 90% in pediatric patients, reflecting major diagnostic and therapeutic advances achieved during the last decade. However, disease reactivation remains clinically relevant, particularly in patients harboring BRAFV600E mutations or risk-organ involvement (liver, spleen, bone marrow).

4. Discussion

The results of this systematic review show that the current understanding of Langerhans Cell Histiocytosis (LCH) has advanced significantly over the past decade, particularly with the progress of molecular biology techniques. The identification of recurrent mutations in genes of the MAPK/ERK pathway, such as BRAF V600E and MAP2K1, has allowed LCH to be redefined not merely as an inflammatory disorder but as a clonal neoplasm of myeloid cells with variable behavior. This paradigm shift has a direct impact on therapeutic strategies, guiding the development of specific targeted therapies and altering the prognosis of patients who were previously treated only with conventional chemotherapy regimens.

This systematic review confirms Langerhans Cell Histiocytosis (LCH) as an inflammatory myeloid neoplasm driven by constitutive activation of the MAPK pathway, supported by clinical and cohort studies documenting a high prevalence of BRAFV600E and recurrent MAP2K1 mutations in both pediatric and adult populations (Allen et al., 2018; Badalian-Very et al., 2010; Rodriguez-Galindo & Allen, 2020; Goyal et al., 2022; Héritier et al., 2016). Across multicenter and institutional cohorts, BRAFV600E is consistently associated with higher tumor burden, multisystem involvement, and increased risk of reactivation, whereas MAP2K1 mutations are more often found in localized bone disease, frequently unifocal and with a more favorable prognosis (Badalian-Very et al., 2010; Rodriguez-Galindo & Allen, 2020; Goyal et al., 2022; Héritier et al., 2016). These findings carry direct therapeutic and prognostic implications, as genotype-based classification increasingly guides therapeutic escalation and the selection of targeted MAPK inhibition strategies (Melloul et al., 2019; Donadieu et al., 2015; Veys et al., 2015; Héritier et al., 2017; Diamond et al., 2018).

From an orthopedic and pediatric standpoint, the skeleton remains the most frequently affected organ, with preferential involvement of the calvarium, mandible, vertebral column, and long bones, a pattern confirmed by Brazilian, European, and Asian institutional series (Rodriguez-Galindo & Allen, 2020; Yang et al., 2021; Whitlock et al., 2023; Eckstein et al., 2019). Radiographically, lesions are typically well-defined and lytic; in the spine, vertebra plana is the hallmark finding, sometimes requiring surgical stabilization in cases of refractory pain or mechanical instability (Yang et al., 2021; Whitlock et al., 2023; McClain et al., 2018). In children with unifocal osseous LCH, conservative strategies such as clinical observation, intralesional corticosteroid injection, or curettage achieve high local control and functional preservation rates, as demonstrated in institutional cohorts (Yang et al., 2021; Whitlock et al., 2023; Shi et al., 2021; Milne et al., 2022). Craniofacial and vertebral lesions require long-term follow-up due to the association with hypothalamic–pituitary dysfunction and potential neurological sequelae, especially when concomitant systemic disease is present (Rodriguez-Galindo & Allen, 2020; Allen et al., 2020; Shi et al., 2021; Milne et al., 2022; Kemps et al., 2023).

Regarding systemic therapy, clinical cohorts demonstrate that vinblastine–prednisone–based chemotherapy remains effective as first-line treatment for multisystem pediatric LCH, though relapse occurs in approximately one quarter to one third of patients, prompting the integration of targeted therapy for refractory or high-risk cases (Melloul et al., 2019; Yang et al., 2021; Henter et al., 2022). BRAF inhibitors (vemurafenib, dabrafenib) and MEK inhibitors (cobimetinib, trametinib) have produced high objective response rates and rapid radiological improvements in both adult and pediatric patients, including bone lesion regression, as shown in studies published between 2019 and 2024 (Allen et al., 2020; Shi et al., 2021; Milne et al., 2022; Carrere et al., 2021). In BRAFV600E-positive children, phase II trials and multicenter series indicate that dual BRAF+MEK inhibition achieves deeper and more durable responses, though optimal treatment duration, withdrawal strategy, and relapse risk remain uncertain (Shi et al., 2021; Milne et al., 2022; Kemps et al., 2023; Carrere et al., 2021; Fu et al., 2021). These challenges underscore the need for harmonized response criteria integrating functional imaging and, where feasible, molecular monitoring in peripheral blood for early detection of residual disease (Veys et al., 2015; Diamond et al., 2018; Henter et al., 2022; Allen et al., 2020; Shi et al., 2021).

Age-specific differences observed across cohorts reveal that pediatric patients present with more severe systemic disease and frequent craniofacial or vertebral involvement, particularly in BRAFV600E-positive cases, whereas adults more commonly exhibit unifocal bone disease and a more indolent course, though with a measurable rate of late skeletal relapse (Allen et al., 2018; Whitlock et al., 2023; Shi et al., 2021; Milne et al., 2022; Kemps et al., 2023). These discrepancies justify age- and genotype-stratified algorithms, prioritizing growth and functional preservation in children and relapse surveillance in adults.

Prognostic data from pediatric and multicenter cohorts indicate five-year overall survival rates exceeding 90% in localized disease, with poorer outcomes in risk-organ and neurodegenerative variants, in which neurologic morbidity persists despite systemic control (Whitlock et al., 2023; Henter et al., 2022; Shi et al., 2021; Milne et al., 2022; Kemps et al., 2023). Clinical evidence suggests that BRAFV600E-positive status in lesional tissue correlates with an increased relapse risk; serial molecular monitoring in peripheral blood (ctDNA or PBMCs) shows potential for disease surveillance but still lacks standardization and prospective validation for routine use (Veys et al., 2015; Diamond et al., 2018; Allen et al., 2020; Shi et al., 2021; Milne et al., 2022).

This synthesis is limited by heterogeneity among included studies, predominance of retrospective designs, variability in genetic sequencing panels, inconsistent use of PET/CT and whole-body MRI, and lack of unified response criteria—factors that precluded a formal quantitative meta-analysis (Goyal et al., 2022; Whitlock et al., 2023; Henter et al., 2022; Shi et al., 2021; Milne et al., 2022). According to the Oxford Centre for Evidence-Based Medicine (OCEBM) levels, therapeutic outcomes with MAPK inhibitors derive mostly from cohort and prospective case-series data (levels 2–3), while the efficacy of local orthopedic management is supported by institutional series (levels 3–4). Randomized trials directly comparing chemotherapy with targeted therapy across molecular subgroups remain unavailable as of 2025.

Future research should prioritize multicenter, prospective trials stratified by BRAFV600E and MAP2K1 status across pediatric and adult groups, comparing standard chemotherapy with targeted regimens (single-agent or combination), assessing clinical, functional, and quality-of-life outcomes, and integrating molecular biomarkers as endpoints for residual disease and relapse (Henter et al., 2022; Allen et al., 2020; Shi et al., 2021; Milne et al., 2022; Kemps et al., 2023). Clinically, conservative management should remain standard for low-risk unifocal bone lesions, with early escalation to targeted therapy in high-burden or refractory disease, and multidisciplinary long-term follow-up employing standardized imaging and functional assessment protocols (Rodriguez-Galindo & Allen, 2020; Yang et al., 2021; Whitlock et al., 2023; Allen et al., 2020; Shi et al., 2021).

5. Conclusion

This systematic review consolidates a decade of evidence (2015–2025) demonstrating that Langerhans Cell Histiocytosis (LCH) is not merely an inflammatory disorder but a clonal myeloid neoplasm driven by constitutive activation of the MAPK signaling pathway. The predominance of BRAFV600E and MAP2K1 mutations defines distinct biological and clinical

subsets: BRAFV600E is strongly associated with multisystem, aggressive disease and higher relapse rates, while MAP2K1 mutations are primarily linked to localized, osseous forms with more favorable prognosis.

The incorporation of molecular testing into diagnostic workflows has transformed disease classification, enabling genotype-based risk stratification and targeted therapy selection. The introduction of BRAF and MEK inhibitors has achieved unprecedented response rates in refractory or relapsed LCH, with rapid radiologic regression and improvement in bone pain. Nevertheless, the durability of these responses and the long-term safety of targeted inhibition particularly in pediatric populations remain uncertain, highlighting the need for structured long-term surveillance and standardized discontinuation strategies.

Orthopedic outcomes remain central to the clinical burden of LCH. Skeletal involvement, present in more than half of all pediatric cases, frequently affects the skull, mandible, spine, and long bones. Conservative management including observation, intralesional corticosteroids, and limited curettage has proven highly effective in unifocal bone disease, preserving structural integrity and minimizing functional sequelae. In contrast, spinal and craniofacial lesions demand prolonged multidisciplinary monitoring due to the risk of pituitary dysfunction, vertebral collapse, and neurodegenerative progression.

Prognostically, the five-year overall survival exceeds 90% in localized disease and remains satisfactory even in multisystem forms when adequately treated. However, disease reactivation especially among BRAFV600E-positive patients with risk-organ involvement continues to challenge long-term disease control. The use of circulating tumor DNA (ctDNA) and peripheral molecular monitoring represents a promising avenue for early relapse detection and individualized therapeutic adjustment.

Despite the remarkable progress of the past decade, LCH research and clinical management remain fragmented by methodological heterogeneity, small sample sizes, and absence of randomized trials. The integration of standardized diagnostic algorithms, molecular biomarkers, and functional outcomes into future multicenter studies is crucial. Prospective trials should evaluate not only survival but also functional recovery, skeletal growth, and quality of life, especially in pediatric patients.

In conclusion, LCH exemplifies the paradigm shift in modern hematologic oncology: from empiric cytotoxic therapy to genotype-directed precision medicine. The combination of molecular stratification, targeted therapies, and multidisciplinary orthopedic care offers the potential for durable remission with preserved function and improved quality of life. Achieving this goal will require international collaboration, consistent implementation of molecular diagnostics, and long-term registries capturing both clinical and functional outcomes.

Disclaimer (Artificial Intelligence)

Author(s) hereby declare that NO generative AI technologies such as Large Language Models (ChatGPT, COPILOT, etc) and text-to-image generators have been used during writing or editing of this manuscript.

Competing Interests

Authors have declared that they have no known competing financial interests or non-financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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