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| cLINICAL UTILITY OF MOLECULAR TESTING IN malignant histiocytoses  DIAGNOSTIC utility  Histiocytic and dendritic cell neoplasms are driven by activing mutations or gene fusions affecting the MAPK pathway1.  These include mutations in *BRAF* (frequently Val600Glu), *NRAS*, *KRAS*, *ARAF* and *MAP2K1*1-9. *NF1* and *PTPN11* genes may also be mutated9 but are not targeted by this gene panel.  Gene fusions that have been observed include those involving *BRAF*, *ALK* and *NTRK1*1 however these are not detected by this assay.  The variant allele frequency of detectable mutations is variable but may be low, reflecting the cellular heterogeneity of histiocytic lesions1.  A subset of histiocytic and dendritic cell neoplasms have clonal immunglobulin rearrangements and/or aberrant somatic hypermutation (particularly when associated with a low-grade B cell lymphoma), most likely constituting examples of transdifferentiation9,10.  BIOMARKERS OF RESPONSE TO THERAPY  Significant clinical response in multiple histiocytic and dendritic cell neoplasm subtypes have been observed to agents targeting the MAPK pathway such as BRAF inhibitors and MEK inhibitors1,11-13.  REFERENCES  **1.** Diamond EL, et al. Diverse and Targetable Kinase Alterations Drive Histiocytic Neoplasms. *Cancer Discov* 2016; **6**(2): 154-65. **2.** Chakraborty R, et al. Mutually exclusive recurrent somatic mutations in MAP2K1 and BRAF support a central role for ERK activation in LCH pathogenesis. *Blood* 2014; **124**(19): 3007-15. **3.** Brown NA, et al. High prevalence of somatic MAP2K1 mutations in BRAF V600E-negative Langerhans cell histiocytosis. *Blood* 2014; **124**(10): 1655-8. **4.** Garces S, et al. Mutually exclusive recurrent KRAS and MAP2K1 mutations in Rosai-Dorfman disease. *Mod Pathol* 2017; **30**(10): 1367-77. **5.** Badalian-Very G, et al. Recurrent BRAF mutations in Langerhans cell histiocytosis. *Blood* 2010; **116**(11): 1919-23. **6.** Haroche J, et al. High prevalence of BRAF V600E mutations in Erdheim-Chester disease but not in other non-Langerhans cell histiocytoses. *Blood* 2012; **120**(13): 2700-3. **7.** Go H, et al. Frequent detection of BRAF(V600E) mutations in histiocytic and dendritic cell neoplasms. *Histopathology* 2014; **65**(2): 261-72. **8.** Giancarlo F, et al. BRAF V600E mutation detected in a case of Rosai-Dorfman disease. *Haematologica* 2018; **103**(8): e377-e9. **9.** Shanmugam V, et al. Identification of diverse activating mutations of the RAS-MAPK pathway in histiocytic sarcoma. *Modern Pathology* 2019; **32**(6): 830-43. **10.** West DS, et al. Clonally related follicular lymphomas and Langerhans cell neoplasms: expanding the spectrum of transdifferentiation. *Am J Surg Pathol* 2013; **37**(7): 978-86. **11.** Durham BH, et al. Histiocytic neoplasms in the era of personalized genomic medicine. *Curr Opin Hematol* 2016; **23**(4): 416-25. **12.** Haroche J, et al. Reproducible and sustained efficacy of targeted therapy with vemurafenib in patients with BRAF(V600E)-mutated Erdheim-Chester disease. *J Clin Oncol* 2015; **33**(5): 411-8. **13.** Hyman DM, et al. Vemurafenib in Multiple Nonmelanoma Cancers with BRAF V600 Mutations. *N Engl J Med* 2015; **373**(8): 726-36. |