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| cLINICAL UTILITY OF MOLECULAR TESTING IN  juvenile myelomonocytic leukaemia  DIAGNOSTIC utility  Juvenile myelomonocytic leukaemia (JMML) is a myeloproliferative neoplasm of childhood, characterised by granulocytic and monocytic proliferation and the absence of t(9;22) *BCR*::*ABL1* fusion gene1.  JMML is characterised by mutations involved in RAS pathway activation in >90% of cases, including mutations in *PTPN11* (35%-40%), *NRAS* (15%-25%), *KRAS* (15%-20%), *CBL* (10%-15%) and *NF1* (5%-10%). These five canonical RAS pathway mutations are generally mutually exclusive1.  Rarely, JMML could occur due to a non-canonical RAS pathway variant, or gene fusions leading to upstream RAS pathway activation1.  Approximately 25% of JMML cases have germline predisposition, occurring as a part of inherited syndromes such as neurofibromatosis type 1 (NF1), or Noonan (or Noonan-like) syndrome due to *PTPN11* or *CBL* mutations1.  In the setting of germline *NF1* and CBL mutations, JMML often develops after acquired loss of heterozygosity (LOH).  Secondary mutations occurring in addition to the canonical RAS pathway driver mutations occur in approximately 30% of cases and are generally subclonal1,2. These include ‘second hits’ in an additional RAS pathway-associated gene, as well as mutations in *SETBP1*, *JAK3*, *ASXL1* and *SH2B3*1,3,4. Secondary mutations occur most commonly in *PTPN11*-mutant JMML2.  Cytogenetic abnormalities are found in up to 30% of patients. Monosomy 7 is the most frequent cytogenetic finding (20% of patients) and is often identified in *KRAS*-mutant JMML2.  PROGNOSTIC utility  Recent studies suggest that the five canonical RAS pathway driver mutations initiate disease by RAS hyperactivation, but are not independently prognostic of outcome2.  The presence of secondary mutations appears to contribute to disease progression, and patients with more than 1 mutation have a worse prognosis2,4,5.  Acquisition of secondary somatic mutations in *SETBP1* mutations has been associated with inferior outcomes in JMML2,4,5  A hypermethylated DNA signature is an independent predictor of poor outcome5.  REFERENCES  **1.** WHO Classification of Tumours Editorial Board. Haematolymphoid tumours. Lyon (France): International Agency for Research on Cancer; forthcoming. (WHO classification of tumours series, 5th ed.; vol. 11). https://publications.iarc.fr. **2.** Wintering A, et al. Juvenile myelomonocytic leukemia in the molecular era: a clinician's guide to diagnosis, risk stratification, and treatment. *Blood Adv* 2021; **5**(22): 4783-93. **3.** Sugimoto Y, et al. Spectrum of molecular defects in juvenile myelomonocytic leukaemia includes ASXL1 mutations. *Br J Haematol* 2010; **150**(1): 83-7. **4.** Sakaguchi H, et al. Exome sequencing identifies secondary mutations of SETBP1 and JAK3 in juvenile myelomonocytic leukemia. *Nat Genet* 2013; **45**(8): 937-41. **5.** Stieglitz E, et al. Subclonal mutations in SETBP1 confer a poor prognosis in juvenile myelomonocytic leukemia. *Blood* 2015; **125**(3): 516-24. |