Guideline for management of non-Down syndrome neonates with a myeloproliferative disease on behalf of the I-BFM AML Study Group and EWOG-MDS^

In neonates with myeloid hyperproliferation, apart from benign causes, Down syndrome (DS) related transient abnormal myelopoiesis (TAM), acute myeloid leukemia (AML) and juvenile myelomonocytic leukemia (JMML) are considered.[1-3] Besides TAM, rarely, non-DS related transient myeloproliferative diseases occur, making clinical decisions challenging.[4] TAM, according to World Health Organization (WHO) classification, only applies to children with (mosaic) Down syndrome.[5] In the past, different terminology has been used in non-DS patients, such as transient myeloproliferative disease (TMD) and transient leukemia. Since distinction from TAM is important, and it is challenging to determine whether this disease will be transient, the consensus group introduced the novel term 'infantile myeloproliferative disease' (IMD), in order to distinguish it from TAM. Both TAM and IMD can usually be managed with a 'watch and wait' strategy, while most full-blown AML or JMML cases require intensive treatment. We collected rare IMD cases from study groups collaborating in the International Berlin-Frankfurt-Münster AML Study Group (I-BFM AML SG). In addition, we reviewed the literature for neonatal cases of malignant myeloid hyperproliferation without DS. Based on these data, we developed, together with I-BFM AML SG and the European Working Group of Myelodysplastic syndromes in Childhood (EWOG-MDS) members, by consensus, clinical recommendations for the diagnostic approach and current adequate classification of malignant myeloid hyperproliferation in infancy. This is meant guiding clinicians in choosing the right strategy, i.e., whether to 'watch and wait' or start highly intensive treatment in individual cases.

We centrally collected detailed information from databases of I-BFM AML SG collaborators to identify clinical and genetic characteristics of additional, not yet reported, cases with IMD. Children younger than one year, diagnosed between 1990 and 2020, were included. Ethical approval and informed consent were obtained by each study group individually. Registration and data forms involved clinical features, hematological data, morphology and immunology, treatment, outcome and follow-up data. Available written reports of cytogenetic findings were collected and centrally reviewed by Dr. A. Buijs (University Medical Center Utrecht) and Prof. Dr. S. Raimondi (St. Jude Children's Hospital, Memphis). We identified 15 new cases of IMD with, in some cases, novel recurrent molecular aberrations (Table 1). No germline aberrations were identified; however, standardized diagnostics did not always include germline testing. Thirteen patients had somatic trisomy 21 (T21) with or without a *GATA1* mutation, one patient had low mosaic somatic trisomy 8 and a *SETD2* mutation and one patient was not tested for somatic aberrations. Notably, among the 15 newly-added cases, in four patients, evaluation for *GATA1* mutations was not performed.

The search for available literature and case reports of non-DS transient leukemia was performed in the PubMed database. Publications indexed until 1 January 2021 were included. Search terms included TMD, TAM and transient leukemia, used separately and combined with non-Down, non-Down syndrome, and without Down syndrome. A cross-reference check was performed in key articles. We included 23 articles that described one or multiple patients that met our search criteria (Table 2). Unfortunately, in these cases too, routine testing of somatic *GATA1* and potential germline mosaic T21 was not always performed.

Congenital/infant leukemia accounts for <1% of all childhood leukemias.[6] When the rare event occurs in which a neonate is suspected of myeloid leukemia, TAM or IMD, clinical decision making can be challenging. Here, representatives of the I-BFM AML SG, together with JMML experts from the EWOG MDS, provide a clinically-applicable consensus of diagnostic logistics for children younger than six weeks. This is based on literature and newly-added cases from our international survey, which may support clinical decision-making in individual cases (Figure 1). During two meetings with leading members from both the I-BFM AML SG and EWOG MDS, relevant literature was discussed and expert experience shared. We reached consensus on diagnostic strategies of neonates with myeloproliferation.

The differential diagnosis of myeloproliferation in infants includes, apart from (congenital) infections and other stressors, JMML, AML, TAM and other types of IMD.[4,6] More frequent benign underlying conditions should be seriously considered before diagnosing a neonate with leukemia and beginning intensive treatment (Figure 1). A medical history and physical examination are important to reveal initial clues regarding infectious causes, other factors inducing stress-hematopoiesis and genetic predisposition (presence of dysmorphic and congenital abnormalities). A physical examination will also reveal hepatosplenomegaly, fluid accumulation and/or skin infiltration. A total blood count and morphological assessment of the peripheral blood smear carried out by an experienced hematologist or morphologist in an expert laboratory are mandatory, and peripheral blood immunophenotyping is, as a minimum measure, advised.[4]

If a malignant condition is conceivable, the most important challenge is to discriminate a rare transient case, where a 'watch and wait' strategy may be justified, from an aggressive leukemia subtype that may require intensive treatment in a limited time span. First, a distinction between megakaryocytic and non-megakaryocytic leukemia is important, based on the morphology and immunophenotyping of the peripheral blood blasts. Megakaryocytic hyperproliferation (French-American-British - FAB - classification M7) can be recognized by moderately basophilic agranular cytoplasm with blebs on morphology, combined with expression of CD41, CD42 and/or CD61 on flow cytometry.[5]

In case of megakaryocytic hyperproliferation, germline T21 and *GATA1* mutations may point towards TAM. TAM blasts can also present without megakaryocytic markers, FAB M0 (undifferentiated).[7] In TAM, early onset and hepatosplenomegaly with monoclonal megakaryocytic hyperproliferation with T21 and a *GATA1* mutation can be confirmed.[8] The origin of TAM lies in the fetal liver which is why, in most cases, peripheral blood sampling is sufficient for a diagnosis and a bone marrow puncture is unnecessary.[1] Without life-threatening disease, a 'watch and wait' policy with close monitoring, including regular physical examination and blood counts, is justified.[8] Low-dose cytarabine treatment is advised in case of multiorgan failure, high WBC >100 x 10^9/l, hepatopathy (high bilirubin/transaminases, ascites), severe hepatosplenomegaly, hydrops fetalis, pleural or pericardial effusions, renal failure, or disseminated intravascular coagulation.[8] This treatment does not prevent the development of ML-DS (myeloid leukemia related to Down syndrome), but substantially reduces mortality in symptomatic patients.[9] After remission, follow-up is advised every three months until the age of four years, because of a 20% chance of ML-DS development during that life span.[8] ML-DS requires more intensive treatment, however this treat-

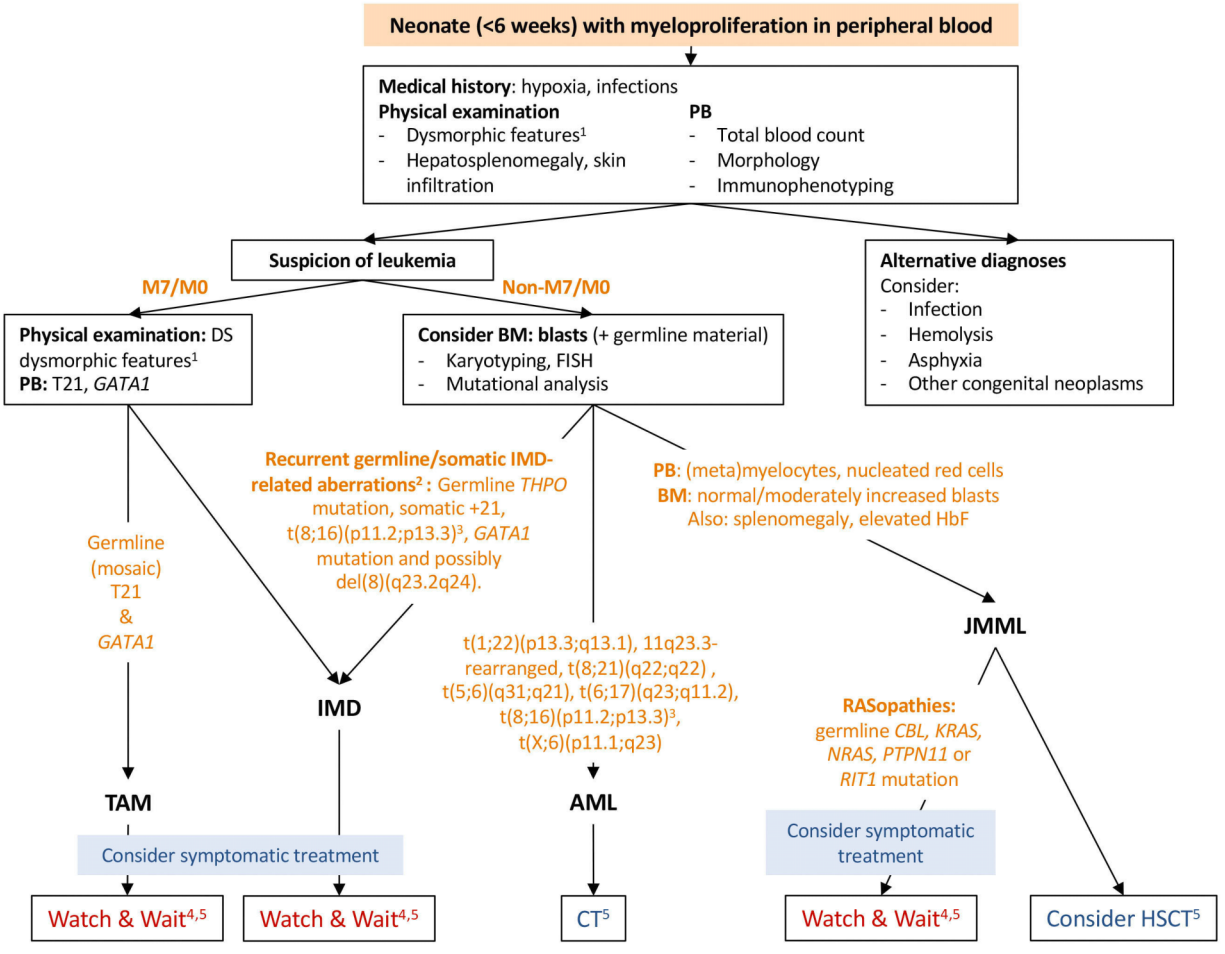

Figure 1. Consensus on diagnostics in neonates with myeloblasts based on available literature and newly added cases [1]In case of doubt always refer to a clinical geneticist. [2]If these are not identified, deep sequencing techniques (SNP-array, RNA-seq, WGS) should be considered. Sporadic identified aberrations are listed in the text. [3]Can be both transient and aggressive leukemia. [4]Only if clinical presentation allows, with close monitoring of clinical symptoms and regular blood counts. [5]In case of doubt, consider consulting international study groups (International Berlin-Frankfurt-Münster AML Study Group, European Working Groups of Myelodysplastic syndromes). References on individual IMD-related aberrations can be found in Table 2. [2-4, 10-12] AML: acute myeloid leukemia; BM: bone marrow; CT: chemotherapy; FISH: fluorescence in situ hybridization; HbF: fetal hemoglobin; HSCT: hematopoietic stem cell transplantation; IMD: infantile myeloproliferative disease (unrelated to Down syndrome); JMML: juvenile myelomonocytic leukemia; NS: Noonan syndrome; PB: peripheral blood; SNP: single nucleotide polymorphism; T21: trisomy 21; TAM: transient abnormal myelopoiesis related to Down syndrome; WGS: whole genome sequencing

ment has high success rates.[8]

In megakaryoblastic cases without germline (mosaic) T21 and a *GATA1* mutation, a bone marrow puncture can be considered. Furthermore, additional mutational analyses for recurrent germline or somatic IMD-related aberrations (such as somatic T21), as well as analyses for recurrent infant AML translocations, are advised (Figure 1; discussed below).

In neonatal non-M7/M0 hyperproliferation, first, discrimination between JMML and AML, and in rare cases, a non-M7 IMD, is important. Bone marrow investigation can be considered for immunophenotyping, karyotyping, fluorescence *in situ* hybridization (FISH) and targeted mutational analyses. Collection of germline material for sequencing discrimination purposes is advisable.

In monocytic proliferation, JMML diagnostics are advised and morphology of the peripheral blood smear, which shows (meta)myelocytes and nucleated red cells combined with the clinical phenotype, is of utmost importance.[3] It is important to identify dysmorphic features of *RAS* pathway related syndromes.[3] Other JMML characteristics are splenomegaly, an elevated fetal hemoglobin value and a normal or moderately increased bone marrow blast count.[3] JMML is in 90% of the cases characterized by mutations in *PTPN11*, *NRAS*, *KRAS*, *NF1* or *CBL*.[3] Germline *CBL*, *KRAS*, *NRAS*, *PTPN11* or *RIT1* mutations indicate an *RAS* pathway driven JMML, in which spontaneous remission often occurs and a 'watch and wait' policy may be considered if clinically feasible.[3] In contrast, patients with a somatic *RAS* driver mutation commonly have aggressive disease requiring allogeneic hematopoietic stem cell transplantation in most cases.[3]

When the clinical picture of a non-megakaryoblastic leukemia is not consistent with JMML, IMD and AML may be seriously considered. Such cases mainly consist of monoblastic AML (FAB M5; immunophenotype CD4+CD11b+CD64+), characteristically present with leukemia cutis, hepatosplenomegaly, hyperleukocytosis and *KMT2A* fusions, and require AML-directed chemotherapy.[2,5,6,10] A diagnostic bone marrow puncture is advised for molecular blast cell characterization. Recurrent translocations, characteristic for infant AML, are t(1;22)(p13.3;q13.1)/*RBM15-MKL1*, 11q23.3/*KMT2A* translocation and t(8;16) (p11.2; p13.3)/*KAT6A-CREBBP*. Further, t(8;21)(q22;q22)/*RUNX1-RUNX1T1*, t(8;1)(p11;q22), t(5;6)(q31;q21), t(6;17)(q23;q11.2) and

t(X;6)(p11.1;q23) have been identified.[2,10-12] Most of these karyotypes are associated with aggressive AML, requiring intensive treatment.[13-15]

Interestingly, in rare myeloid leukemia cases, a 'watch and wait' policy can be considered, as illustrated by reports of incidental cases with successful 'watch and wait' strategies (Tables 1,2). These cases include monoclonal infant AML M4/M5-cases with somatic t(8;16); however, t(8;16) can also be present in full-blown AML.[10] IMD associated with germline *THPO* mutations should be seriously considered in families with a positive history of essential thrombocytosis and myeloproliferative disease in the elderly (Table 2). Furthermore, we found increasing evidence on somatic T21, *GATA1* mutations and del(8)(q23.2q24) in IMD (Table 1,2). SNP array analysis can aid in the identification of subclonal T21 with small clone sizes. Finally, some aberrations have only been described once, nevertheless, they might become recurrent, such as a del(5q), *SETD2* or germline *NSD1* mutation (Tables 1,2).

In conclusion, this review and consensus-based diagnostic guideline may aid in clinical decision-making for the rare infant cases with myeloid hyperproliferation (Figure 1),

Table 1. IMD-cases without germline (mosaic) trisomy 21 from international database*

UPN	Study group	Age	Sex	Clinical presentation[1]	FAB	Genetic tests	Germline	Somatic	Treatment	CR/event	Vital status (FU time)
1	Slovakia	Newborn	F	HSM	M7	FISH, PCR	Normal	T21[2]	N/A	CR	Alive (6.5 years)
2	Japan	1.5 months	M	HSM	M7	Karyotype	Normal	T21[2]	None	CR	Alive (5 years)
3	Japan	1 month	F	HM, CL, VSD Alagille syndrome)	N/A	Karyotype, FISH	Normal	T21[2]	Low-dose AraC	AML (at 5.5 months); received AML-DS treatment; progressive disease; respiratory failure	Died (at 18 months)
4	Czech	Newborn	M	None[1]	M7	Karyotype, FISH	Normal	T21, *GATA1*	None	CR	Alive (9 years)
5	Sweden	6 days	M	None[1]	N/A	Karyotype, FISH, PCR	Normal	T21, *GATA1*	None	CR	Alive (3 years)
6	Austria	5 days	F	None[1]	M7	Karyotype, FISH, PCR	Normal	T21, *GATA1*	None	CR (1 month); AML M7 (at 15 months), same aberrations	
7	Slovakia	Newborn	F	HM, CL	N/A	FISH, PCR	Normal	T21, *GATA1*	None	CR	Alive (9.5 years)
8	Slovakia	1 month	F	CL	M1	FISH, PCR	Normal	T21, *GATA1*	None	CR	Alive (11 years)
9	Slovakia	N/A[3]	M	HM, CL	N/A	Not tested at time of IMD[3]	Normal	N/A	None	AML (at 3 years) with somatic T21 and *GATA1*-mutation AML BFM 2004 protocol; CR at day 15; ASCT.	Alive (6.5 years)
10	Spain	Newborn	M	Few petechiae	M7	Karyotype, FISH, CGH, NGS (117 genes)	Normal	*SETD2*, trisomy 8	None	CR, developed AML (at 4 months), CR after first induction	Alive (3 years)
11	Germany	6 weeks	F	None	N/A	Karyotype, PCR	Normal	T21, *GATA1*	None	CR	Alive (3 years)
12	Germany	Newborn	M	None	N/A	Karyotype, PCR	Normal	T21, (mosaic BM) *GATA1*	None	CR	Alive
13	Germany	Newborn	F	ASD II	N/A	Karyotype, FISH, PCR	Normal (fibroblasts)	Mosaic T21, *GATA1*	Prednison[4]	CR	Alive (1 year)
14	Germany	3 weeks	N/A	HSM, VSD	N/A	Karyotype, FISH, PCR	Normal	T21, GATA1	None	CR (8 weeks), developed AML (at 10 months)	Died (2 days after AML diagnosis)
15	Germany	Newborn	F	None	N/A	Karyotype, FISH, PCR	46,XX,idic(21)(p11)c [15]	T21, GATA1	None	CR	Alive (1 year)

*Inclusion criteria: historical non-TAM, non-JMML cases, cured with no/only symptomatic treatment, age <1 year at diagnosis, diagnosed from 1990-2020. Exclusion criteria: transient abnormal myelopoiesis (TAM) according to WHO definition. [1]Questioned for hepatosplenomegaly (HSM), intravascular coagulation, cutaneous lesions (CL), central nervous system (CNS)-involvement or other extramedullary disease. [2]*GATA1* not tested in every case. [3]IMD diagnosis not definite, was made in retrospect, based on blood counts. [4]Initial diagnosis acute lymphoblastic leukemia (ALL). AML: acute myeloid leukemia; araC = cytarabine; ASCT: allogenic stem cell transplantation; ASD: atrial septum defect; BM: bone marrow; CGH: comparative genomic hybridization; CR: complete remission; DS: Down syndrome F: female; FAB: French-American-British classification; FISH: fluorescence *in situ* hybridization; FU: follow-up; HM: hepatomegaly; IMD: infantile myeloproliferative disease (unrelated to Down syndrome); M: male; N/A: data not available; NGS: next generation sequencing; PCR: polymerase chain reaction; T21: trisomy 21; UPN: unique patient number; VSD: ventricular septum defect; WHO: World Health Organization.

Table 2. **Previously reported IMD-cases without germline (mosaic) trisomy 21 from literature**

UPN[ref]	Age	Sex presentation[1]	Clinical	FAB/IF	Genetic tests	Germline	Somatic	Treatment	CR/event	Vital status (FU time)
16[a]	Newborn	F	None	Not specific	Karyotype (PB lymphocytes), *GATA1* screening	Mosaic trisomy 12[2]	*GATA1*	None	CR	Alive (3 months)
17[b]	4 weeks	F	None	Immature	Karyotype (also fibroblasts), monoblasts	*THPO* mutation unclear mutational analyses	None	Low-dose AraC	CR	Alive (3 years)
18[c]	6 weeks	M	HSM	N/A	N/A	Familial thrombo-cytosis (*THPO*)	None	None	CR	Alive (5 years)
19[d]	2 months	M	HSM	Myelo-monocytic	Karyotype, RT-PCR, FISH	NS (clinical diagnosis)	None	None	CR	Alive (3.8 years)
20[e]	Newborn	F	None	Myelo-monocytic	DNA sequencing	*PTPN11* mutation (NS) (also hair follicles)	None	None	CR	N/A
21[f]	12 days	F	None	Myeloid	Karyotype, FISH, *GATA1*-analysis, SNP-array, WES (also in CR)	*NSD1* mutation (Sotos syndrome)[5]	Del(8) (q23.2q24) & del(5)(q31.1q31.3)	None	CR; AML (11 months), CT	Alive
22[g]	6 days	M	HSM	Myeloid	Karyotype[#], FISH (also in CR)	Chr.6 duplication within q25.3-q26	T21[3]	None	CR	N/A
23[h]	Newborn	M	None	Myeloid, megakaryocytic	Karyotype, FISH (also skin fibroblasts)	Yqs[4]	T21; At 3 months: del(13)(q13q31)	None	CR; leukemia (20 months), CT	N/A
24[i]	Newborn	M	None	Myeloid	Karyotype, FISH (also in CR)	Normal	T21, *GATA1* mutation	None	CR	Alive (2.5 years)
25[j]	Newborn	M	HSM	M7	Karyotype, PCR, RT-PCR, FISH (also oral mucosa and skin fibroblasts)	Normal	T21, *GATA1* mutation	Low-dose AraC	CR	N/A
26[k]	Newborn	M	None	Myeloid	Karyotype, *GATA1*-analysis (also in CR)	Normal	T21, *GATA1* mutation	None	CR; AML ,(7 months) CT; ML-DS protocol	Alive (6 years)
27[l]	Newborn	M	HSM	Myeloid	FISH (also buccal mucosal cells, urine epithelial cells and hair follicles)	Normal	T21, *GATA1* mutation	None	CR	Alive (2 years)
28[m]	5 days	F	HM	M0/M7	Karyotype (also skin fibroblasts), FISH, PCR	Normal	T21, *GATA1* mutation	None	CR	Alive (7 months)
29-36[n]	Neonate	F (n=4) M (n=3)	N/A	N/A	Karyotype (also in CR), FISH (PB in CR, skin or buccal)	Normal	T21, *GATA1* mutation	None (n=3), Low-dose AraC (n=4)	CR; progression to AML (n=2)	N/A
37[o]	Newborn	F	HSM	Myeloid	FISH, *GATA1*-analyses	Normal	T21, *GATA1* mutation	Low-dose AraC	CR	Alive (3 years)

Table 2. Continued on following page.

UPN[ref]	Age	Sex	Clinical presentation[1]	FAB/IF	Genetic tests	Germline	Somatic	Treatment	CR/event	Vital status (FU time)
38-39[p]	Newborn (twins)	F	None	Myeloid	FISH, karyotype, NGS (35 myeloid genes)	Normal	T21, *GATA1* mutation	None	CR	Alive (1.5 years)
40-41[q]	Newborn	F	HSM	Megakaryocytic	Karyotype (also in CR), PCR *GATA1*	Normal	T21, *GATA1* mutation	None	CR; MDS (14 months),	N/A
	Newborn	M	HM						leukemia (17 months) CT CR	Alive (16 months)
42[r]	Newborn	M	HSM	Myeloid, AML M2	Karyotype (also in skin fibroblast)	Normal	T21, +22[3]	None	CR; AML (7 months,) t(1;10), +16, +21, +22, CT	Alive (5 years)
43[r]	Newborn	M	CL	Immature myeloid	Karyotype (repeated in CR)	Normal	T21	None	CR	Alive (5 years)
44-51[s]	1-30 days	N/A	CL (n=6)	M4/M5	Karyotype, FISH or RT-PCR	Normal	t(8;16)(p11.2;p13.3)	None	CR; recurrence <48 months (n=4) CT, SCT (n=1)	Alive (n=6; variable FU) Died (n=1)
52[t]	Newborn	F	CL	M4 (myeloid sarcoma)	Karyotype, FISH (also in CR), molecular testing	Normal	Cryptic t(8;16)(p11.2; p13.3) insertional translocation	None	CR	Alive (23 months)
53[u]	Newborn	M	None	Megakaryocytic	Karyotype, FISH, chromosomal microarray, *GATA1*-analysis on UCB	None found	None found	None	CR	Alive (2 years)
54[v]	Newborn	M	Blasts in cerebral spinal fluid	M7	Karyotype, FISH, BAC-array, SNP-array	13q12.11 deletion (300 kb; 3 genes: *GJB6*, *MIR4499*, *CRYL1*)	Del(3)(q21.2q23), del(7)(q22.1q31.1), del(7)(q31.1q31.2), del(7)(q36.1) & del(8)(q23.2q24)	None	CR	Alive (3 years)
55[w]	Newborn	M	HSM, CL	Megakaryocytic F	ISH, WES, whole transcriptome sequencing	Normal	*GATA1*, *JAK1*, *SPIRE2* & *FN1* mutation	None	CR	N/A

[1]Checked for hepatosplenomegaly (HSM), intravascular coagulation, cutaneous lesions (CL), CNS - central nervous system involvement or other extramedullary disease. [2]Uncertain whether this was germline mosaic. [3]*GATA1* not tested. [4]Satellited Y chromosome. [5]This case was previously described, at that time Sotos diagnosis was not known yet (WES was performed after). AML: acute myeloid leukemia; araC = cytarabine; BAC: bacterial artificial chromosome; CR: complete remission; CT: chemotherapy; F: female; FAB: French-American-British classification; FISH: fluorescence in situ hybridization; FU: follow-up; HM: hepatomegaly; IF: immunophenotype markers; IMD: infantile myeloproliferative disease (unrelated to Down syndrome); M: male; MDS: myelodysplastic syndrome; ML-DS: myeloid leukemia related to Down syndrome; N/A: data not available; NGS: next generation sequencing; NS: Noonan syndrome; PB: peripheral blood; PCR: polymerase chain reaction; RT-PCR: reverse transcription PCR; SCT: stem cell transplantation; SNP: single nucleotide polymorphism; T21: trisomy 21; UCB: umbilical cord blood; UPN: unique patient number; WES: whole exome sequencing.

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especially if a 'watch and wait' policy is considered and clinically feasible. Despite our extensive research, we were only able to include a limited number of patients; this underlines the rarity of the disease and makes general conclusions challenging. To identify these individual cases, an extensive and ongoing (international) collaboration of pediatric oncologists, cytogeneticists, immunologists, molecular biologists and clinical geneticists is mandatory for clinical decision-making and the development of diagnostics tools and treatment. Genomic sequencing can identify novel aberrations that could be recurrent. We here present a consensus for the preferred diagnostic logistics, based on a broad international consortium with clinicians and investigators from the I-BFM AML SG and EWOG MDS. This consensus may support decision-making in these rare infants presenting with myeloproliferative disease.

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