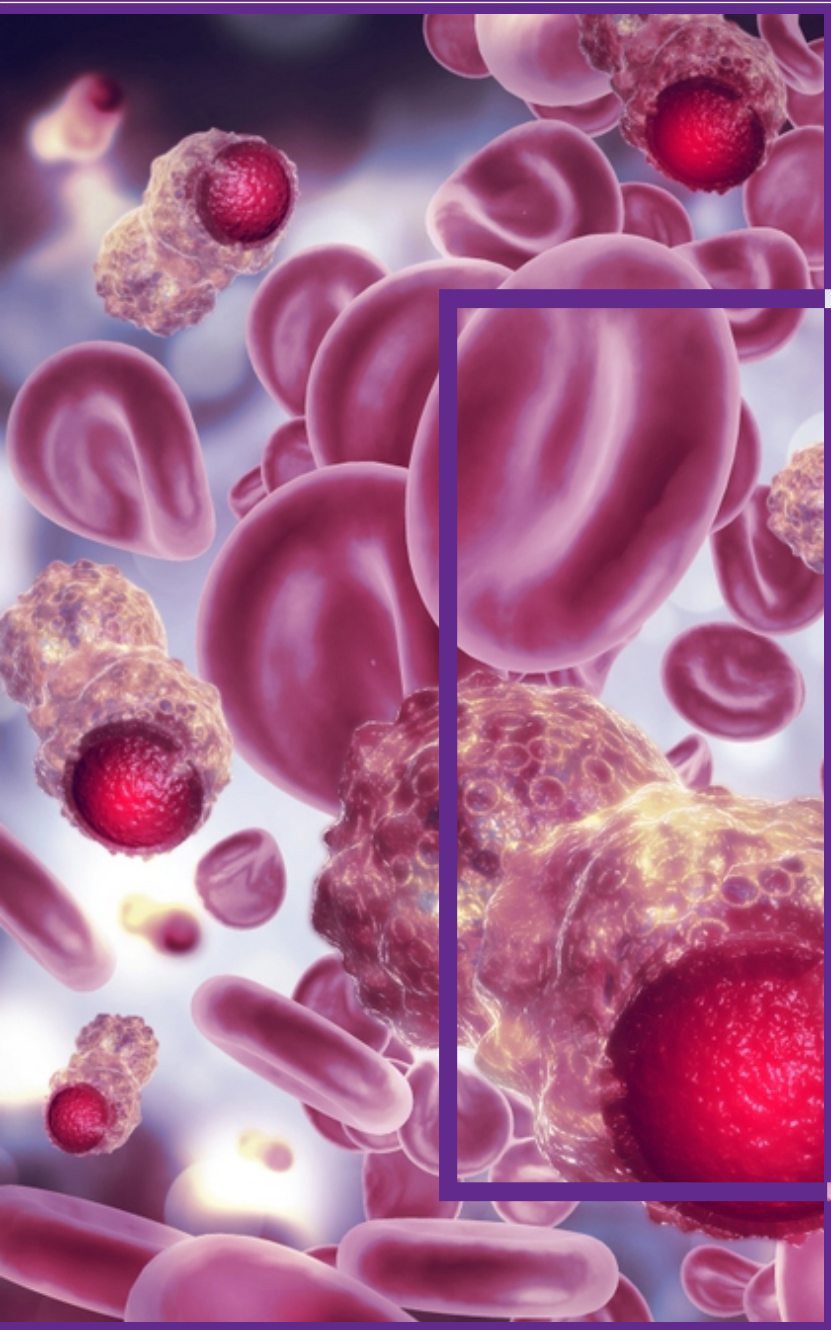


Neuberg DIAGNOSTICS

CENTER FOR GENOMIC MEDICINE

OncoCEPT HAEM

OncoCEPT - HAEM

- Sample Type:- Blood or Bone Marrow
- Next Generation Sequencing
- TAT:-10 days*

Genes Covered

- 40 key DNA target genes
- 29 driver genes
- (a broad fusion panel)

Diseases Covered

Disorder wise:

1. Myeloproliferative Neoplasms
- a. Polycythaemia Vera (PV)
- b. Primary Myelofibrosis (PMF)
- c. Essential thrombocythaemia (ET)
- d. Chronic myeloid leukemia, BCR-ABL1 positive
- e. Chronic neutrophilic leukaemia
- f. Chronic eosinophilic leukaemia, NOS
- g. Myeloproliferative Neoplasm, unclassifiable

2. Mastocytosis

3. Myeloid/lymphoid neoplasms with eosinophilia & gene rearrangement
- a. Myeloid/lymphoid neoplasms with PDGFRA rearrangement
- b. Myeloid/lymphoid neoplasms with PDGFRB rearrangement
- c. Myeloid/lymphoid neoplasms with FGFR1 rearrangement
- d. Myeloid/lymphoid neoplasms with PCM1-JAK2

4. Myelodysplastic/myeloproliferative neoplasms
- a. Chronic myelomonocytic leukaemia (CMML)
- b. Atypical chronic myeloid leukaemia, BCR-ABL1 negative (aCML)
- c. Juvenile myelomonocytic leukaemia (JMML)
- d. Myelodysplastic/myeloproliferative neoplasm with ring sideroblasts & thrombocytosis
- e. Myelodysplastic/myeloproliferative neoplasm, unclassifiable (MDS/MPN-U)

5. Myelodysplastic syndromes(MDS)
- a. MDS with single lineage dysplasia
- b. MDS with ring sideroblasts
- c. MDS with multilineage dysplasia
- d. MDS with excess blasts
- e. MDS with isolated del(5q)
- f. MDS, unclassifiable
- g. Childhood myelodysplastic syndrome

*TAT mentioned is for working days for >90% samples

Diseases Covered

Disorder wise:

6. Myeloid neoplasms with germline predisposition (CEBPA, RUNX1, ETV6, GATA2)

7. Acute myeloid leukaemia(AML) & related precursor neoplasms
- a. AML with t(8;21)/RUNX1-RUNX1T1
- b. AML with inv(16)/CBFB-MYH11
- c. AML with PMLRARA/variant RARA
- d. AML with t(9;11)/KMT2A-MLLT3 as well as other KMT2A rearrangements
- e. AML with t(6;9)/DEK-NUP214
- f. AML with t(1;22)/RBM15-MKL1
- g. AML with t(9;22)/BCR-ABL1
- h. AML with mutated NPM1
- i. AML with biallelic mutation of CEBPA
- j. AML with mutated RUNX1
- k. AML with myelodysplasia related changes
- l. Therapy related myeloid neoplasms
- m. AML, not otherwise specified
- n. Myeloid sarcoma

8. Acute leukaemias of ambiguous lineage
- a. Acute undifferentiated leukaemia
- b. Mixed phenotype acute leukaemia with t(9;22)/BCR-ABL1
- c. Mixed phenotype acute leukaemia with t(v;11q23.3)/KMT2A rearranged
- d. Mixed phenotype acute leukaemia, B/myeloid
- e. Mixed phenotype acute leukaemia, T/myeloid

9. Precursor lymphoid neoplasms : B-lymphoblastic leukaemia/lymphoma (B-ALL/LBL)
- a. B-ALL/LBL, not otherwise specified
- b. B-ALL/LBL with t(9;22)/BCR-ABL1
- c. B-ALL/LBL with t(v;11q23.3)/KMT2A rearranged
- d. B-ALL/LBL with t (12;21) / ETV6-RUNX1
- e. B-ALL/LBL with t(1;19)/TCF3-PBX1
- f. B-ALL/LBL with ZNF384 related fusion

10. Mature B-neoplasms
- a.Chronic lymphocytic leukaemia (CLL)
- b.Hairy cell leukaemia (HCL) (BM sample preferred)
- c.Lymphoplasmacytic lymphoma/ Waldenstrom macroglobulinemia (LPL/WM) (BM sample preferred)

CBC/BM findings under evaluation whenever a myeloid neoplasm is suspected(after ruling out other reactive/secondary causes):

1. Polycythemia
2. Cytopenia(Anaemia, leucopenia, thrombocytopenia)
3. Leukocytosis(Neutrophilia/eosinophilia/ monocytosis/basophilia)
4. Thrombocytosis
5. Acute leukaemia(blasts/atypical cells)
6. Dyspoiesis(Dyserythropoiesis/ dysgranulopoiesis/dysmegakaryopoiesis)
7. Ring sideroblasts
8. Myelofibrosis
9. Atypical lymphoid cells with hairy cytoplasmic projections
10. Rouleaux formation with lymphoplasmacytic cells

List of Genes in Panel

DNA

HOTSPOT GENES			
ABL1	FLT3	KIT	SETBP1
BRAF	GATA2	KRAS	SF3B1
CBL	HRAS	MPL	SRSF2
CEBPA	IDH1	MYD88	U2AF1
CSF3R	IDH2	NPM1	WT1
DNMT3A	JAK2	PTPN11	

FULL GENES		
ASXL1	IKZF1	SH2B3(LNK)
BCOR	NF1	STAG2
CALR	PHF6	TET2
ETV6	PRPF8	TP53
EZH2	RB1	ZRSR2
	RUNX1	

RNA

FUSION DRIVER GENES				
ABL1	EGFR	JAK2	MYBL1	RARA
ALK	ETV6 (TEL)	KMT2A(MLL)	MYH11	RBM15
BCL2	FGFR1	MECOM	NTRK3	RUNX1(AML1)
BRAF	FGFR2	MET	NUP214	TCF3(E2A)
CCND1	FUS	MLLT10	PDGFRA	TFE3
CREBBP	HMGA2	MLLT3	PDGFRB	

Mutations (DNA)

AML			
NPM1	FLT3-TKD	ASXL1	
CEBPA	TP53	DNMT3A	
RUNX1	WT1	IDH1	
KIT	TET2	IDH2	
FLT3-ITD			

MDS/MPN			
SF3B1	SRSF2	NRAS	ZRSR2
JAK2	DNMT3A	TP53	STAG2
MPL	U2AF1	SETBP1	IDH1
CALR	TP53	Others	IDH2
TET2	EZH2		BCOR

PMF	
JAK2	IDH1
MPL	IDH2
CALR	SRSF2
ASXL1	SF3B1
EZH2	TET2

CNL
CSF3R
SETBP1
ASXL1
JAK2

CMML	
ASXL1	NRAS
TET2	CBL
SRSF2	SETBP1
RUNX1	NPM1

t-MNs	
TP53	IDH2
TET2	NRAS
PTPN11	FLT3
IDH1	

Mastocytosis	
KIT	CBL
TET2	RUNX1
SRSF2	RAS family
ASXL1	

JMML	
PTPN11	CBL
KRAS	SETBP1
NRAS	SH2B3
NF1	ASXL1

MNGP	
CEBPA	GATA2
RUNX1	Same as JMML
ETV6	CSF3R

CEL	
TET2	EZH2
ASXL1	JAK2
DNMT3A	KIT

TAM	
EZH2	SH2B3
JAK2	RAS pathway genes
MPL	

PV
JAK2V617F
JAK2 exon 12
SH2B3/LNK

ET
JAK2
CALR
MPL

MDS		
SF3B1	RUNX1	STAG2
TET2	U2AF1	IDH1
ASXL1	TP53	IDH2
SRSF2	EZH2	CBL
DNMT3A	ZRSR2	NRAS
	Others	BCOR

BPDCN	
TET2	IDH2
NPM1	KIT
ASXL1	RB1
RAS family	BRAF
NRAS	TP53
KRAS	

aCML
SETBP1
CSF3R

APL
FLT3-ITD
FLT3-TKD

- Acute myeloid leukaemia (AML)
- Primary Myelofibrosis (PMF)
- Therapy related myeloid neoplasms (t-MNs)
- Myeloid proliferations ass. with Down's (TAM)
- Chronic eosinophilic leukaemia (CEL)
- Acute promyelocytic leukaemia (APL)
- Chronic neutrophilic leukaemia (CNL)
- Mastocytosis
- Chronic myelomonocytic leukaemia (CMML)
- Juvenile myyelomonocytic leukaemia (JMML)
- Myelodysplastic Syndrome / myeloproliferative neoplasms (MDS/MPN)
- Myelodysplastic Syndrome(MDS)
- Myeloid neoplasms with germine predisposition(MNGP)
- Atypical chronic myeloid leukaemia (aCML)
- Essential Thrombocythemia (ET)
- Polycythemia (PV)
- Blastic plasmacytoid dendritic cell neoplasm(BPDCN)

Fusions (RNA)

Acute myeloid leukaemia(AML) and related precursor neoplasms		
RUNX1-RUNX1T1 t(8;21)		**CBFB-MYH11 inv(16)**
PML-RARA t(15;17)		**DEK-NUP214 t(6;9)**
RBM15-MKL1 t(1;22)		**AML with BCR-ABL1**
KMT2A REARRANGEMENTS		
MLLT3 t(9;11)	TET1	CASP8AP2
AFF1/AF4	PICALM	CBL
MLLT1-ENL	ABI1	CREBBP
MLLT10/AF10	CASC5	DCP1A
ELL	MYO1F	DCPS
PTD	SEPT5	FNBP1
MLLT4/AF6	ACTN4	GAS7
EPS15	FLNA	KIA1524
MLLT11/AF1Q	FOXO3	BTBD18
SEPT9	CEP170B	MYH11
EPS15	MAML2	NEBL
SEPT6	SEPT11	NRIP3
MLLT6/AF17	ABI2	PDS5A
AFF3/LAF4	ACACA	SEPT2
ARHGEF12	AFF4/AF5	SMAP1
GMPS	ARHGEF17	TOP3A

Acute promyelocytic leukaemia
RARA REARRANGEMENTS: 3 types bcr1,bcr2,bcr3
IRF2BP2-RARA
NABP1-RARA t(2;17)
TBL1XR1-RARA t(4;17)
FIP1L1-RARA t(5;17)
NPM1-RARA t(11;17)
NUMA1-RARA
ZBTB16-RARA t (11;17)
ADAMTS17-RARA
STAT5B-RARA
PRKAR1A-RARA t(17;17)
BCOR-RARA t(X;17)
PML-RARA

Chronic eosinophilic leukaemia
ETV6 REARRANGEMENTS
FLT3
NTRK
LYN
SYK
ABL1
ETV6-JAK2
BCR-JAK2

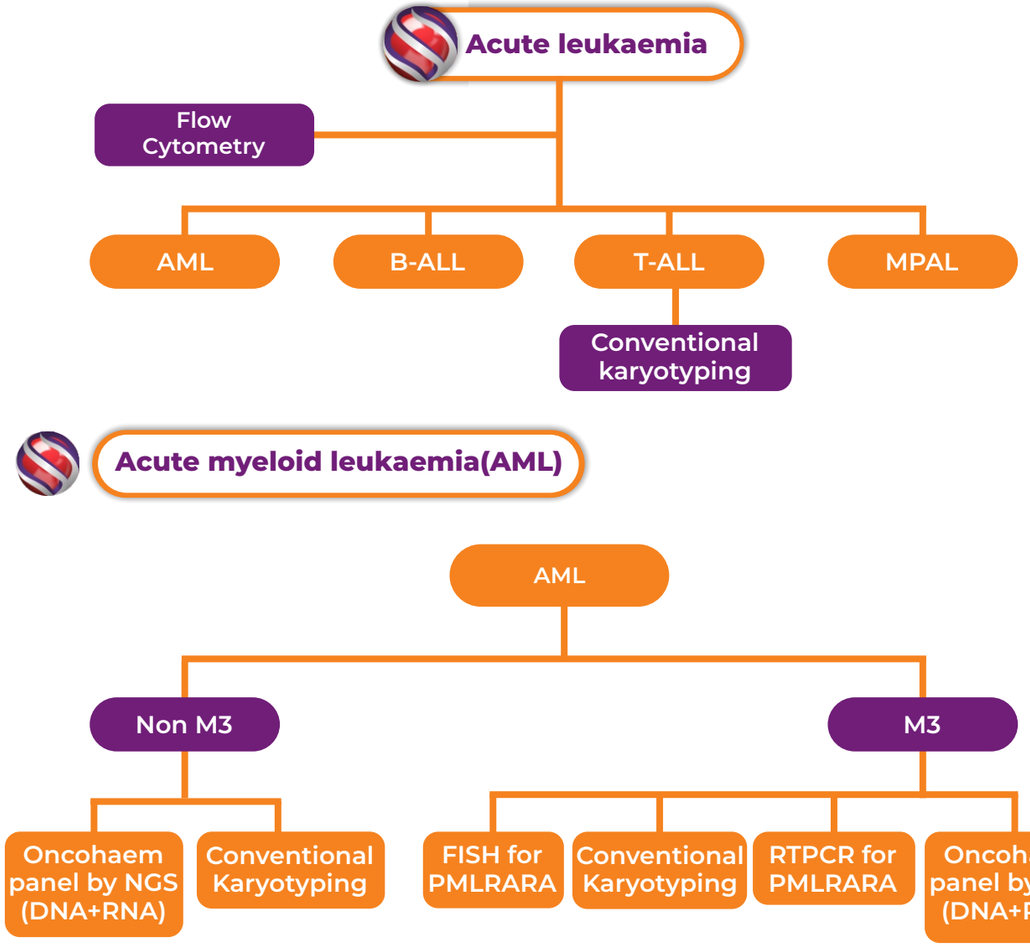
Pediatric -AML
RBM15-MKL1 t(1;22)
KAT6A-CREBBP
DEK-NUP214 t(6;9)
KMT2A Rearrangements
MLLT3
MLLT10
MLLT11

Chronic myeloid leukaemia
BCR-ABL1

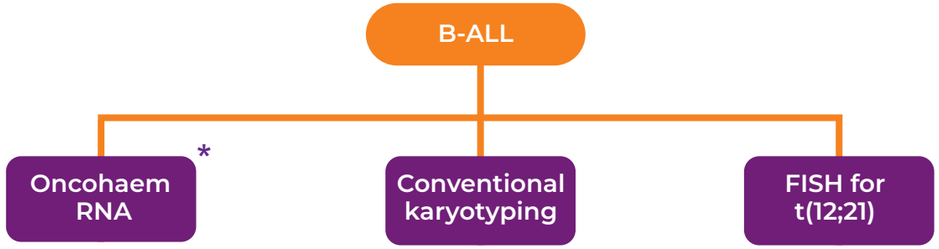
B-lymphoblastic leukaemia/lymphoma	
t(9;22)/BCR-ABL1	t(1;19)/TCF3-PBX1
t(v;11q23.3)/KMT2A	ZNF384 related Fusions
t(12;21) /ETV6-RUNX1	

Myeloid/lymphoid neoplasms with eosinophilia & gene arrangement			
PDGFRB REARRANGEMENTS	**FGFR1 REARRANGEMENTS**	**JAK2 REARRANGEMENTS**	
CCDC6	GOLGA4	ZMYM2	PCM1
SART3	TNIP1	CNTRL	ETV6
GIT2	HIP1	FGFR1OP	BCR
ERC1	KANK1	BCR	**PDGFRA REARRANGEMENTS**
BIN2	MYO18A	MYO18A	ETV6
NIN	COL1A1	TRIM24	FIP1L1
CCDC88C	DTD1	FGFR1OP2	KIF5B
TP53BP1	GOLGB1	TPR	CDK5RAP2
NDE1	CEP85L	RANBP2	STRN
RABEP1	TRIP11	LRRFIP1	FOXP1
SPECC1	MPRIP	CUX1	TNKS2
ETV6	CPSF6	CPSF6	BCR
WDR48	TPM3	SQSTM1	
CAPRIN1	PDE4DIP		
	PRKG2		

BONE MARROW EXAMINATION IS MUST FOR ALL SUSPECTED MYELOID NEOPLASMS (except under special circumstances)



B-lymphoblastic leukaemia(B-ALL)



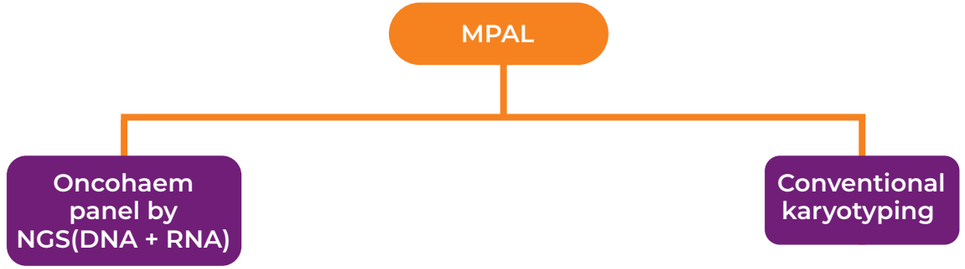
- t(12;21), t(9;22), t(1;19), KMT2A rearrangements – Identifies cryptic abnormalities
- TCF3-ZNF384 related fusion

- Hyperdiploidy and hypodiploidy
- Other aneuploidies & structural chromosomal abnormalities

- Intrachromosomal amplification of chromosome 21
- t(12;21)
- Indirect evidence of hyperdiploidy/ hypodiploidy

* **Ideally Oncohaem panel by NGS (DNA + RNA)**

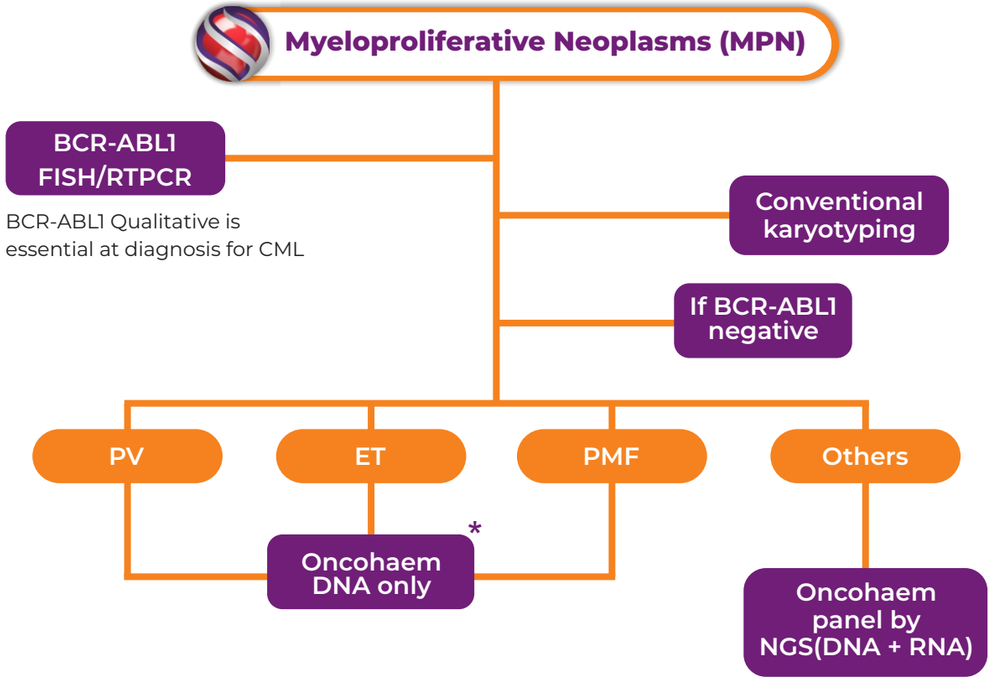
Mixed phenotype acute leukaemia (MPAL)



- KMT2A rearrangements
- t(9;22)

- Aneuploidies
- Structural chromosomal abnormalities

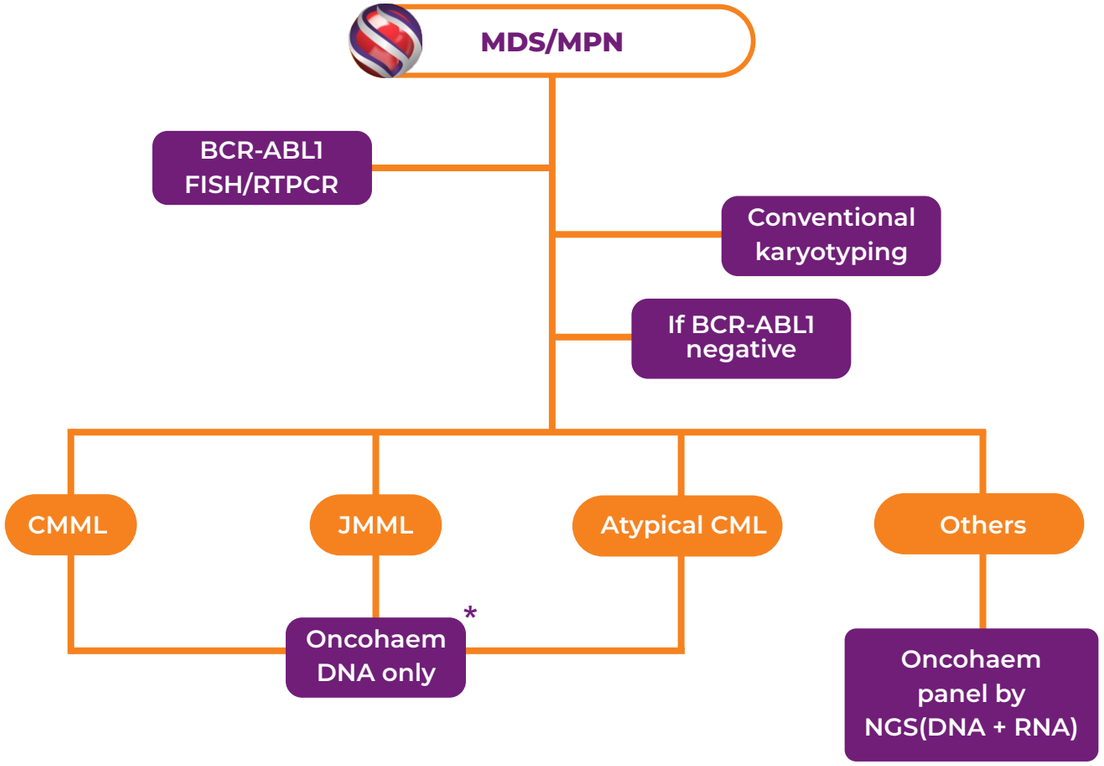
Myeloproliferative Neoplasms (MPN)



* **Ideally Oncohaem panel by NGS (DNA + RNA)**

- Chronic myeloid leukaemia(CML)
- Polycythaemia Vera(PV)
- Primary Myelofibrosis(PMF)
- Essential Thrombocythaemia(ET)
- Chronic neutrophilic leukaemia(CNL)
- Chronic eosinophilic leukaemia(CEL)
- MPN-U

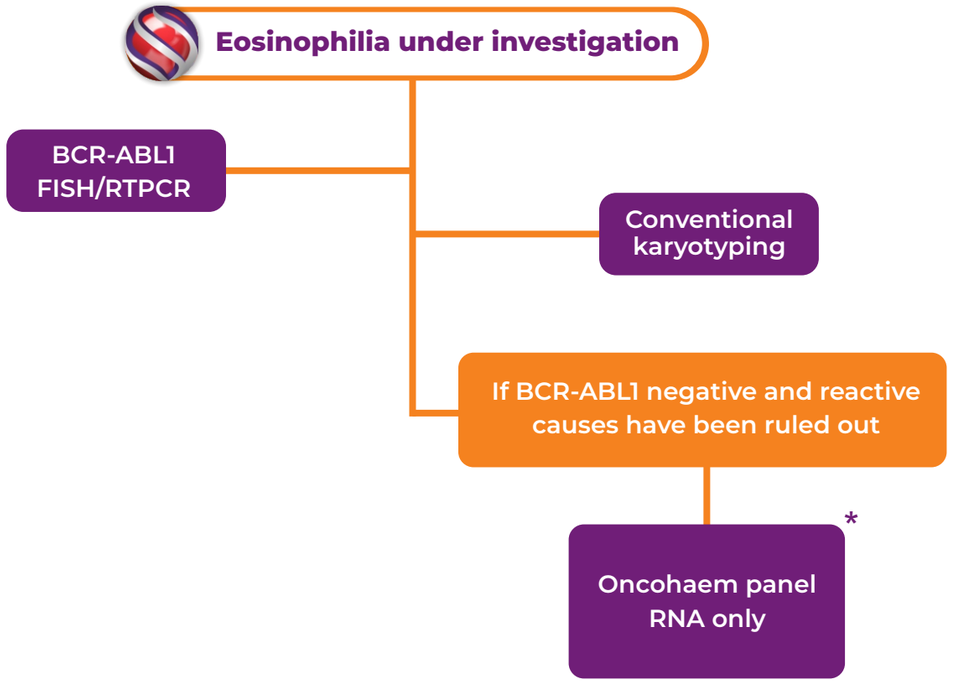
Myelodysplastic syndrome/ Myeloproliferative neoplasm (MDS/MPN)



* Ideally Oncohaem panel by NGS (DNA + RNA)

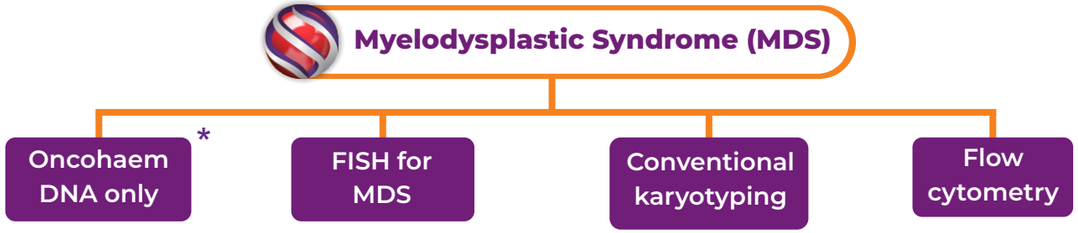
- Chronic myelomonocyticleukaemia(CMML)
- Atypical CML(aCML)
- Juvenile myelomonocytic leukaemia(JMML)
- MDS/MPN-RS-T
- MDS/MPN-U

Eosinophilia under investigation



* Ideally Oncohaem panel by NGS (DNA + RNA)

Myelodysplastic Syndrome (MDS)



- Identifies mutations in genes implicated in MDS.
- Gives a supporting evidence of clonality

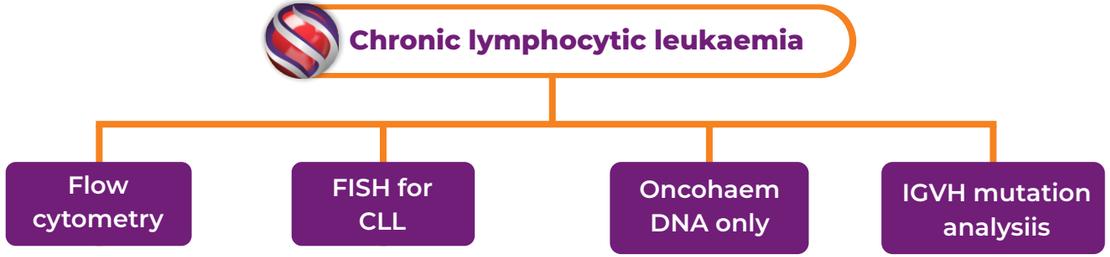
- FISH for deletion 5q/monosomy 5
- FISH for monosomy 7

- For identifying MDS defining cytogenetic abnormalities
- Other structural & numerical chromosomal abnormalities

- Optional for demonstration of additional evidence of dysplasia
- For confirmation of lineage of blasts and to rule out other abnormality/disorder

* **Ideally Oncohaem panel by NGS (DNA + RNA)**

Chronic lymphocytic Leukaemia (CLL)



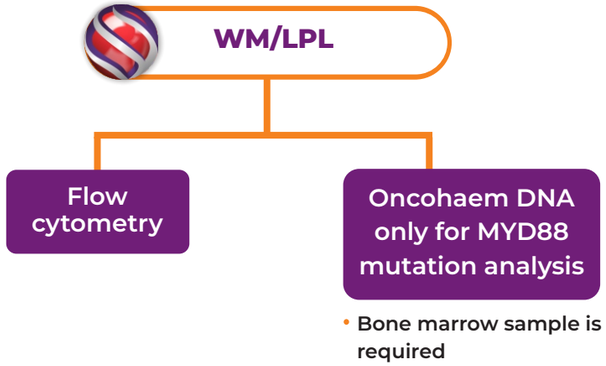
- For confirmation of Chronic lymphocytic leukaemia & exclusion of other Non Hodgkin lymphoma

- Especially for del17p(TP53)
- For knowing other abnormalities like del(13q), trisomy 12, del(11q), etc

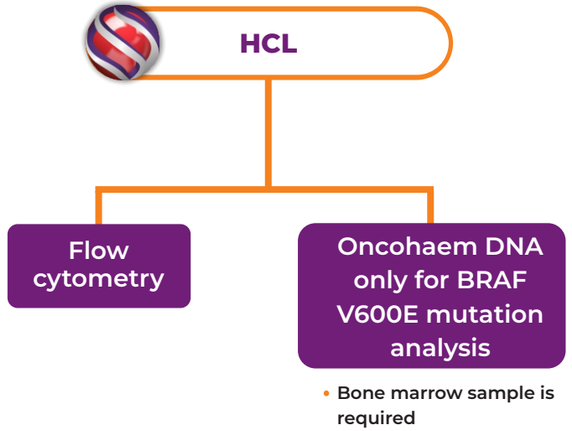
- For knowing TP53 mutation (for prognostication) as well as mutations in SF3B1 and MYD88 genes
- (TP53 mutation and FISH for TP53 deletion are different)

- For prognostication

Other Disorders



- **Bone marrow sample is required**



- **Bone marrow sample is required**

- Hairy cell leukaemia(HCL)
- Waldenstrom Macroglobulinemia/Lymphoplasmacytic lymphoma(WM/LPL)

Current analysis of hematological malignancies involves multiple sequential tests and laborious workflows. Adoption of next-generation sequencing (NGS) methods into clinical research laboratories has created an unprecedented opportunity to profile the multiple relevant driver genes in myeloid malignancies. Targeted NGS assay is designed to assist in the understanding of myeloid cancers. Specifically, it interrogates all relevant DNA mutations and fusion transcripts associated with myeloid disorders in a single NGS run.

Why OncoCEPT - HAEM?

- Targetable fusions/rearrangements like PDGFRA, PDGFRB, etc. can be checked
- Rare transcripts, which are not regularly checked or are usually missed, can also be detected. e.g. ETV6-JAK2 and ETV6-FLT3 can be found in CEL which can be detected by this technique.
- Transcripts that are cryptic can also be detected, which karyotyping may fail to identify.
- Fusions resulting from translocations can be confirmed. e.g. not all translocation characterized as t(5;12)(q31-33;p12) lead to ETV6-PDGFRB fusion.
- Fusions suspected but not found by karyotyping can be detected.
- Multiple fusions of a particular gene can be seen, whereas, FISH can only detect a particular translocation depending upon the probe used.
- Testing individually for each fusion by FISH is expensive , however, here, whole panel can be covered in a very reasonable rate.
- Mutations other than FLT3, JAK2, NPM1 & CEBPA are also covered like – IDH2, DNMT3A, etc.
- A suspected case can be confirmed if mutation can be found. e.g. a suspected case of JMML having a mutation KRAS can confirm the diagnosis.
- Drugs are now available that can be used to target the mutations. e.g. IDH1 inhibitor.
- Mutation can helps in knowing the prognosis of the disease. e.g. TP53 mutation in AML carries adverse prognosis.

Your PARTNERS in HEALTH

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