Ärftlighet vid AML

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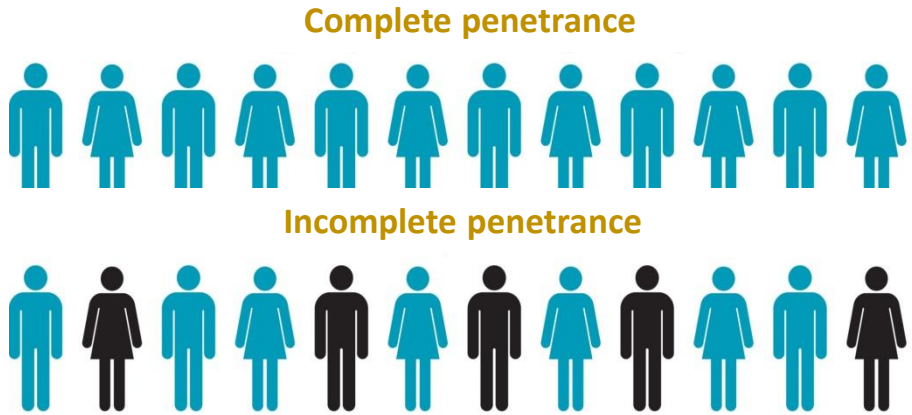
Genes reported in TWIST panel

Mars 2021-Clinical genetics Uppsala

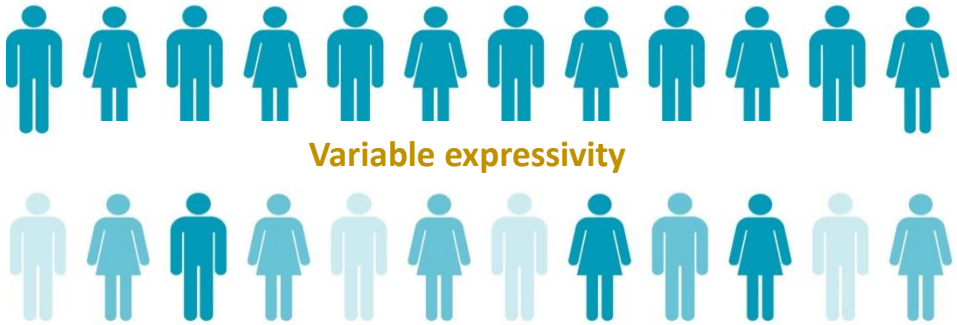
ABL1
ANKRD26 (inklusive 5'-UTR)
ASXL1
ATRX
BCOR
BCORL1
BCL2
BTK
BRAF
CALR
CBL
CBLB
CDKN2A
CEBPA
CSF3R
CUX1
CXCR4
DDX41
DNMT3A
ETV6/TEL
EZH2
PHF6
FBXW7
FLT3
GATA1
GATA2 (inklusive intron 4)
GNAS
HRAS
IDH1
IDH2
IKZF1
JAK2
JAK3
KDM6A
KIT
KRAS
KMT2A
MPL
MYD88
NF1
NOTCH1
NPM1
NRAS
PDGFRA
PLCG2
PPM1D
PTEN
PTPN11
RAD21
RUNX1
SAMD9
SAMD9L
SBDS
SETBP1
SF3B1
SMC1A
SMC3
SRSF2
SRP72
STAG2
STAT3
STAT5B
TERT
TET2
TP53
U2AF1
WT1
ZRSR2

Genetic terms

Penetrance: Frequency (%) of carriers who have symptoms-disease risk

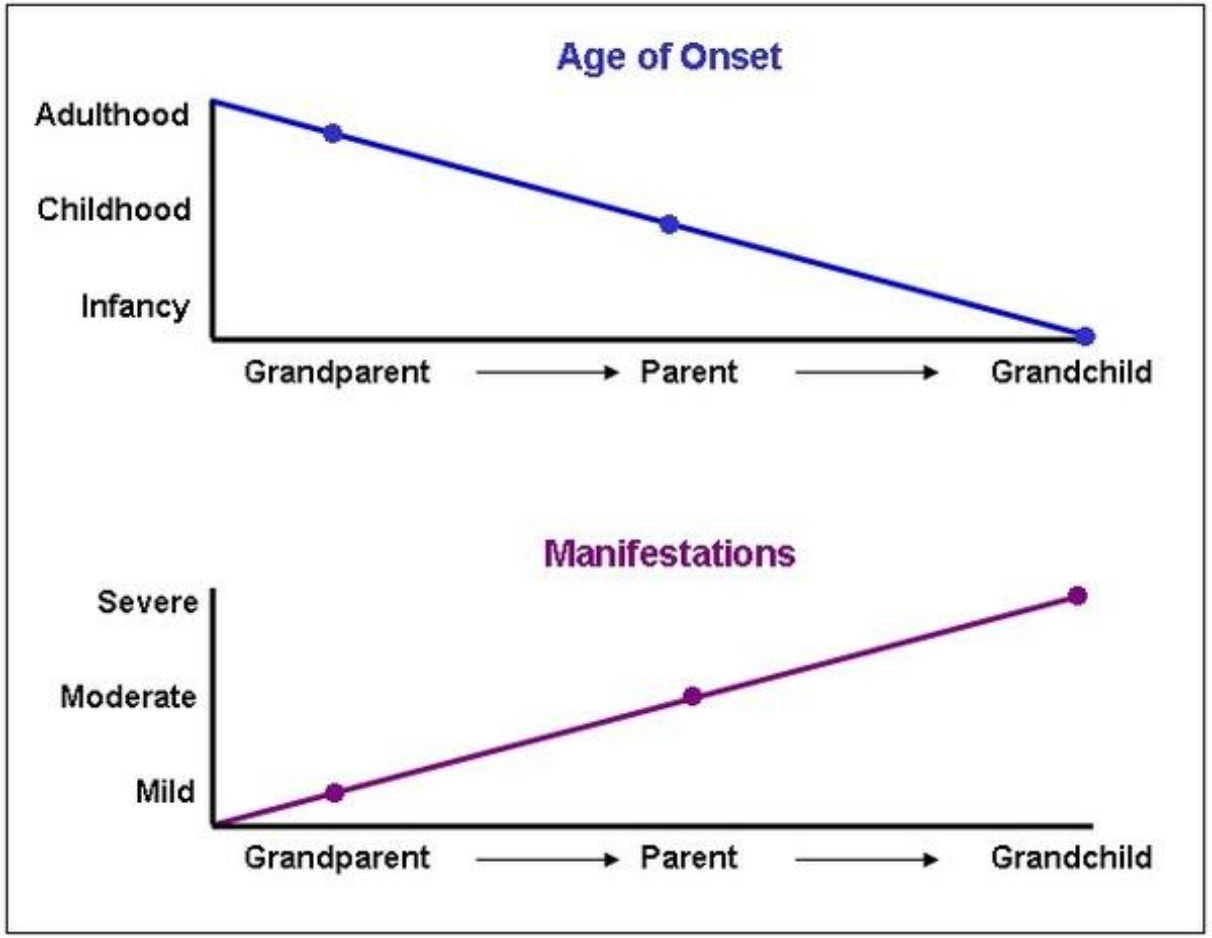


Expressivity: The phenotypiv variation among individuals with a specific variant



Genetic terms

Anticipation: Earlier age at diagnosis and more severe symptoms in the next generations



WHO 2016 classification

Myeloid neoplasm classification
Myeloid neoplasms with germ line predisposition without a preexisting disorder or organ dysfunction
AML with germ line *CEBPA* mutation
Myeloid neoplasms with germ line *DDX41* mutation*
Myeloid neoplasms with germ line predisposition and preexisting platelet disorders
Myeloid neoplasms with germ line *RUNX1* mutation*
Myeloid neoplasms with germ line *ANKRD26* mutation*
Myeloid neoplasms with germ line *ETV6* mutation*
Myeloid neoplasms with germ line predisposition and other organ dysfunction
Myeloid neoplasms with germ line *GATA2* mutation
Myeloid neoplasms associated with BM failure syndromes
Myeloid neoplasms associated with telomere biology disorders
JMML associated with neurofibromatosis, Noonan syndrome or Noonan syndrome-like disorders
Myeloid neoplasms associated with Down syndrome*

Arber D et al. Blood 2016

Acta Medica Scandinavica. Vol. CXXVII, fasc. I—II, 1947.

From the University Institute for Human Genetics, Copenhagen,
(Director: Tage Kemp, M. D.) and
The University Institute of Pathological Anatomy, Copenhagen.
(Director: Professor J. Engelbreth-Holm, M. D.)

Familial Leukemia.[1]

A Preliminary Report.

By

AAGE VIDEBÆK.

(Submitted for publication August 6, 1946.)

1861 1999 2004 2011 2012 2015 2016

First publication

RUNX1

CEBPA

GATA2

ANKRD26

SRP72

ETV6

DDX41

ATG2B

SAMD9

SAMD9L

Why have we missed them?

- 3 generations **detailed pedigree**
- Rare?
- Denovo mutations, incomplete penetrance, variable expressivity
- Not unusual among older patients

Why should we recognize them?

Family members

- As part of the family investigation
- To explain symptoms/signs
- To avoid unnecessary medication
- To identify patients who may be candidates for Allo-HSCT
- To identify healthy individuals
- Follow-up

Patient with AML/MDS

- Offer an explanation
- Choice of donor (engraftment failure, donor-derived leukaemia)
- Define risk for other family members
- Choice of conditioning (Fanconi anemi, telomeropathies)
- Follow up (even after allo-SCT)

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Myeloid neoplasms with germ line predisposition and preexisting platelet disorders
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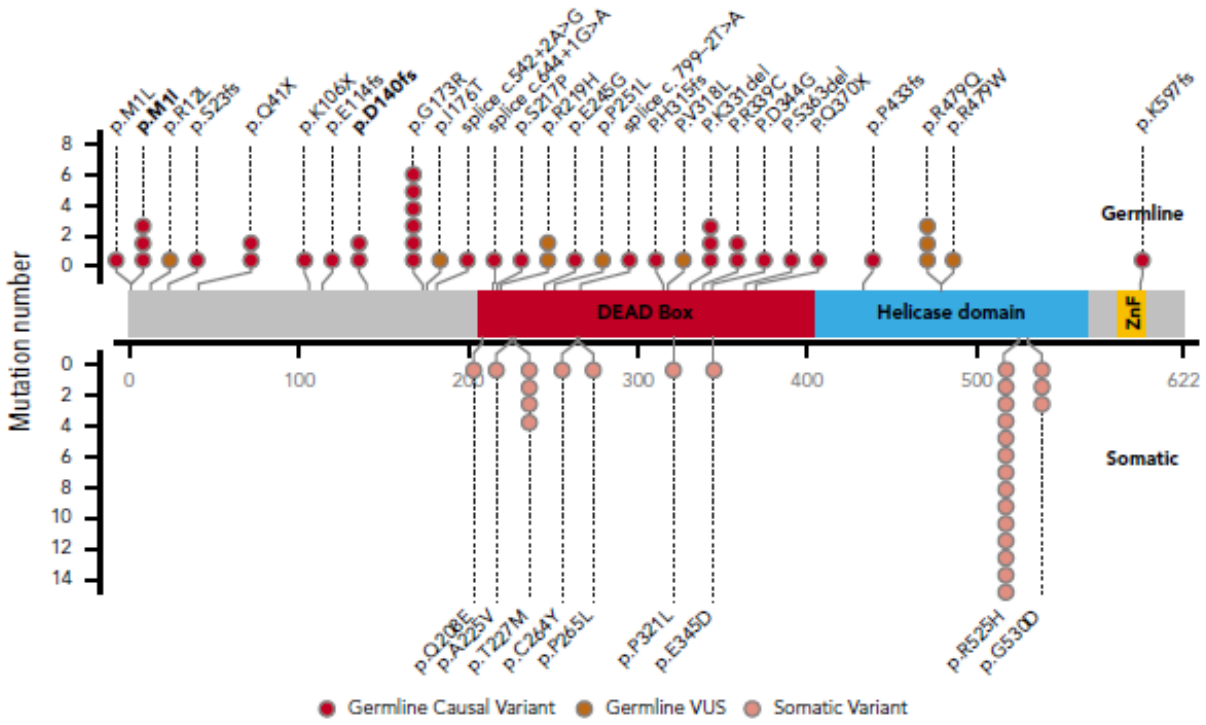
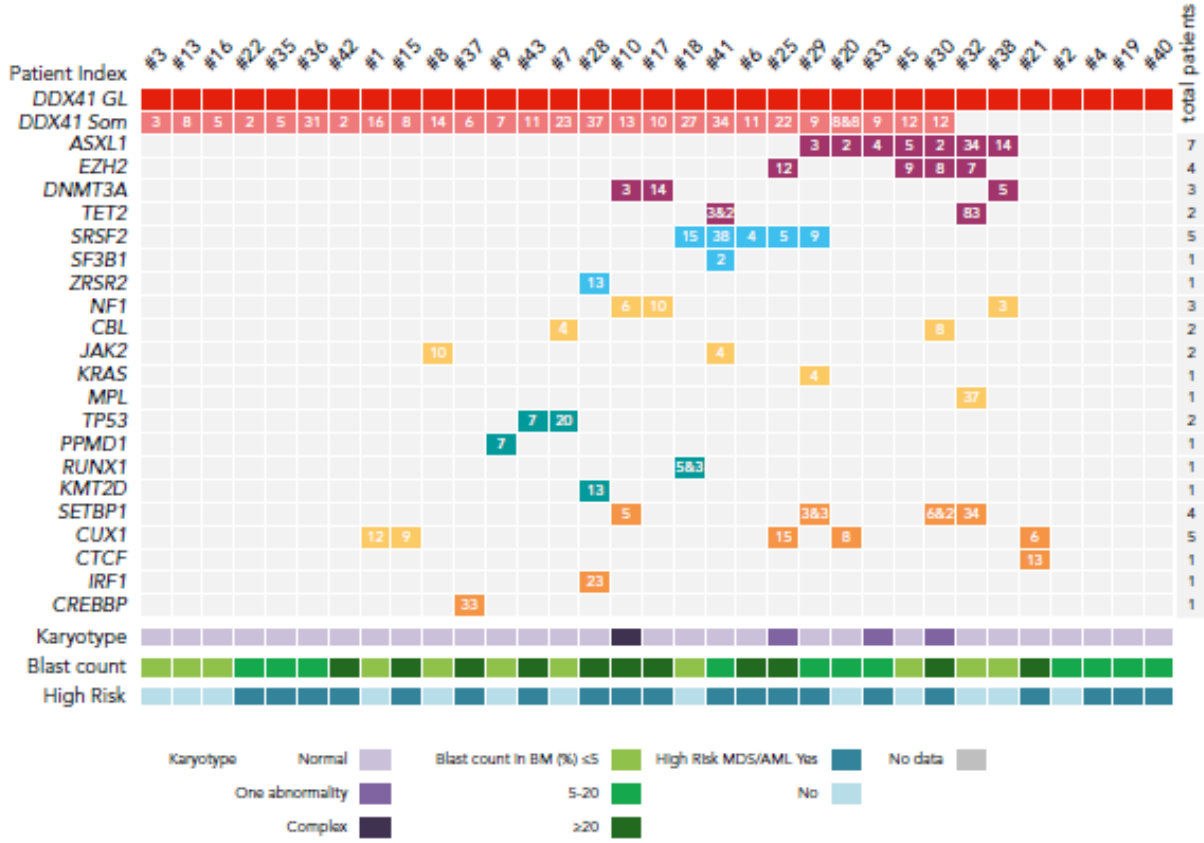
Arber D et al. Blood 2016

MNs with germline *DDX41* mutations

- Dubbel *DDX41* mutations
  - Truncating germline variant-missense somatic the usual patern
- High penetrance
- Advanced age at diagnosis
- Favorable prognosis
- Pre-existing cytopenia is usual

MNs with germline *DDX41* mutations

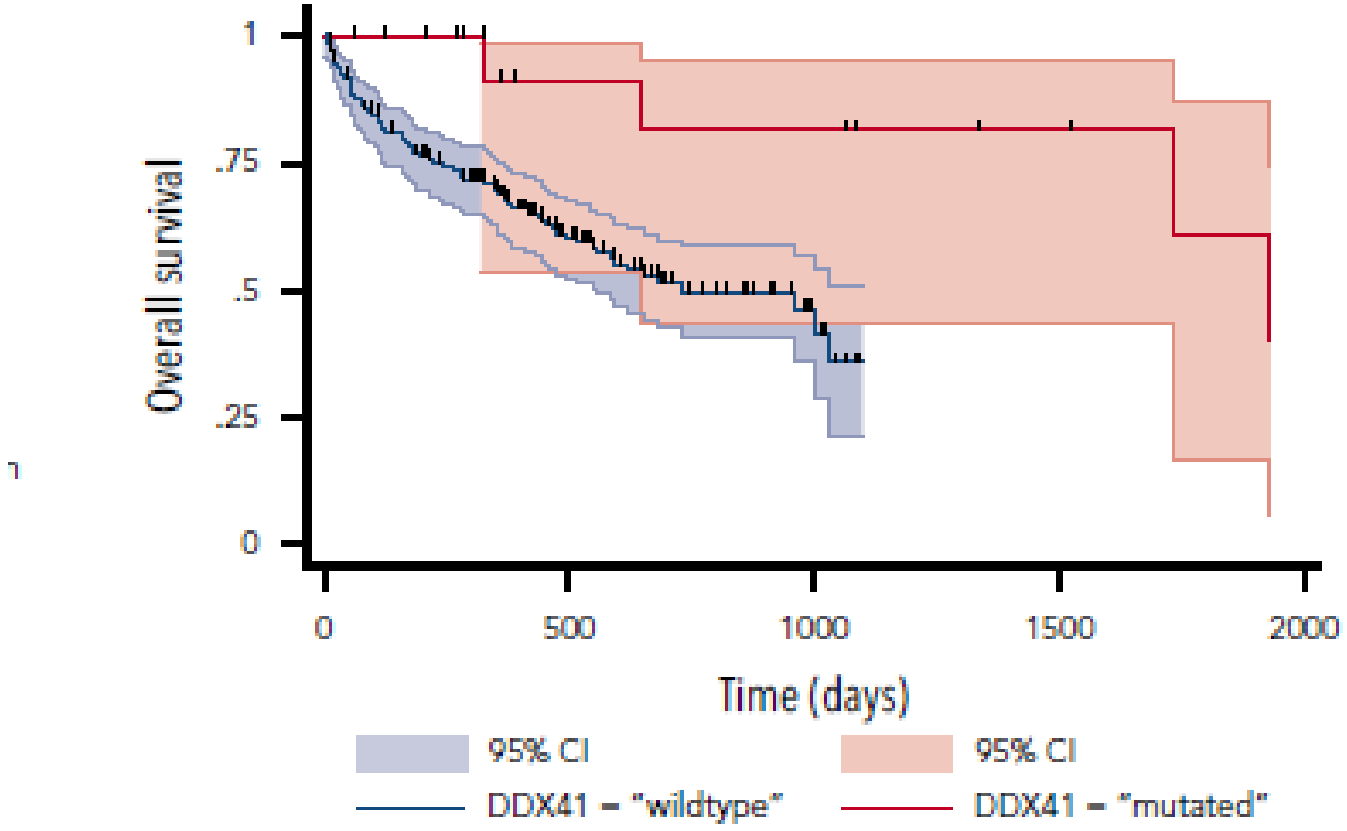




Only 0.5% of the cohort carried isolated *DDX41* somatic mutations indicating that DDX41 is rarely involved in the oncogenesis of MNs in the absence of a germline predisposing variant

Sebert M et al. Blood 2020

MNs with germline *DDX41* mutations



Whether engraftement is delayed in the Allo-HSCT context is under debate

Sebert M et al. Blood 2020

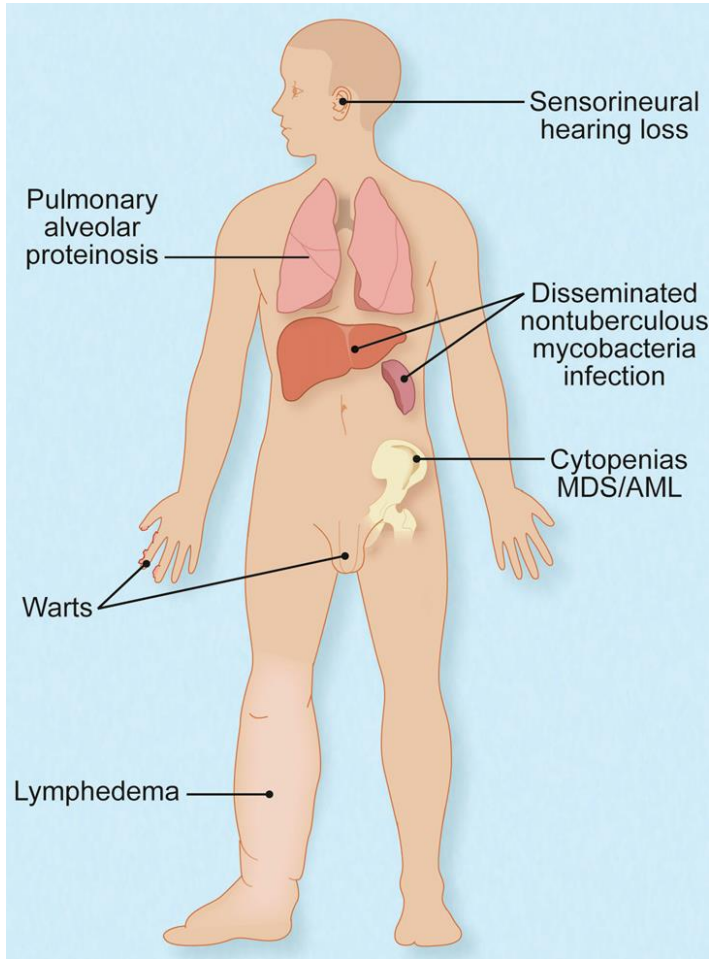
MNs with germline *RUNX1* mutations (FPD/MM)

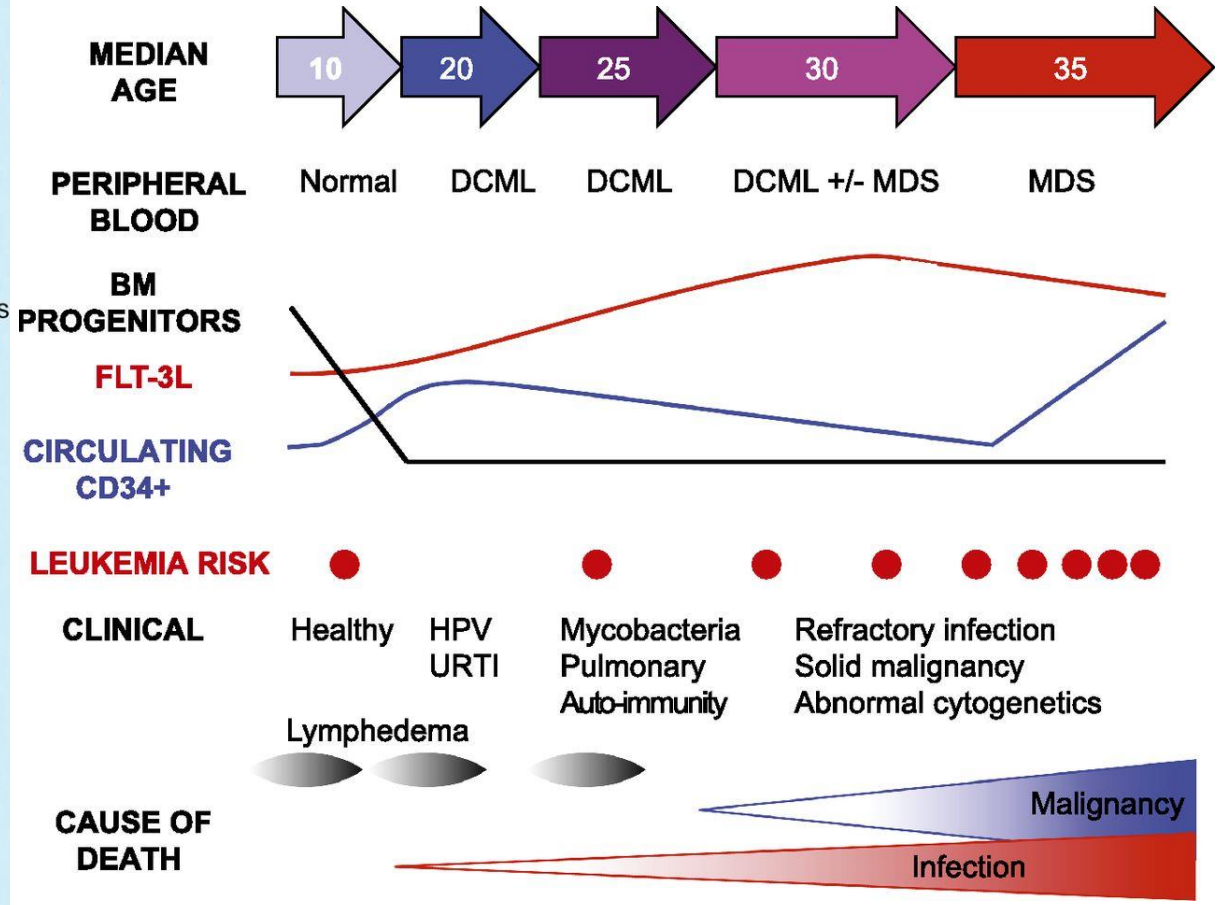
- SNVs or large deletions
- Incomplete penetrance (20-60%)
- Early age at diagnosis (30-40 y)
- Anticipation
- High risk even for T-ALL

MNs with germline GATA2 mutations

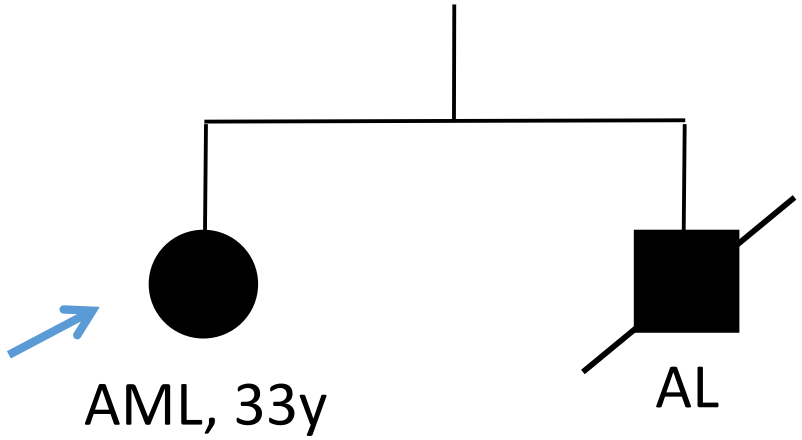
- SNVs or large deletions
- High penetrance (90%)
- Early age at diagnosis
- Anticipation
- Enrichment for aberrations involving chromosome 7

MNs with germline GATA2 mutations





Case 1



We need guidelines

- Whom to test
- Which test
- Management

AML national guidelines 2018

11.6 Misstanke om ärftlig leukemisjukdom

Rekommendation

Patienter med misstanke om ärftlig form av leukemi bör diskuteras med och vid behov remitteras till en klinisk genetisk verksamhet för ytterligare utredning samt ev. genetisk vägledning (+). Det är viktigt att patienten är fullt införstådd med utredningens syfte. Den kliniska handläggningen bör ske i samråd med hematologisk expertis som är förtrogen med handläggning av ärftliga former av leukemi.

Who, how, when

Genetic counseling

Significance for the whole family

Nordic Working Group on Myeloid Neoplasms with Germline Predisposition

Finland	Kirsi Jahnukainen
	Ulla Wartiovaara-Kautto
	Outi M Kilpivaara
Sweden	Panagiotis Baliakas
	Bianca Tesi
	Jörg Cammenga
	Eva Hellström-Lindberg
Norway	Astrid Olsnes Kittang
	Ingunn Dybedal
	Randi Hovland
	Cecilie Rustad
Denmark	Kirsten Grønbæk
	Klas Raaschou-Jensen
	Charlotte Kvist Lautrup
	Mette Klarskov Andersen

NMDS group

Nordic Working Group on Myeloid Neoplasms with Germline Predisposition

HemaSphere
Powered by EHA

EHA EUROPEAN HEMATOLOGY ASSOCIATION

Guideline Article - Consensus based

OPEN ACCESS

Nordic Guidelines for Germline Predisposition to Myeloid Neoplasms in Adults: Recommendations for Genetic Diagnosis, Clinical Management and Follow-up

Panagiotis Baliakas[1], Bianca Tesi[2], Ulla Wartiovaara-Kautto[3], Asbjørg Stray-Pedersen[4], Lone Smidstrup Friis[5], Ingunn Dybedal[6], Randi Hovland[7], Kirsi Jahnukainen[8], Klas Raaschou-Jensen[9], Per Ljungman[10], Cecilie F. Rustad[11], Charlotte K. Lautrup[12], Outi Kilpivaara[13], Astrid Olsnes Kittang[14], Kirsten Grønbæk[15], Jörg Cammenga[16], Eva Hellström-Lindberg[17], Mette K. Andersen[18]

Whom to test

A: Patients with positive family history or signs/symptoms indicative of a hereditary condition predisposing for myeloid neoplasms (MN) especially MDS/AML.

- A1: Patient with MDS/AML and symptoms/signs of a hereditary condition predisposing for MN development*[1] diagnosed before the age of 50.
- A2: Two individuals (first or second degree relatives, FDR and SDR, respectively) with MDS/AML or long lasting thrombocytopenia or symptoms/signs indicative of a hereditary condition predisposing for MN development*[1], one of whom diagnosed before the age of 50.
- A3: One individual with MDS/AML and two FDR or SDR with a diagnosis of solid tumor malignancy*[2] one of whom diagnosed before the age of 50.
- A4: ≥3 FDR or SDR with MN or long-lasting thrombocytopenia or symptoms/signs indicative of a hereditary condition predisposing for MN development*[1], independently of age.

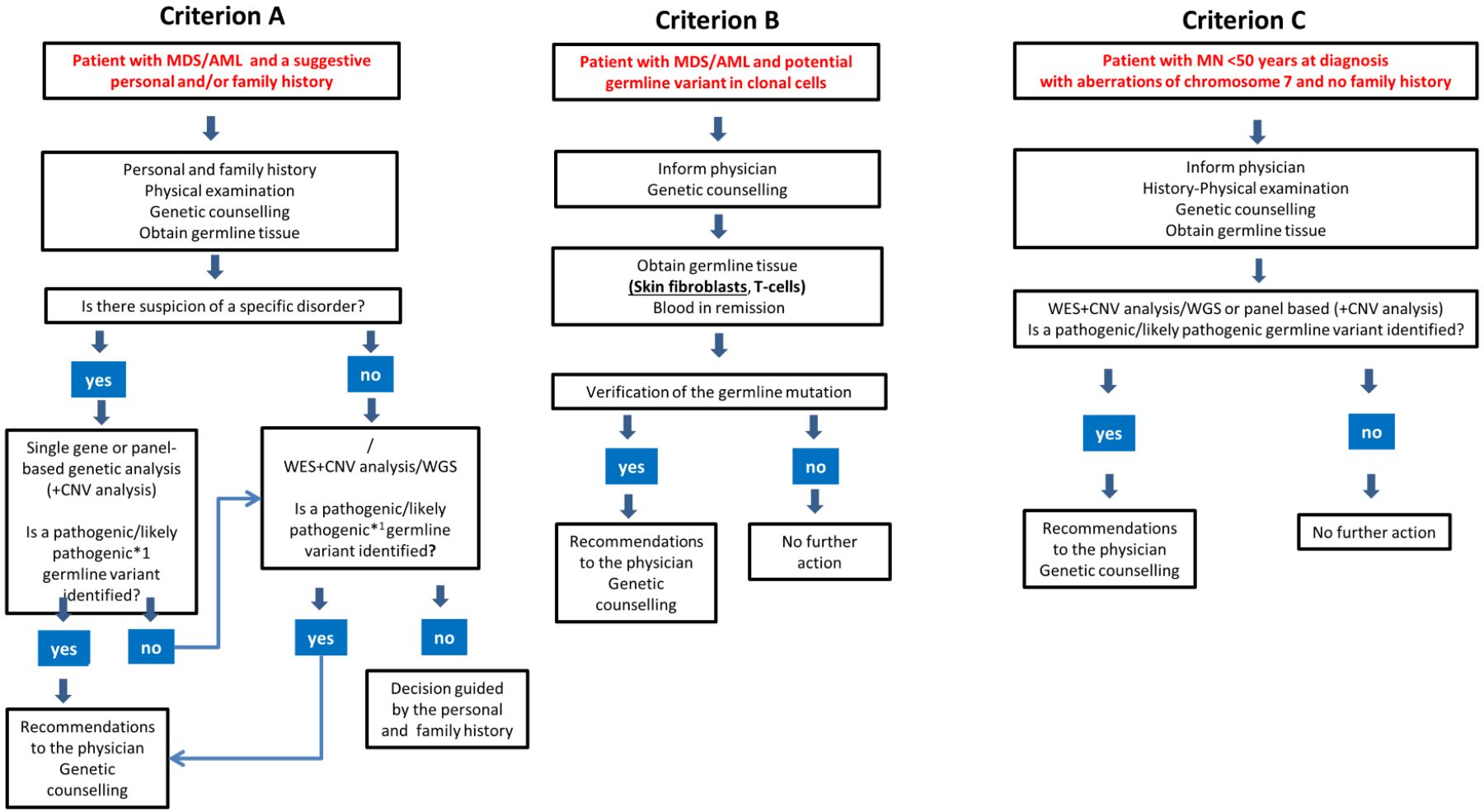
*[1]: excessive toxicities with chemotherapy or radiation, multiple cancer diagnoses, therapy-related leukaemia, poor mobilization of a sibling candidate donor[28,40], consanguinity, skin or nail abnormalities, unexplained liver disease, pulmonary fibrosis or alveolar proteinosis, short stature, microcephaly or characteristic skeletal abnormalities or other congenital abnormalities, Café au lait spots, hypopigmented macules, lymphedema, immune deficiencies, atypical infections, excessive warts.
*[2]: other haematological malignancies or cancer forms suggestive of constitutional mismatch repair deficiency syndrome, Li-Fraumeni syndrome, *BRCA2* related syndromes (such as sarcomas, adrenocortical carcinomas, brain tumors, gastrointestinal, genitourinary, breast, ovarian and pancreas cancer)

Whom to test

B: Patients with MN where the diagnostic work-up for the determination of the somatic genomic background has detected variants suspected to be germline (near heterozygous or near homozygous).

C: Patients not fulfilling the criteria A and B diagnosed with MDS/AML before the age of 50 carrying aberrations of chromosome 7 [monosomy 7/del(7q)/der(7)].

How to test



*1: If no pathogenic/likely pathogenic variant is detected consider funtional studies such us measurement of telomere length, chromosomal breakage analysis etc. In case of variants of unknown significance (VUS) perfom segregation analysis

How to monitor ”healthy” carriers

	Baseline	Follow-up
Complete blood count (CBC)	YES	Every six months
Bone marrow biopsy	YES	Only in case of change in CBC
NGS-myeloid gene panel	YES (bone marrow)	Once a year* (blood)
Control of other relevant organs	As indicated depending on the underlying condition	As indicated depending on the underlying condition

*The emergence of a clone should not solely be an indication for action. The gene, the variant allele frequency (VAF), the number of pathogenic variants as well as the dynamics over time should be taken into account.

Recommendations for Allo-HSCT

- Indications for allo-HSCT
- Timing for allo-HSCT
- Choice of donor
- Conditioning
- Follow-up after allo-HSCT

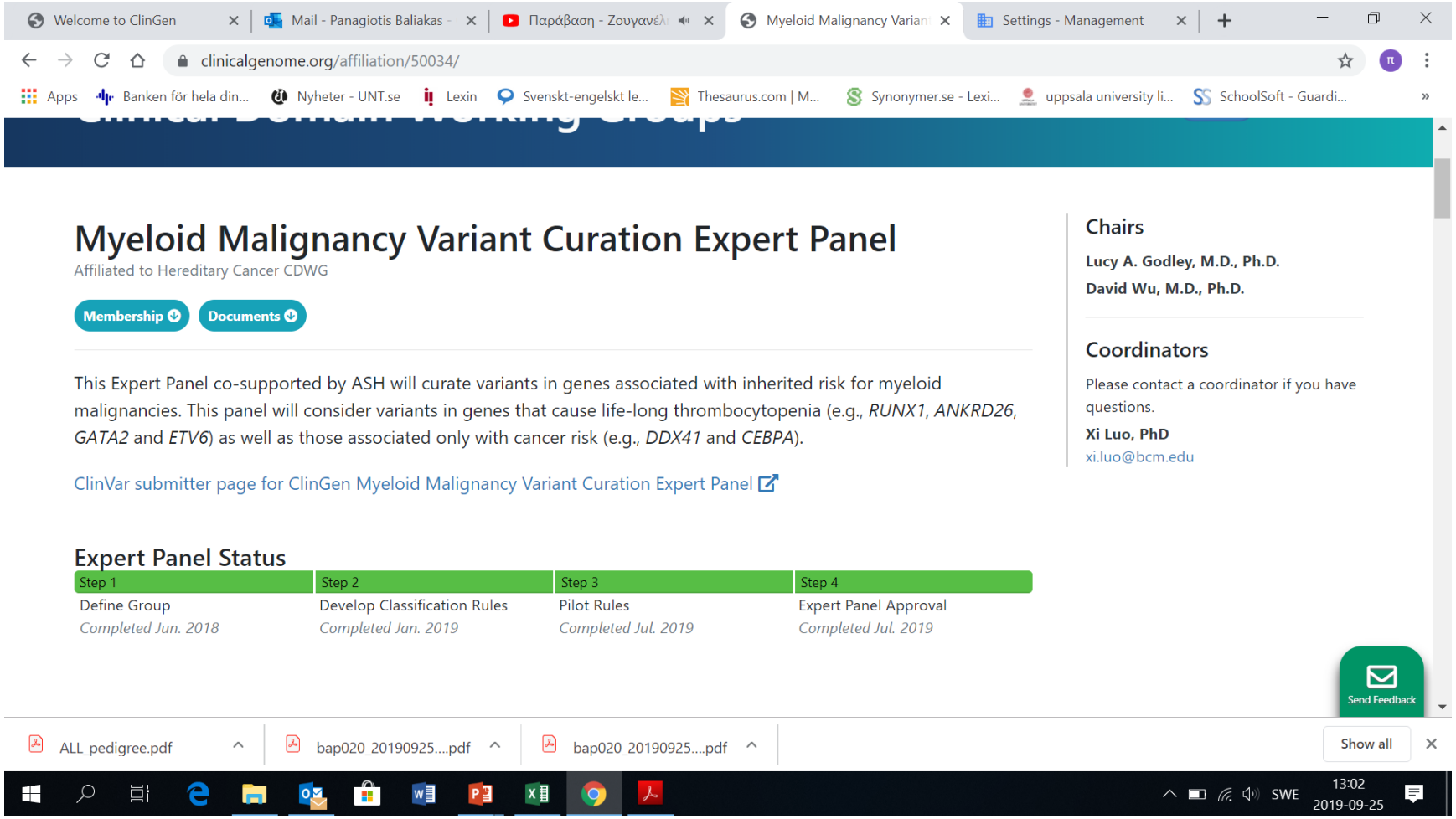
We still have a long way to go....

- Update of the guidelines
- Involve other specialists
- Educate hematologists/geneticists
- Report our findings in the databases
- Active research
- .....

ClinGen

ClinGen is a National Institutes of Health (NIH)-funded resource dedicated to building a central resource that defines the clinical relevance of genes and variants for use in precision medicine and research.

ClinGen


Welcome to ClinGen
Mail - Panagiotis Baliakas
Παράβαση - Ζουγανέλ
Myeloid Malignancy Variant
Settings - Management
clinicalgenome.org/affiliation/50034/
Apps
Banken för hela din...
Nyheter - UNT.se
Lexin
Svenskt-engelskt le...
Thesaurus.com | M...
Synonymer.se - Lexi...
uppsala university li...
SchoolSoft - Guardi...
Myeloid Malignancy Variant Curation Expert Panel
Affiliated to Hereditary Cancer CDWG
Membership
Documents
This Expert Panel co-supported by ASH will curate variants in genes associated with inherited risk for myeloid malignancies. This panel will consider variants in genes that cause life-long thrombocytopenia (e.g., RUNX1, ANKRD26, GATA2 and ETV6) as well as those associated only with cancer risk (e.g., DDX41 and CEBPA).
ClinVar submitter page for ClinGen Myeloid Malignancy Variant Curation Expert Panel
Chairs
Lucy A. Godley, M.D., Ph.D.
David Wu, M.D., Ph.D.
Coordinators
Please contact a coordinator if you have questions.
Xi Luo, PhD
xi.luo@bcm.edu
Expert Panel Status
Step 1
Define Group
Completed Jun. 2018
Step 2
Develop Classification Rules
Completed Jan. 2019
Step 3
Pilot Rules
Completed Jul. 2019
Step 4
Expert Panel Approval
Completed Jul. 2019
Send Feedback
ALL_pedigree.pdf
bap020_20190925....pdf
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2019-09-25

ClinGen

blood advances

American Society of Hematology
2021 L Street NW, Suite 900,
Washington, DC 20036
Phone: 202-776-0544 | Fax 202-776-0545
bloodadvances@hematology.org

ClinGen Myeloid Malignancy Variant Curation Expert Panel recommendations for germline RUNX1 variants

Similar approach for *GATA2* is ongoing

Why is it important with national/international consensus?

MYELOID NEOPLASIA

High frequency of germline *RUNX1* mutations in patients with *RUNX1*-mutated AML

KEY POINTS

- Up to 30% of ***RUNX1*** mutations in the Leucegene AML cohort were confirmed to be germline.
- ***RUNX1*** germline–mutated AML shows a high frequency of ***NRAS*** mutations and other mutations known to activate various signaling pathways.

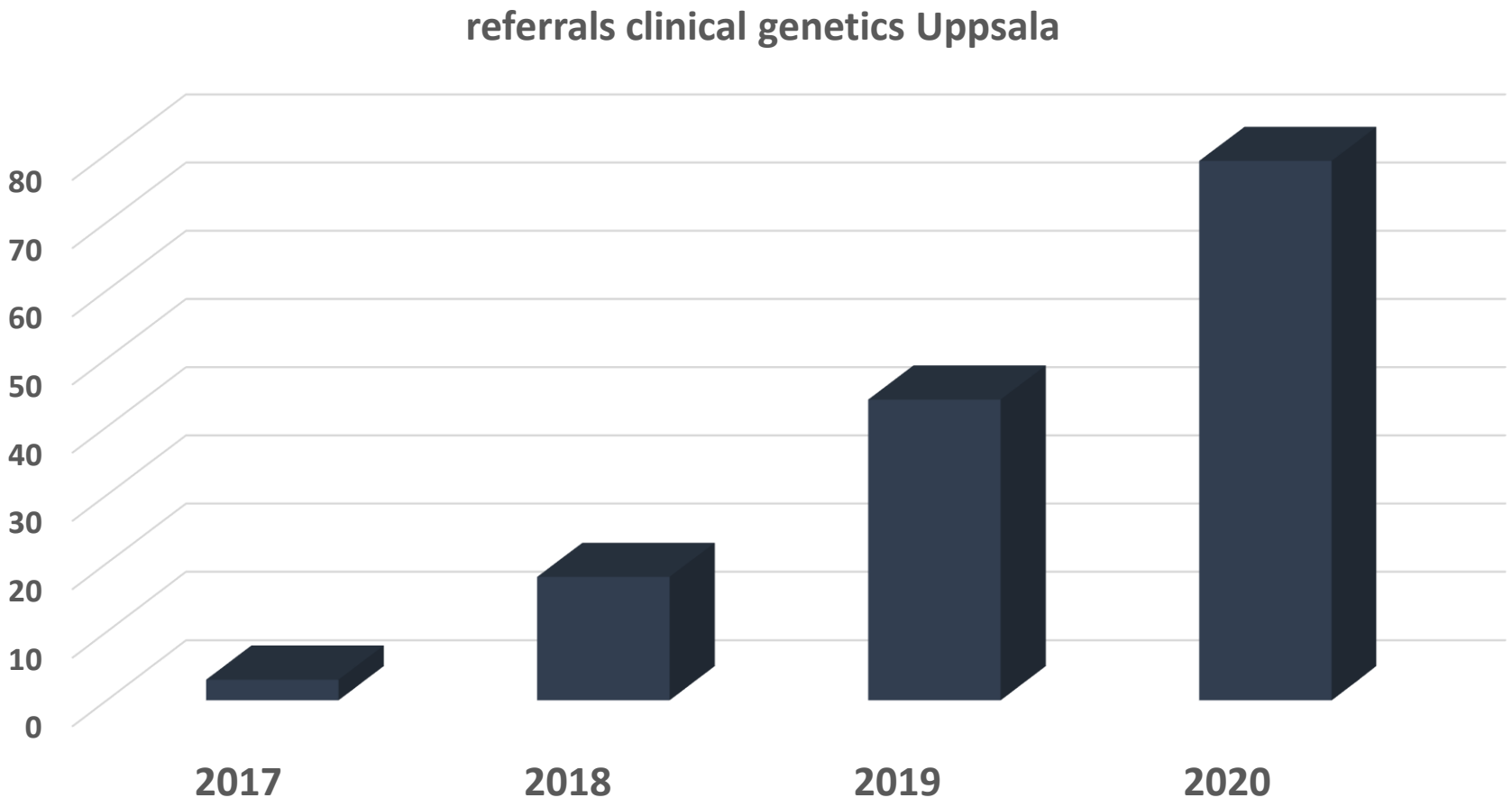
Why is it important with national/international consensus

Table 1. Comparison of *RUNX1* variant curation between Simon *et al* and the MM-VCEP.

ID	Variant (cDNA/protein)	Described in MDS/ AML	Described in *RUNX1* -FPD	Functional impact on RUNX1	MM-VCEP ACMG/AMP criteria code	MM-VCEP *RUNX1*- specific criteria	Further explanation of criteria	MM-VCEP classification
1	c.44_45delAG/ p.Q15fsX	-	-	Truncated RUNT	PVS1_moderate, PS4_supporting, PM2	PS4_supporting, PM2	PVS1 cannot be used for an early truncating variant only affecting RUNX1 isoform C.	VUS
2	c.179C>T/ p.A60V	PMID 12399980	Lorente NP (thesis, 2002)	-	BS1	BS1, BS3	This variant meets the calculated BS1 threshold (Latino subpopulation) and BS3 (normal transactivation and normal DNA binding/subcellular localization, PMID 22012064). The presence of the variant in patients with a *RUNX1*-phenotype is not sufficient to call a variant pathogenic, in particular not if the variant is present in gnomAD at a MAF incompatible with disease prevalence.	BEN
3+4*	c.421T>G/ p.S141A	-	RUNX1db	Normal transactivation (PMID 12807883)	PS4_supporting, PP3, BS3_supporting	PS4_supporting, PM1_supporting, PP3	Variant not present in RUNX1db. While there is no effect on heterodimerization ability with CBF (PMID 12807883), data from an additional secondary assay or transactivation assay are missing, thus not permitting application of any BS3 strength level.	VUS
5	c.427G>T/ p.E143X	-	-	Truncated RUNT	PVS1, PS4_supporting, PM2	PVS1, PS4_supporting, PM2		PATH
6	c.454_456insA/ p.K152fsX	PMID 20421268	-	Truncated RUNT	PVS1, PS4_supporting, PM2,	PVS1, PS4_supporting, PM2	Nomenclature is not HGVS conform. We assume this variant is not present in gnomAD (PM2) and leads to NMD (PVS1).	PATH
7	c.496C>T/ p.R166G	PMID 11049997	-	LOF/dominant negative (PMID 11049997)	PS4_supporting, PM2, PM5, PP3,	PS4_supporting, PM5, PM1, PM2, PP3	R166Q has been curated by the MM-VCEP as PATH.	LPATH
8	c.496C>T/ p.R166X	PMID 11023523	PMID 29146883	Truncated RUNT	PVS1, PS4, PM2, PP1	PVS1, PS4, PM2, PP1_strong		PATH
9+10	c.610C>T/ p.R204X	PMID 10068652	PMID 10508512	LOF (PMID 10068652)	PVS1, PS4, PM2, PP1	PVS1, PS4, PM2, PP1		PATH
11	c.619C>T/ p.R207W	PMID 28927163	-	-	PS4_supporting, PM2, PP3	PS4_supporting, PM2, PP3	*In-silico* prediction alone (e.g. in this case pathogenic predictions by using SIFT, Polyphen, VEST, CHASM, and REVEL) is only supporting evidence and insufficient to classify a variant as pathogenic.	VUS
12	c.1243_1244insC/ p.Q415fsX	-	-	Elongated RUNX1 isoform	PVS1_strong, PS4_supporting, PM2	PVS1_strong, PS4_supporting, PM2		LPATH

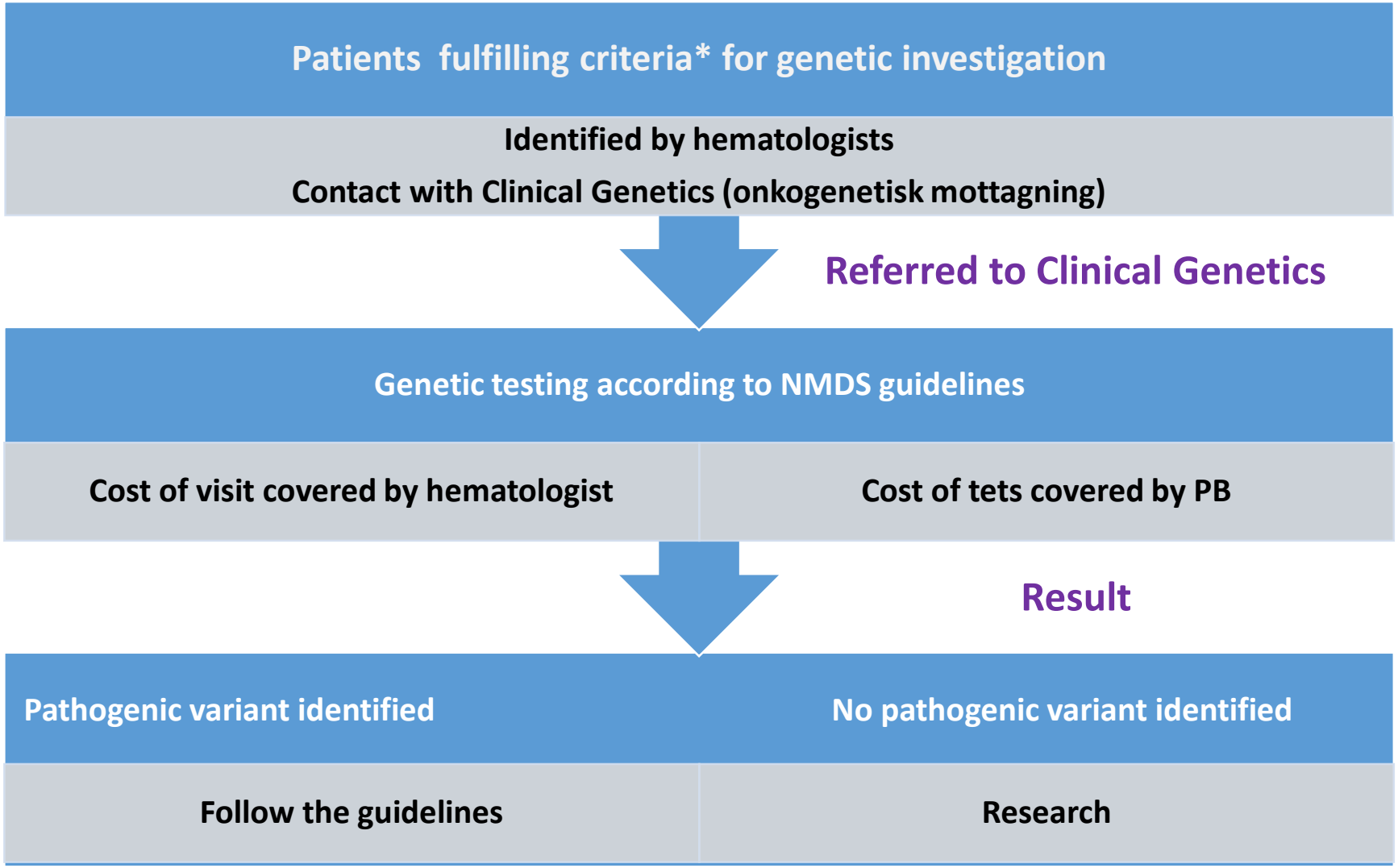
The part highlighted in green stems from the Simon *et al* study (PMID 32315381), the part highlighted in purple and surrounded by a black box is the MM-VCEP assessment.
*Patients are related.
Abbreviations: ACMG: American College of Medical Genetics and Genomics, AML: acute myeloid leukemia, AMP: Association for Molecular Pathology, BEN: benign, FPD: familial platelet disorder, HGVS: Human Genome Variation Society, LOF: loss-of-function, LPATH: likely pathogenic, MAF: minor allele frequency, MDS: myelodysplastic syndrome, MM-VCEP: Clinical Genome Myeloid Malignancy Variant Curation Expert Panel, NMD: nonsense-mediated decay, PATH: pathogenic, VUS: variant of unknown significance.

New indications-new routines



Clinical genetics Uppsala

Prospective clinical study



~50 pts per year
Cost for testing: 30000kr/pt
Inclusion of 100-200 pts
Main endpoint: ≥20% pts with a pathogenic varint
Timespan: 1-2 years

*: Arm A/Arm B. Arm B (reserach cohort): MDS/AML <50y without any clinical indication for germline background

Follow the guidelines....

If there are no guidelines..make them

Do not be afraid to think out of the box

Thank you for your attention

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