Taking care of patients with possible hereditary hematological disease

Panagiotis Baliakas, MD-PhD

Dept of Immunology, Genetics and Pathology

Science for Life Laboratory, Uppsala University

Clinical Genetics, University Hospital, Uppsala

UPPSALA UNIVERSITET

SciLifeLab

AKADEMISKA SJUKHUSET

The challenges of HHMs

Identification of individuals being at high risk for HMM

Relatively rare or underappreciated-Enriched in specific subgroups

- *GATA2* in 72% of teenagers with MDS and monosomy 7
- *TP53* mutations in 50% of low hypodiploid ALL

Variations regarding disease phenotype

- High expressivity/Low penetrance

The challenges of HHMs

Clinically relevant when it comes to the selection of a donor

- Slow or failed engraftment
- EBV related PTLD (posttransplant lymphoproliferative disease)
- Donor derived leukemia

May influence the therapeutic approach

Limited knowledge of the additional somatic events

Absence of standard diagnostic routine

Paucity of clinical guidelines

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

ELN guidelines 2017

Myeloid neoplasms with germline predisposition without a pre-existing disorder or organ dysfunction

- Acute myeloid leukemia with germline *CEBPA* mutation
- Myeloid neoplasms with germline *DDX41* mutation[b]

Myeloid neoplasms with germline predisposition and pre-existing platelet disorders

- Myeloid neoplasms with germline *RUNX1* mutation[b]
- Myeloid neoplasms with germline *ANKRD26* mutation[b]
- Myeloid neoplasms with germline *ETV6* mutation[b]

Myeloid neoplasms with germline predisposition and other organ dysfunction

- Myeloid neoplasms with germline *GATA2* mutation
- Myeloid neoplasms associated with bone marrow failure syndromes
- Myeloid neoplasms associated with telomere biology disorders
- Myeloid neoplasms associated with Noonan syndrome
- Myeloid neoplasms associated with Down syndrome[a]

Guide for molecular genetic diagnostics[c]

Myelodysplastic predisposition/acute leukemia predisposition syndromes

- *CEBPA*, *DDX41*, *RUNX1*, *ANKRD26*, *ETV6*, *GATA2*, *SRP72*, 14q32.2 genomic duplication (*ATG2B/GSKIP*)

Cancer predisposition syndromes[d]

- Li Fraumeni syndrome (*TP53*)
- Germline *BRCA1/BRCA2* mutations

Bone marrow failure syndromes

- Dyskeratosis congenita (*TERC*, *TERT*)
- Fanconi anemia

Döhner H et al. Blood 2017

Even more complex than it seems...

Class	Patient Population	Specific Syndromes
MDS/AL Predisposition Syndromes	MDS AML ALL	FPD/AML (*RUNX1*) Germline *ANKRD26* mutation Germline *DDX41* mutation Germline *ETV6* mutation Familial AML with mutated *CEBPA* Familial AML with *GATA2* mutation 14q32.2 genomic duplication (*ATG2B/GSKIP*) Germline *PAX5* mutation (ALL only) Germline *SH2B3* mutation (ALL only) Trisomy 8 mosaicism
Bone Marrow Failure Syndromes	AA MDS AML	Dyskeratosis congenita Fanconi anemia
Genetic Syndromes	ALL	Ataxia Telangiectasia (*ATM*) Bloom syndrome (*BLM*) Down syndrome (Trisomy 21) Leopard/Noonan syndrome (*PTPN11*) Neurofibromatosis I (*NF1*) Nijmegen Breakage syndrome (*NBS1*) Wiskott Aldrich syndrome (*WAS*)
Familial MPNs	PV, ET, PMF, CML	14q32.2 genomic duplication (*ATG2B/GSKIP*) *RBBP6* mutations
Familial Lymphomas	CLL HL/NHL	Familial CLL Familial Lymphoma Predisposition Germline *MKL1* mutation Germline *MLL* mutation Germline *ASXL1* mutation
Cancer Predisposition Syndromes	All	Li-Fraumeni syndrome (*TP53*) Hereditary breast & ovarian cancer (*BRCA1/2*) Lynch syndrome Cowden syndrome (*PTEN*)
Familial MM/LPL	MM, MGUS, LPL	Familial MM/LPL

Codley LA. Blood 2016

Are they really new???

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.

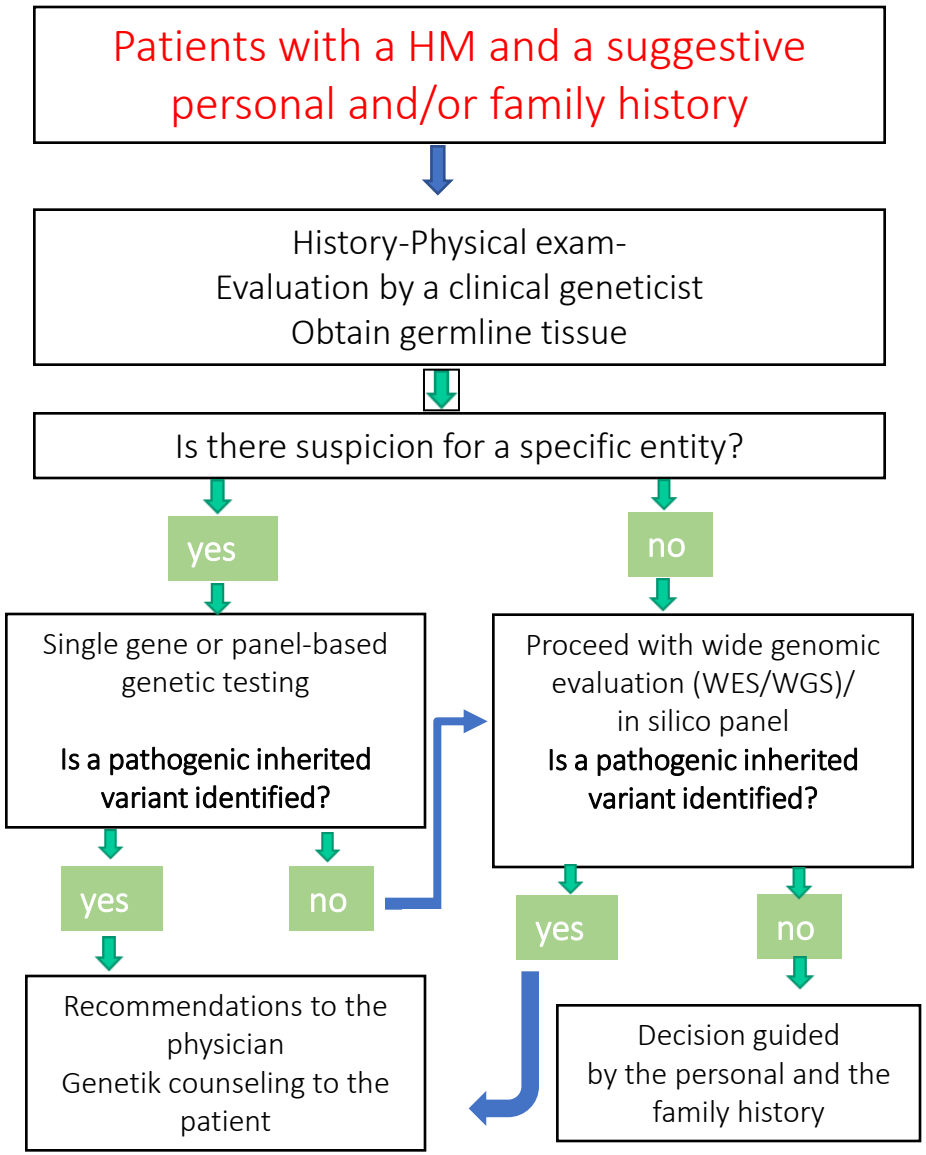
By

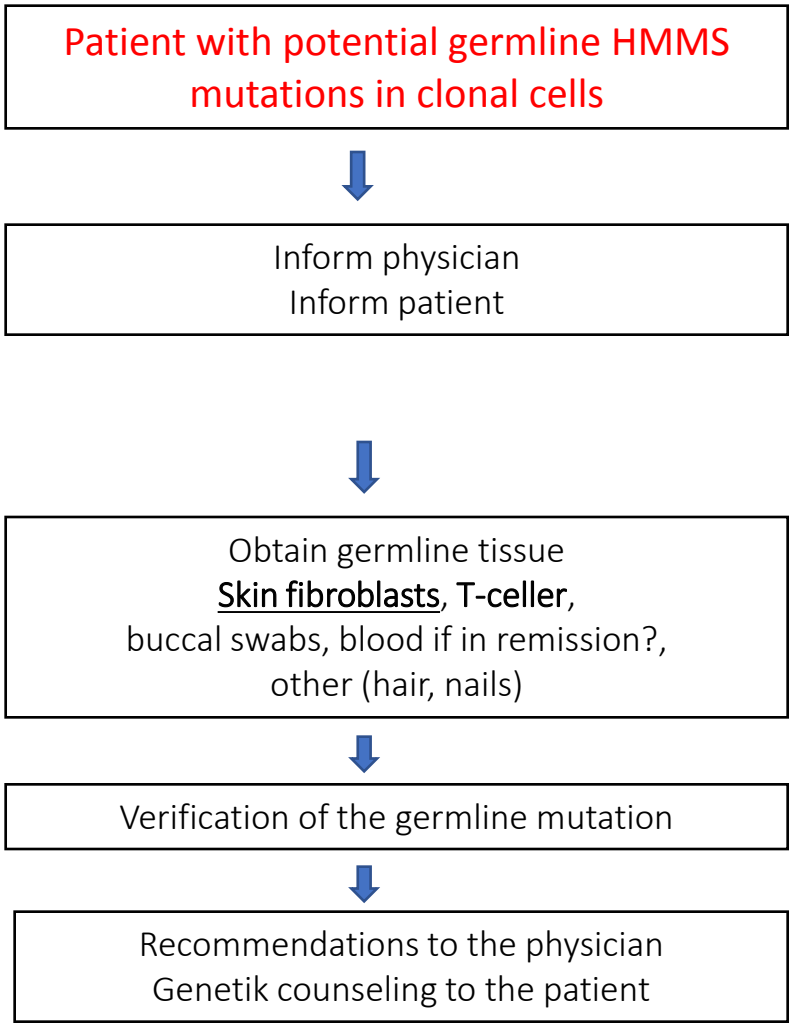
AAGE VIDEBÆK.

(Submitted for publication August 6, 1946.)

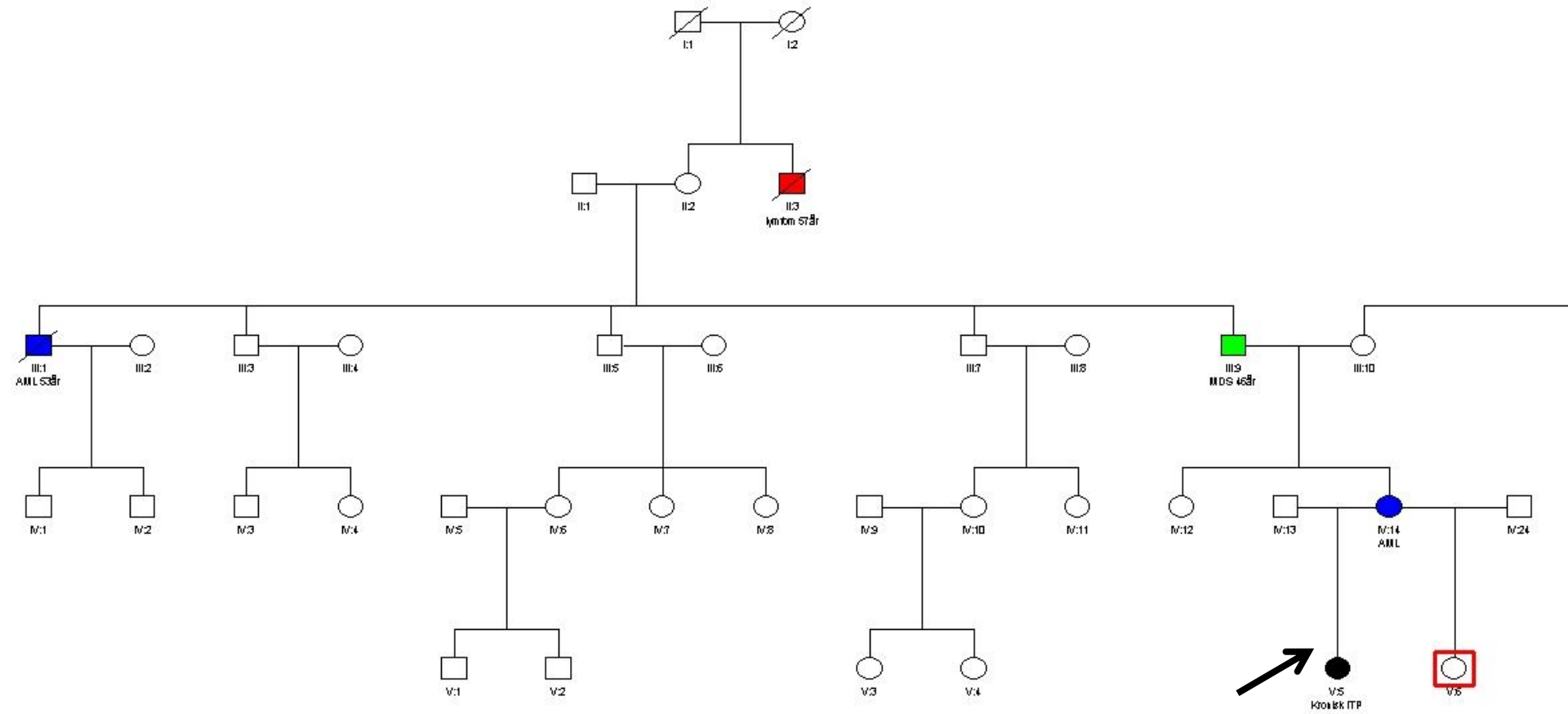
Reference: Biermer et al. Ein Fal von Leukamie. Virch. Arch. ***20:552,*** 1861.

The local experience





Case report 1

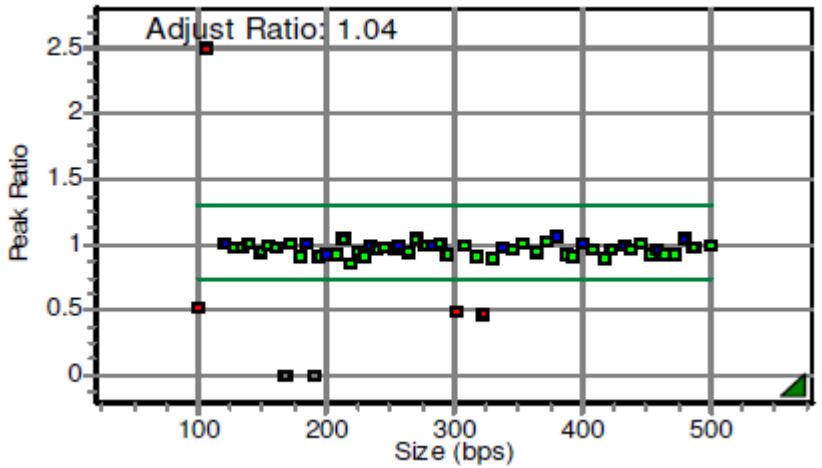


Indication for WES?

Case report 1

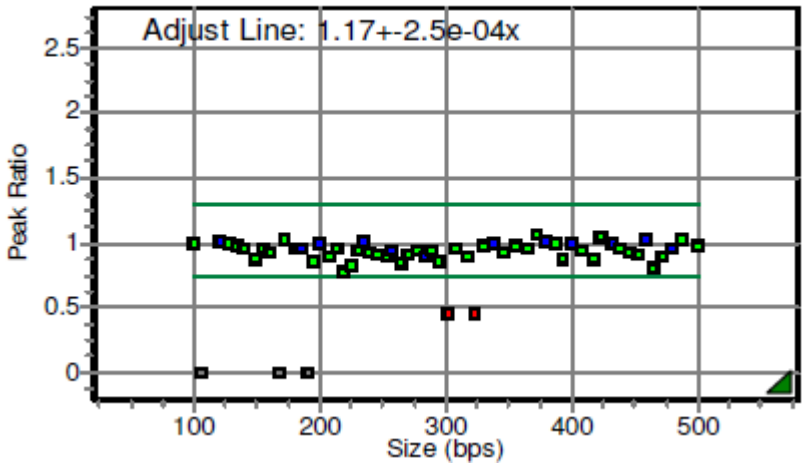
Index patient (Blood)

28	RUNX1_ex01	213.5	1.046
29	RUNX1_ex02	172.2	1.009
30	RUNX1_ex03	353.9	1.013
31	RUNX1_ex04b	240.5	0.960
32	RUNX1_ex05	423.6	0.967
33	RUNX1_ex06	438.6	0.963
34	RUNX1_ex07	386.0	0.930
35	RUNX1_ex08	155.3	0.991
36	RUNX1_ex09	301.5	0.486
37	RUNX1_ex10	323.6	0.482



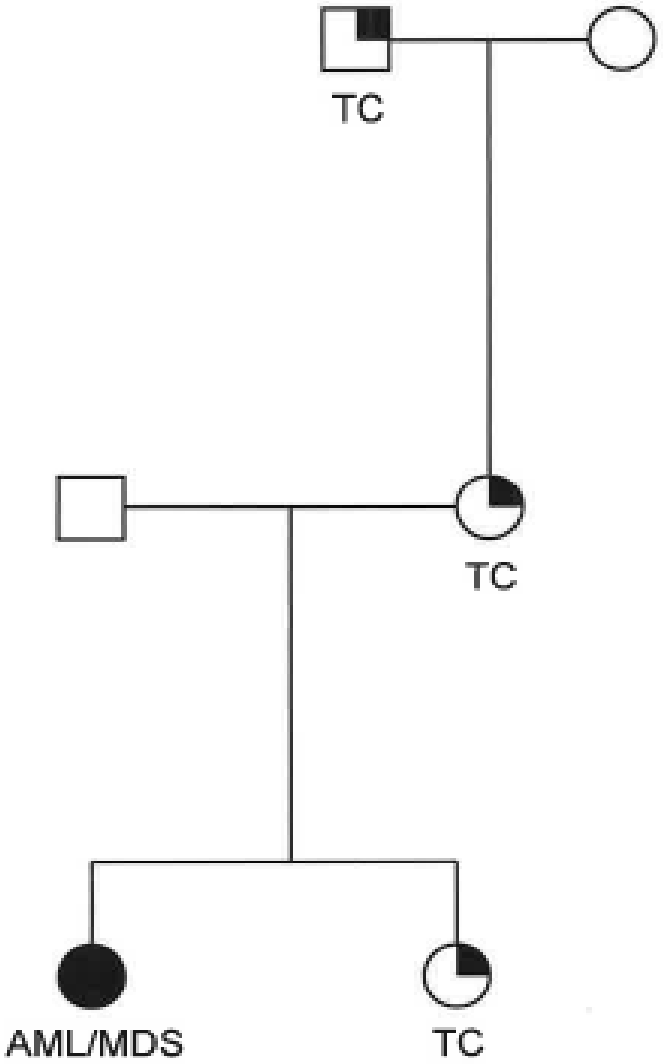
Grandfather (Fibroblasts)

28	RUNX1_ex01	213.6	0.964
29	RUNX1_ex02	172.4	1.039
30	RUNX1_ex03	354.1	0.983
31	RUNX1_ex04b	240.7	0.936
32	RUNX1_ex05	423.5	1.044
33	RUNX1_ex06	438.5	0.960
34	RUNX1_ex07	386.1	0.988
35	RUNX1_ex08	155.5	0.966
36	RUNX1_ex09	301.5	0.450
37	RUNX1_ex10	323.7	0.465



Engvall et al. In preparation

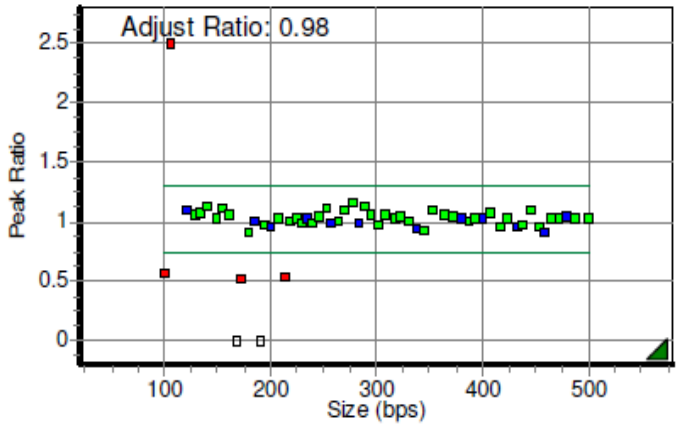
Case report 2

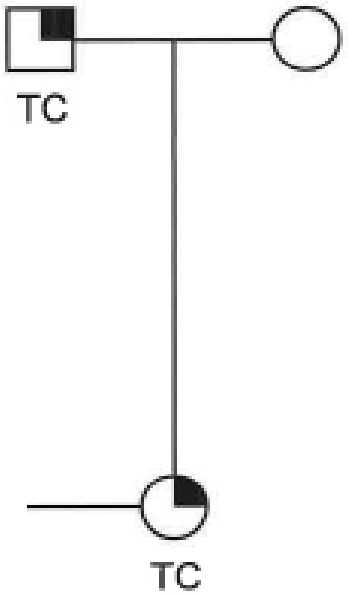


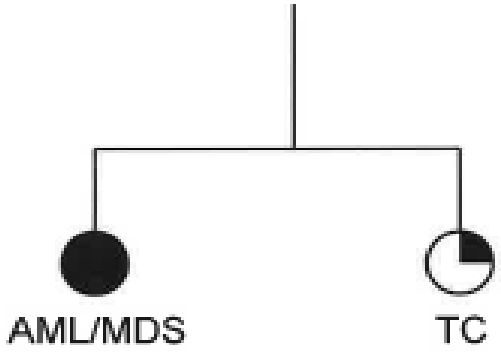
Engvall et al. In preparation

Case report 2

28	RUNX1_ex01	213.5	0.546
29	RUNX1_ex02	172.2	0.522
30	RUNX1_ex03	353.9	1.102
31	RUNX1_ex04b	240.5	1.001
32	RUNX1_ex05	423.6	1.029
33	RUNX1_ex06	438.6	0.972
34	RUNX1_ex07	386.0	1.011
35	RUNX1_ex08	155.3	1.115
36	RUNX1_ex09	301.5	0.977
37	RUNX1_ex10	323.6	1.044







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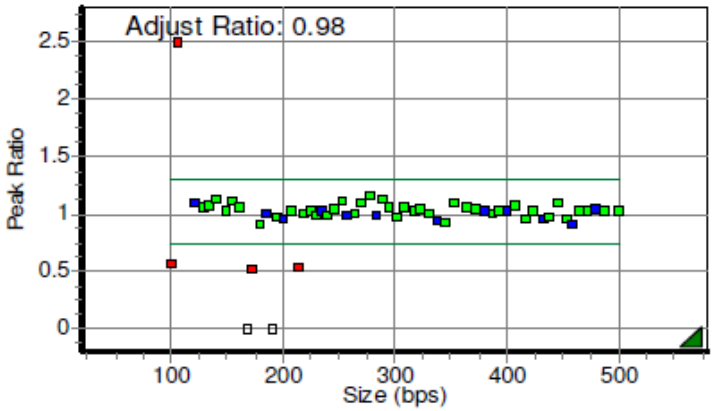


Engvall et al. In preparation

Case report 2

Male

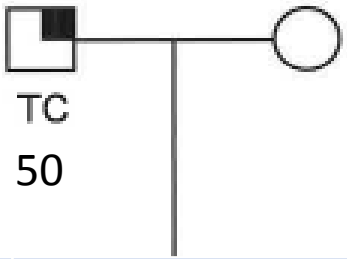
arr[hg19] 21q22.12(36,289,021-36,510,008)x1

Female

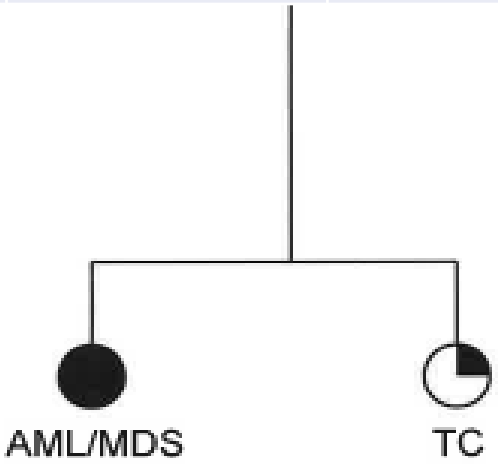
arr[hg19] 21q22.12(36,289,047-36,510,008)x1

Engvall et al. In preparation

Case report 2



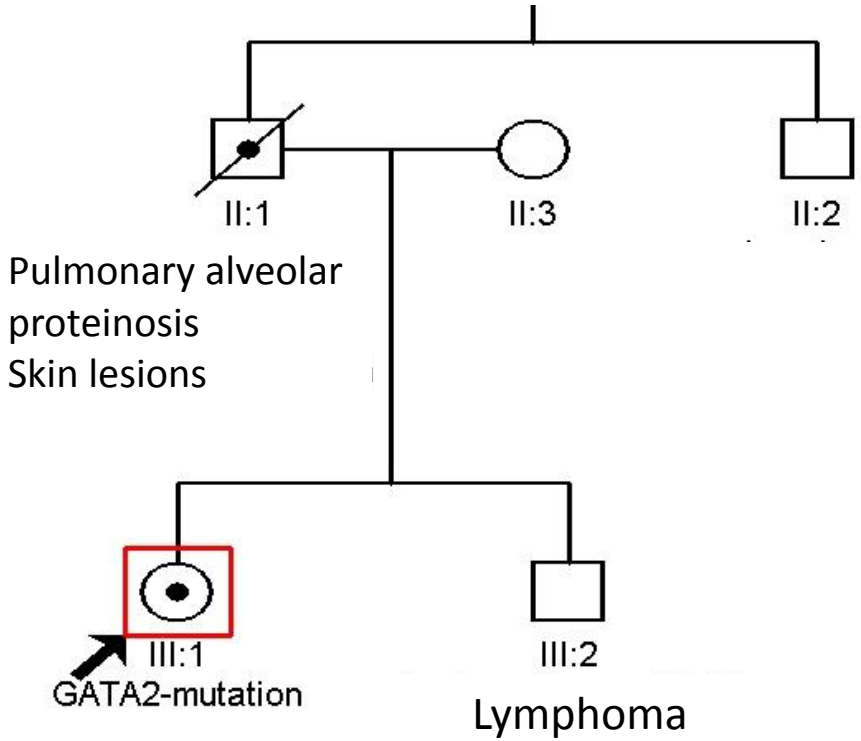
Gene	cDNA	Protein	Whole blood VAF	T-cells VAF	Interpretation
BCOR	c.3645delG	p.1216fs*44	64% (3478)	<1% (2157)	Pathogenic
PHF6	c.947A>T	p.N316I	51% (5446)	<1% (8402)	VUS



Engvall et al. In preparation

Case report 3

Should we care only about the risk for AML/MDS?



Case report 4

Are all FPD/MM equal?

IV:1 IV:2

TC

Review Series

blood

PRECISION HEMATOLOGY

Genetic predisposition to hematologic malignancies: management and surveillance

Lucy A. Godley[1,2] and Akiko Shimamura[3]

[1]Section of Hematology/Oncology, The University of Chicago Comprehensive Cancer Center, and [2]Center for Clinical Cancer Genetics, The University of Chicago, Chicago, IL; and [3]Dana-Farber/Boston Children's Cancer and Blood Disorders Center, Harvard Medical School, Boston, MA

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JOURNAL OF CLINICAL ONCOLOGY

REVIEW ARTICLE

Germline Genetic Predisposition to Hematologic Malignancy

Elissa Furutani and Akiko Shimamura

Many issues to be addressed

Who to test (phenotype, age, other?)

Which analysis (targeted or broad analyses)

Which genomic aberrations (SNVs,CNVs, both?)

How to follow the patient?

How to counsel the family?

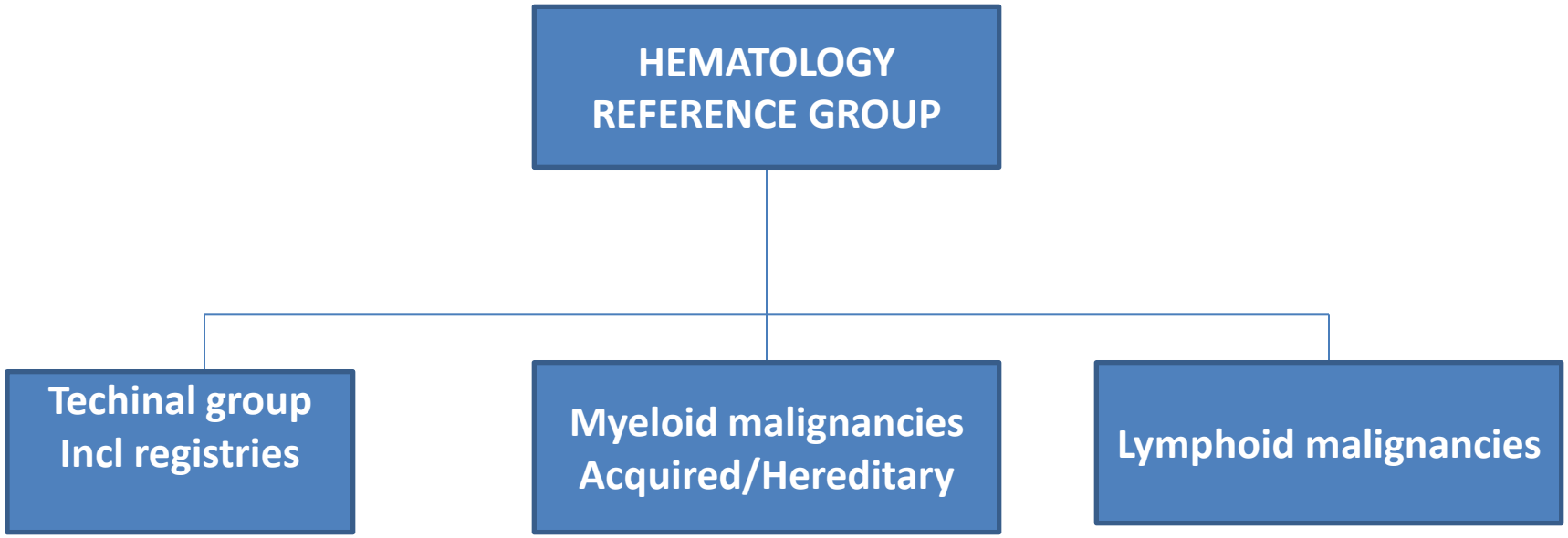
Ethical considerations.....

Many issues to be addressed

- Who to test (phenotype, age, other?)
- Which analysis (targeted or wide a
- Which genomic
- counsel the family?
- Ethical considerations.....

Urgent need for consensus and national guidelines

Hematological malignancies within GMS



Baliakas Panagiotis, Barbany Gisela, Belander Strålin Karin, Bjorck Eric, Cammenga Jörg, Engvall Marie, Hellström-Lindberg Eva, Höglund Martin, Jädersten Martin, Larazevic Vladimir, Lehmann Sören, Nordgren Ann, Öster Fernström Annette, Tesi Bianca, Tran Ann-Nhi

Cavelier Lucia, Fioretos Thoas, Rosenquist Richard

Who to test for HHMs

Young individuals (<50) with MNs (AML/MDS) independently of a positive family history

Young individuals (<50) with long-lasting cytopenias

- Family history?

Patients with MN (>50) with a positive family history

- Two individuals with MNs in a three-generation pedigree at least one diagnosed <50
- One individual with MN plus at least one individual with a condition indicative of a clinical syndrome predisposing to MNs in a three-generation pedigree
- One individual with MN plus two individuals with solid tumors , one diagnosed <50 in a three-generation pedigree

Study	Cohort	Technique	Results	Comment
Zhang J et al NEJM 2015	N=588 (leukemia) <20 years	WGS/WES 565 genes 60 cancer genes 476 other	26/588 (4.4%)*[1]	226 VUS in the 60 genes 4348 non silent mutation in the 476 genes 40% with positive family history (FD or SD relative)
Churpek J et al Blood 2015	17 families ≥2 MDS/AML	Panel 264 genes	5/17 (29%)	67% of asympromatic RUNX1 carriers >50: clonal hem (VAF: 20-71%)
Keel S et al Haematologica 2016	98 AA (<18: n=53, 18-40: n=45)*[2] 135 MDS (<18: n=46, 18-46: n=64)*[3]	Panel BMFS	5/99 AA (5%) 2 DC, 2 MPL, 1 TP53 15/113 (13.6%) 5 GATA2, 4 DC, 3 TP53, 1 SDS, 1 RUNX1, I FA	AA: 2/5 *2 MDS 12/15: *3
Bluteau et al Blood 2017	179 pts with inherited BMF suspicion non-FA 37% >18	WES	86/179 (48%)	52% neg
Schwartz J et al Nat Com 17	77 children	WES (n=54) TSCA (n=23)	6/77 (8%) 2 NF1, 2 NRAS/PTPN11, 1 RUNX1, 1 GATA2	8 VUS SAMD9/SAMD9L
Dinardo et al CLML 2016	BMF/MDS/AA <50, n=8 (A) RUNX1/GATA2/CEBPA+, n=17 (B) HM+ MM or +FH, n=13 (C) HM+ +HFH, n=11	Panel (28 genes)	A: 3/8, FA, DC, RUNX1 B: 2/17, RUNX1 C: 2/13, TP53 D:2/11, RUNX1, DDX41	

*[1]: The lowest prevalence of germline mutations despite the inclusion of hypodyploid ALL
*[2]: positive family history : 40%, Physical anomalies: 11%
*[3]: positive family history : 52%, Physical anomalies: 24%

Who to test for HHMs

Young individuals (<50) with MNs (AML/MDS) independently of a positive family history

Young individuals (<50) with long-lasting cytopenias

- Family history?

Patients with MN and a **positive family history**

- Two individuals with MNs in a three-generation pedigree at least one diagnosed <50
- One individual with MN plus at least one individual with a condition indicative of a clinical syndrome predisposing to MNs in a three-generation pedigree
- One individual with MN plus two individuals with solid tumors , one diagnosed <50 in a three-generation pedigree

What to ask the patient?

Do you/does anyone in your family have chronic low blood counts, including low red blood cells (anemia), low platelets, (thrombocytopenia or ITP), low white blood cells (leukopenia, monocytopenia, lymphopenia)? Has anyone required a transfusion for a low blood count?	A, B, C, F, H, J, K
Did you/does anyone in your family bleed or bruise easily? If yes, have they required transfusions for bleeding?	A, B, C
Do you/does anyone in your family have or have had warts (genital, hands, feet, or any other site)? If yes, where and for how many years?	F
Do you/does anyone in your family get infections easily or severe or unusual types of infections? If yes, how many infections and what type? (e.g., pneumonia, meningitis) and at what age(s)? Did they require hospitalization or antibiotics?	F, J, K
Does anyone in the family have swelling of one limb larger than the others (also known as lymphedema)? If yes, what limb and is there a known reason why that limb is swollen?	F
Do you/does anyone in your family have deafness? If yes, at what age did it occur and is there a known reason for why that person cannot hear?	F, I, J
Do you/does anyone in your family have abnormal nails (e.g. misshapen or missing not due to injury)?	H, J, K
Did you/does anyone in your family get grey hair in their 20s or earlier? Whom and at what age?	H, J
Have you or anyone in your family had skin cancer or abnormal coloration of the skin, especially around the neck region?	H, J, K, N
Have you/anyone in your family had a specific skin problem called eczema?	C
Do you or anyone in your family have lung disease, including pulmonary fibrosis, IPF, or early onset emphysema?	H, J
Do you or anyone in your family have a lung disease called pulmonary aveolar proteinosis?	F
Do you/does anyone in your family have a liver disease called cirrhosis? If yes, at what age and is there a known reason why you/they have cirrhosis (for example, heavy alcohol use)?	H, J
Have you or other family members had other types of cancer, such as head and neck cancer?	H, J, K, L, M
Have you or other family members had other types of cancer, such as cervical or anal cancer cancer?	H, J, K, L
Have you or other family members had other types of cancer, such as early onset breast cancer, sarcoma, or brain or colon cancers?	L, M, N

Churpek et al. Blood 2016

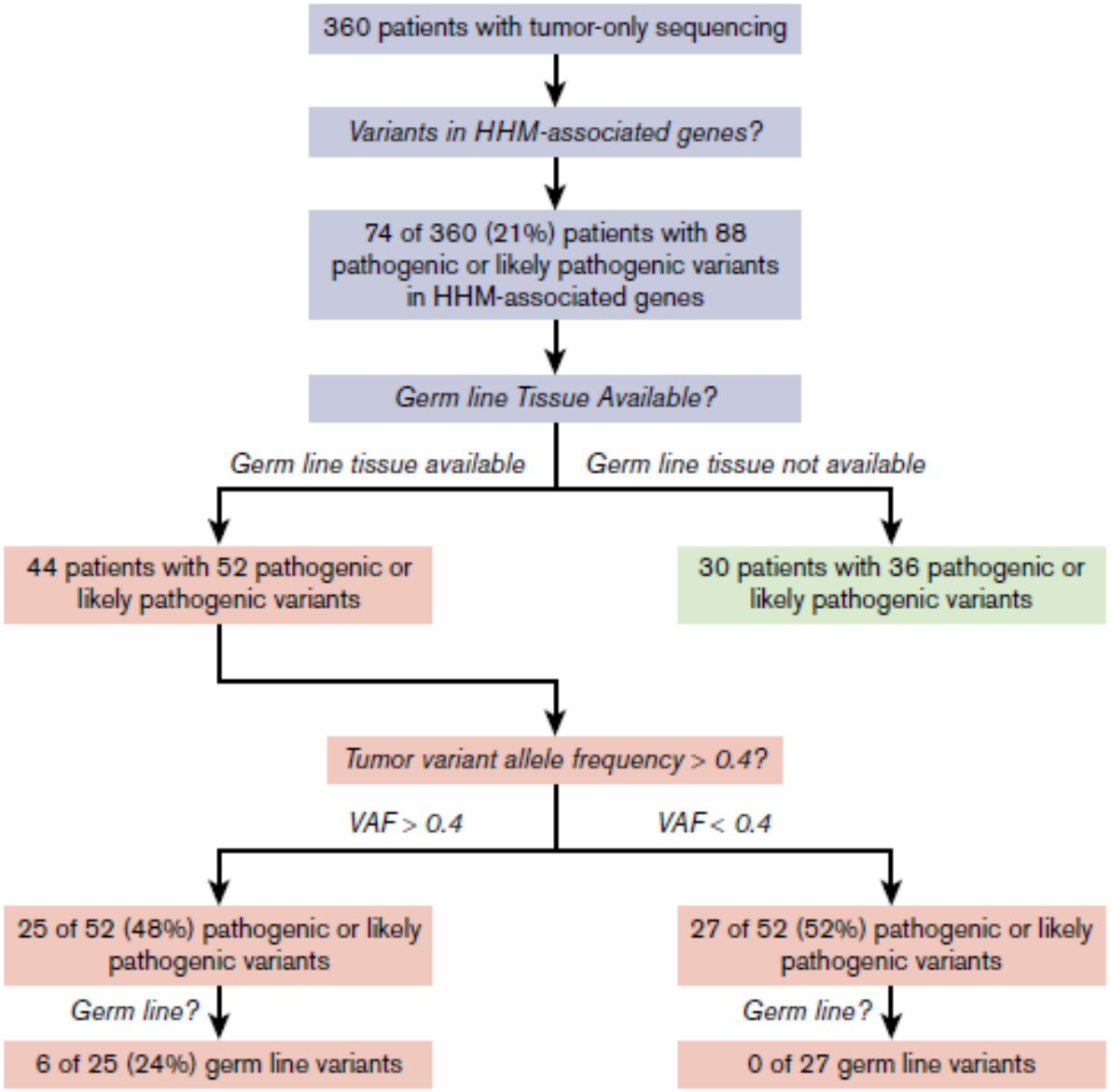
Who to test for HHMs

Patients with MNs with a germline mutation detected during the diagnostic work up of the MN

- near-heterozygous (40%-60%) or near-homozygous (90%)

Family relatives of an index patient diagnosed with MN-GP

Identifying the ”germline” in the clone



Drazer MW et al. Blood advances 2017

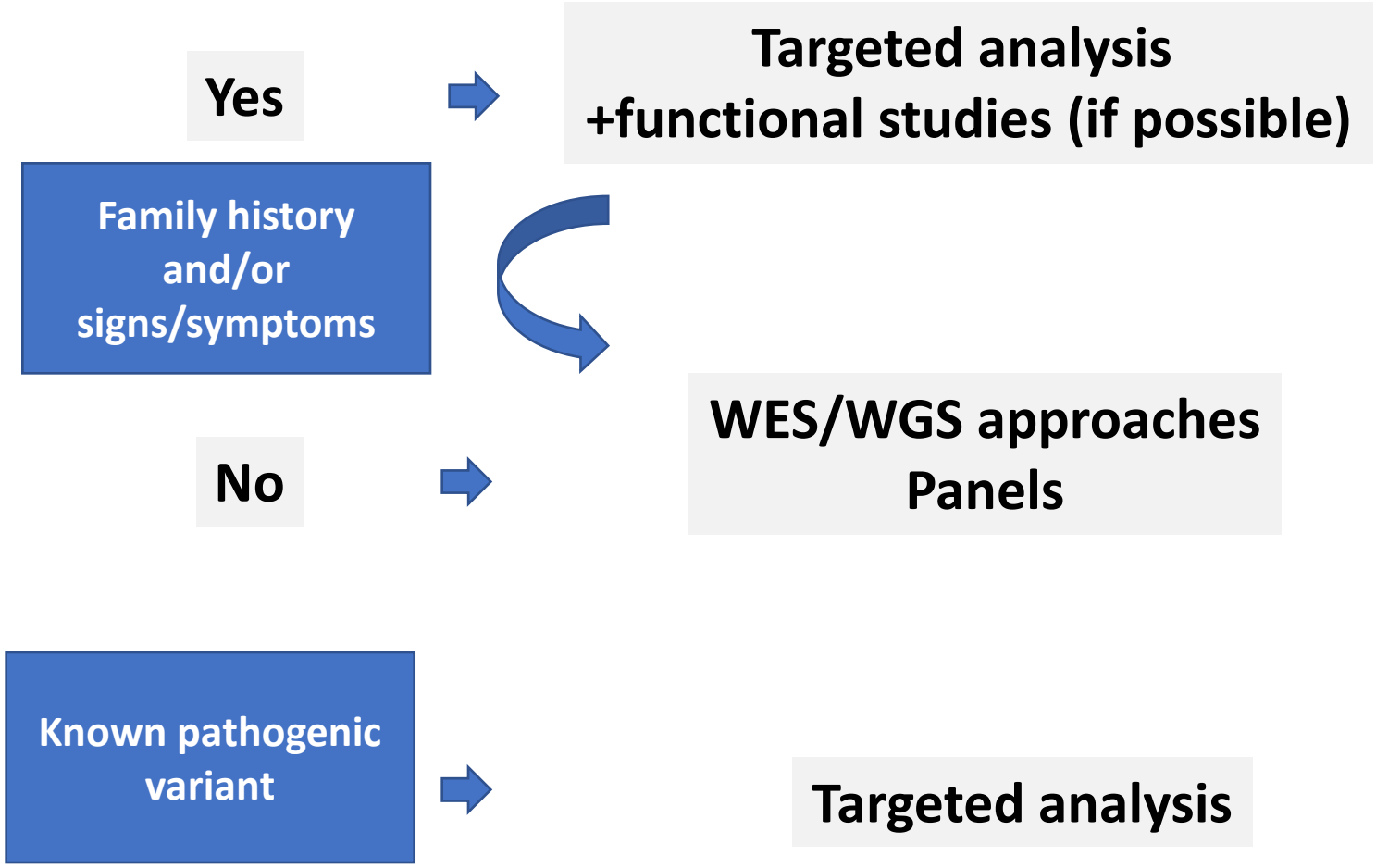
Who to test for HHMs

Patients with MNs with a germline mutation detected during the diagnostic work up of the MN

- near-heterozygous (40%-60%) or near-homozygous (90%)

Family relatives of an index patient diagnosed with HMM

Which is the optimal methodology?



How I treat HHMs?

Due to the young age: Intention to cure

Should we offer Allo-HSCT to all young patients with HHM?

The clonal genetic background may determine the therapeutic approach

Surveilance of other organs in case of a syndromic condition

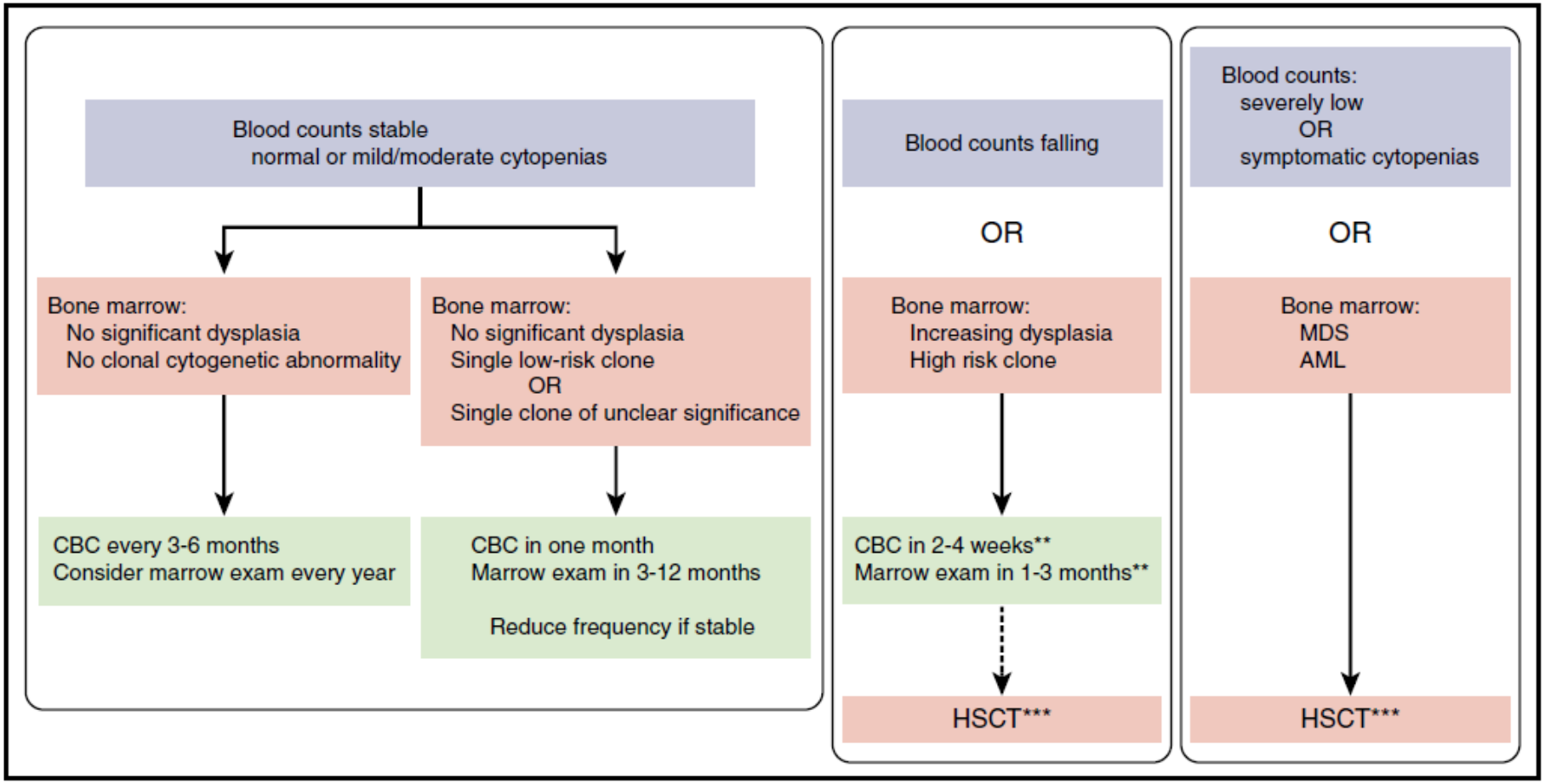
Codley/Shimamura. Blood 2017

Key to understanding the development of the HHM: In depth characterization of the clone

All HHMs will be analysed with both traditional and novel methodologies

If no somatic variant is detected: performance of WES

Follow-up of ”healthy” carriers



Codley/Shimamura. Blood 2017

Follow-up of ”healthy” carriers

Baseline (when???)

- Bone marrow biopsy
- Cytogenetics
- NGS

Follow-up

- Blood status every 6 months
- NGS 1-2 years (blood)
- Biobanking of samples including serum/plasma

Surveilance of all organs that may be affected in case of a syndromic condition

Follow-up of ”healthy” carriers

Change of the blood status

- Repeat BMB/Cytogenetics/NGS

Detection of a novel somatic variant without any change of the blood status

- Repeat NGS in 3-6 months (family history, type of mutation, VAF, number of mutations, dynamics overtime)
- Blood status every 3 months
- BMB if >1 mutations or if VAF>20%

Disease evolution in familiar AML/MDS

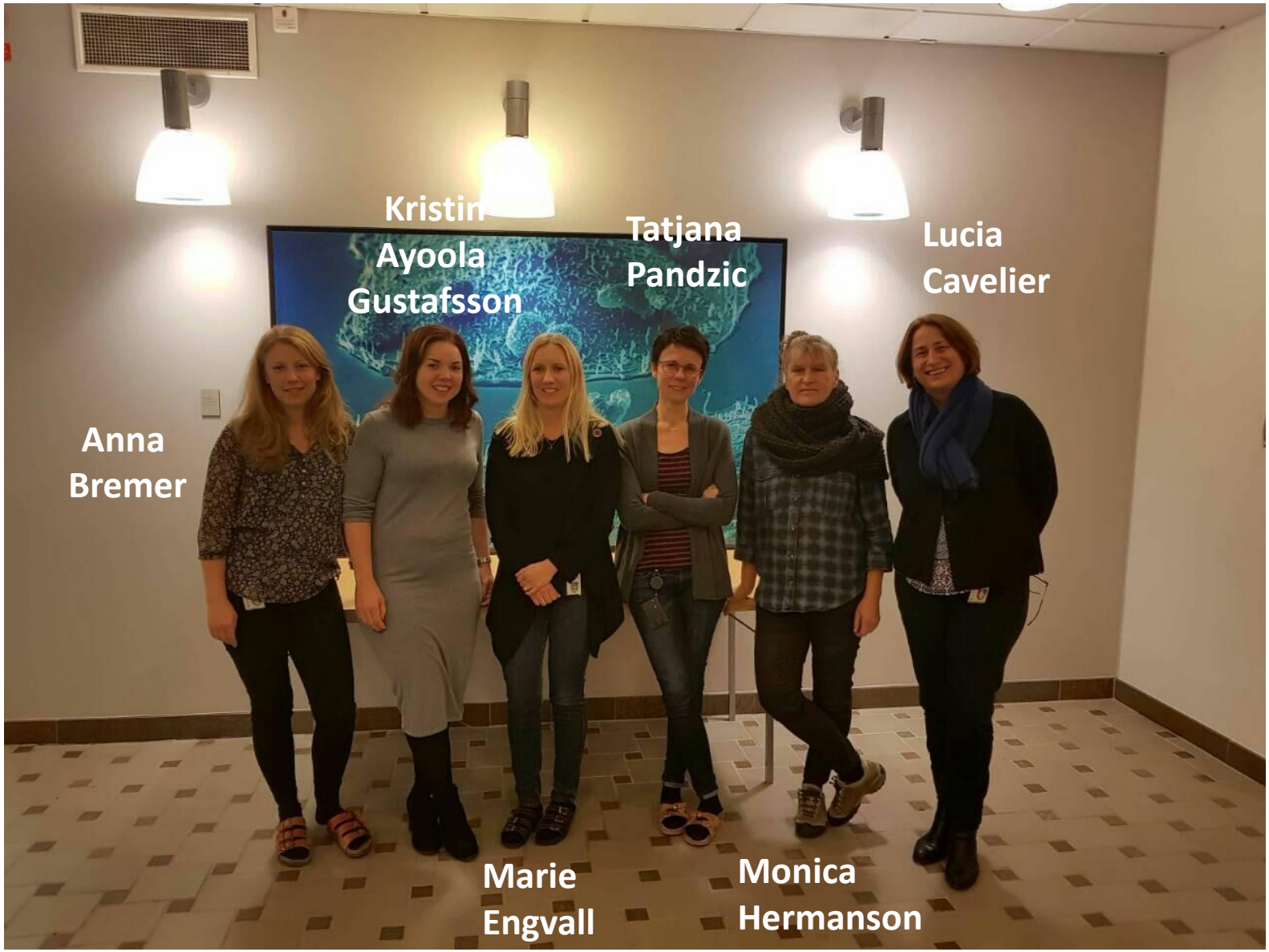
- Clonally skewed hematopoiesis frequently preceds development of AML/MDS

- Specific ”partners” in clonal evolution
  - *GATA2*: *ASXL1*, -7, +8
  - *RUNX1*: *CDC25C*, *BCOR, ASXL1*, del(5q)

- Can the emergence of a high risk genetic feature justify an early intervention?

Still many unanswered questions

- When should we be able to verify/exclude a HHM diagnosis?
- Should we perform skin biopsy to all patients?
- What about families with high suspicion of HHM where no pathogenic variant could be identified?
- When is the optimal timing for genetic counseling?



Clinical Genetics, University Hospital Uppsala, Sweden

GMS

Barbany Gisela

Belander Strålin Karin

Bjorck Eric

Cammenga Jörg

Engvall Marie

Hellström-Lindberg Eva

Höglund Martin

Jädersten Martin

Larazevic Vladimir

Lehmann Sören

Nordgren Ann

Öster Fernström Annette

Tesi Bianca

Tran Ann-Nhi

Fioretos Thoas

Rosenqusit Richard

Oncogenetic Dep Uppsala

Ylva Karlsson

Stefanos Tsiaprazis

Anette Mellin

Karin Runestram

Cate Franze

Hematology Dep Uppsala

Honar Cherif

Martin Höglund

Helene Hallbook

Elisabeth Ejerblad

Mattias Mattsson

Anna Eriksson

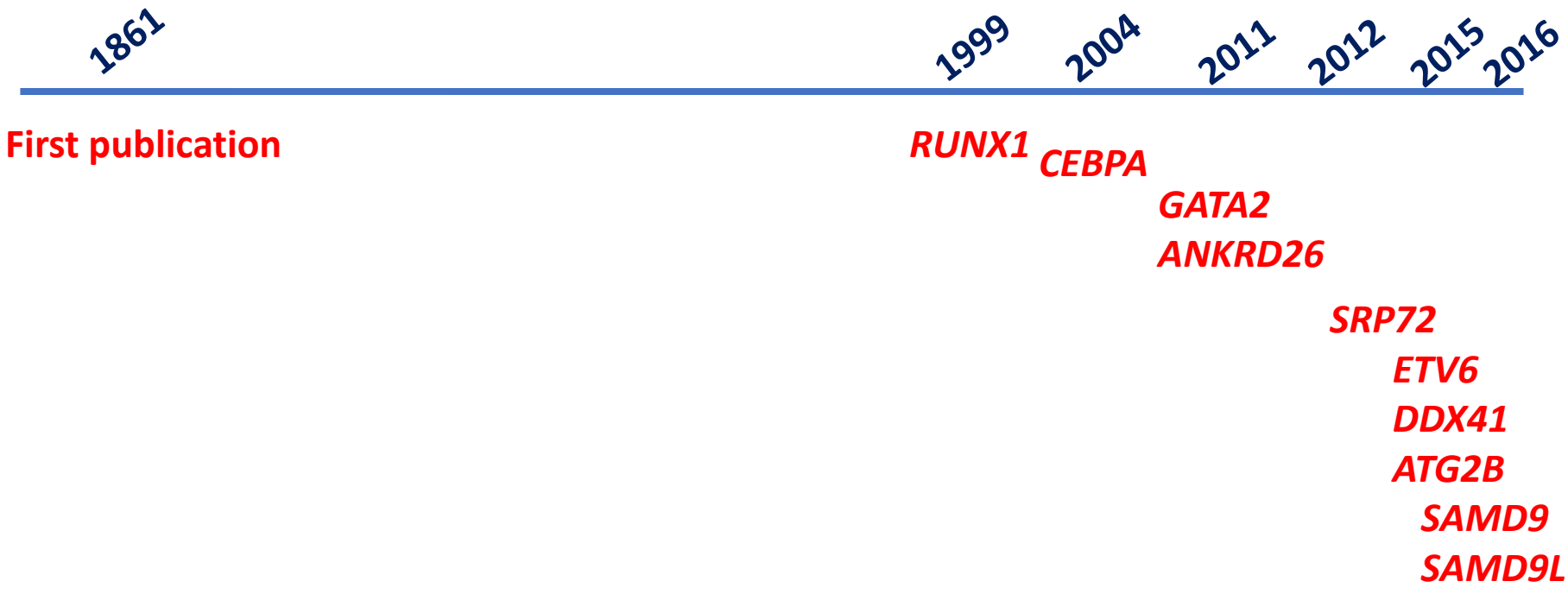
Hematopathology Uppsala

Rose-Marie Amini

Maysaa Abdula

Christer Sundström

Questions?


1861
1999
2004
2011
2012
2015
2016
First publication
RUNX1
CEBPA
GATA2
ANKRD26
SRP72
ETV6
DDX41
ATG2B
SAMD9
SAMD9L