SEVERE CHRONIC
NEUTROPENIA
International Registry

Klinik der Neutropenien

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Severe Chronic Neutropenia International Registry

www.scnir.de

Course of blood counts by age

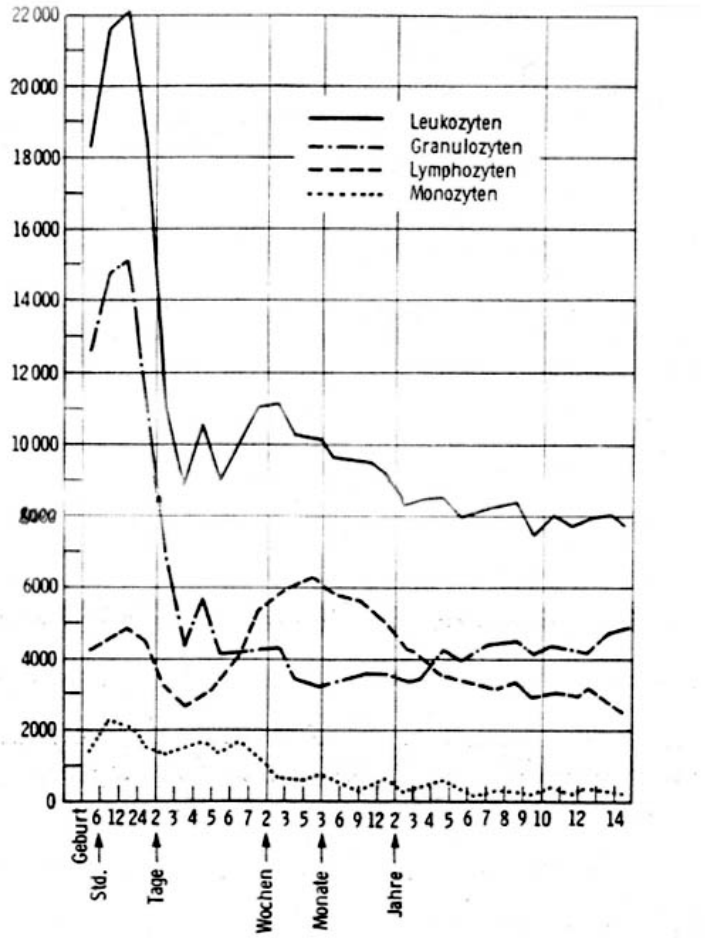

Abb. 10.33 Zahl der Leukozyten pro Mikroliter von der Geburt bis zum 15. Lebensjahr (aus Wissenschaftliche Tabellen, Documenta Geigy, 7 Auflage. Thieme, Stuttgart 1975).

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Causes of Neutropenia

- Defective production in the bone marrow
- Increased destruction of mature neutrophils
- Retention of neutrophils in the bone marrow compartment

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Neutropenia
Grade of Severity

- **mild neutropenia**,
  absolute neutrophil count (ANC) below **1500** per mm^3,
  but higher than **1000** per mm^3

- **moderate neutropenia**,
  ANC between **500** per mm^3 and **1000** per mm^3

- **severe neutropenia**,
  ANC below **500** pro mm^3

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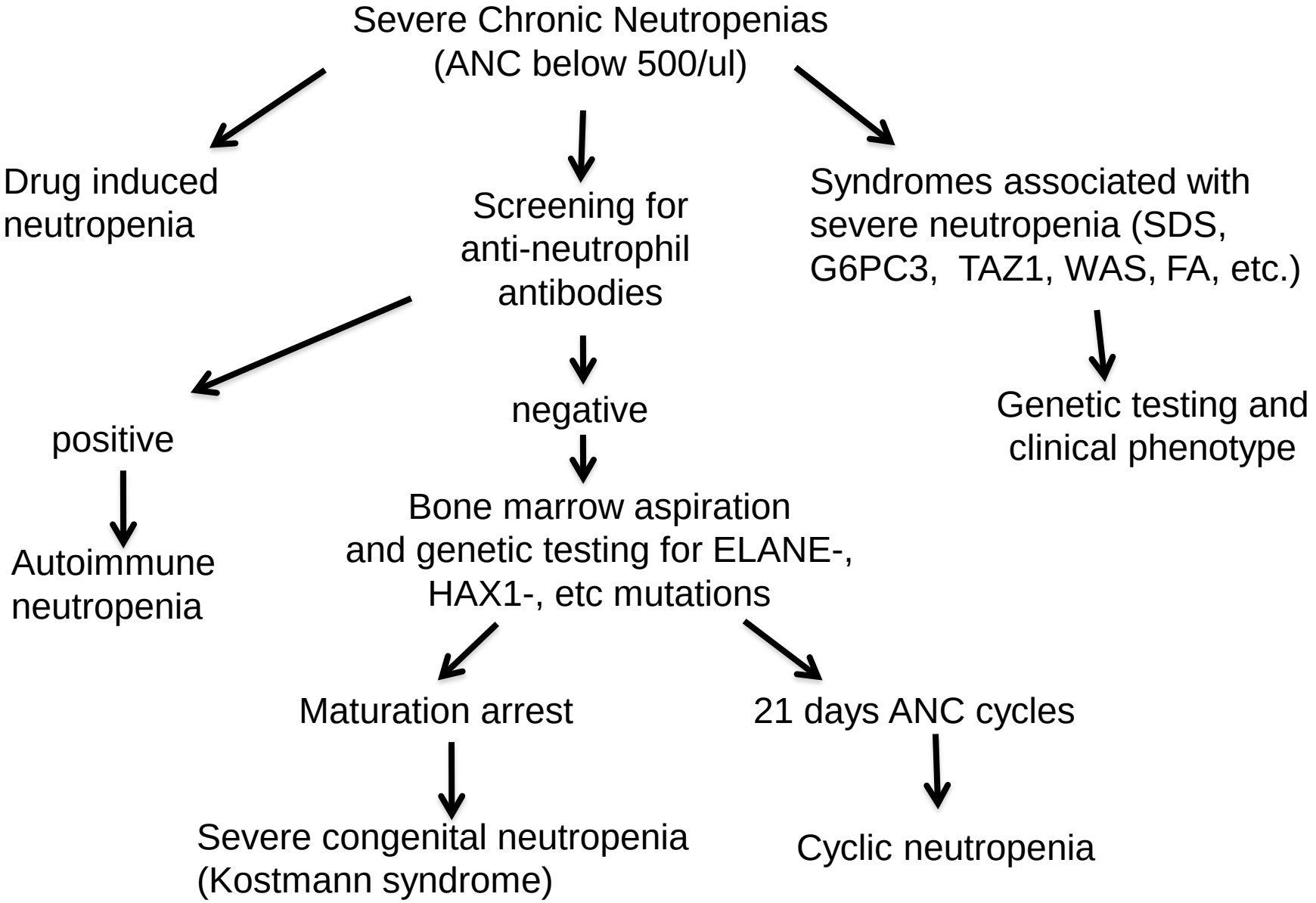
Neutropenia related Symptoms

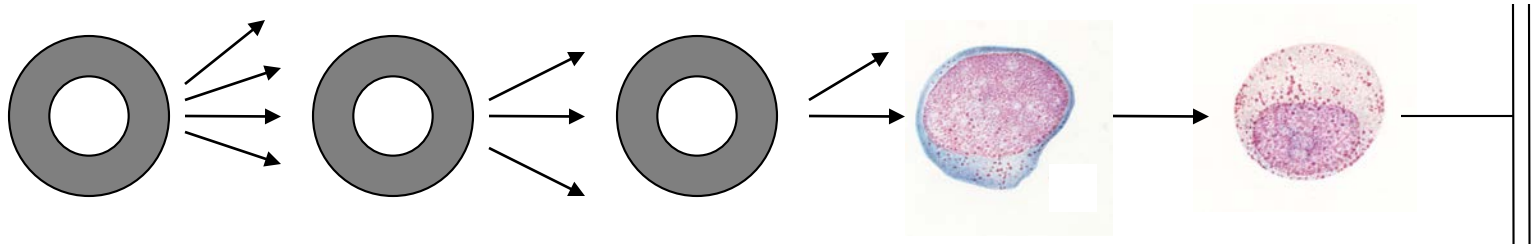
- In neutropenia patients with defective production symptoms correlate with severity and duration of neutropenia:

  The lower the absolute neutrophil count, the higher the risk of infection (if neutropenia lasts for more than three days)

- In patients with **AIN** there is **no correlation** between neutrophil counts and symptoms


Severe Chronic Neutropenias
(ANC below 500/ul)
Drug induced neutropenia
Screening for anti-neutrophil antibodies
Syndromes associated with severe neutropenia (SDS, G6PC3, TAZ1, WAS, FA, etc.)
positive
negative
Genetic testing and clinical phenotype
Autoimmune neutropenia
Bone marrow aspiration and genetic testing for ELANE-, HAX1-, etc mutations
Maturation arrest
21 days ANC cycles
Severe congenital neutropenia (Kostmann syndrome)
Cyclic neutropenia

Severe congenital neutropenia



pluripotent stem cell | CFU-GEMM | CFU-GM | myeloblast | promyelocyte | maturation arrest

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Congenital Neutropenia Characteristic Infections

- Severe bacterial infections usually start during early infancy

- Typical infections include:
  - omphalitis
  - skin or liver abscesses
  - pneumonia
  - gingivitis or aphthous stomatitis
  - otitis media

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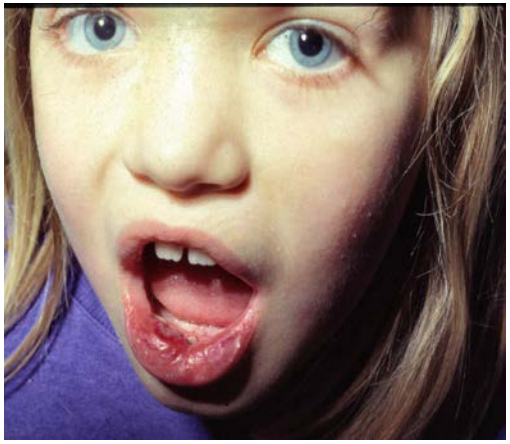
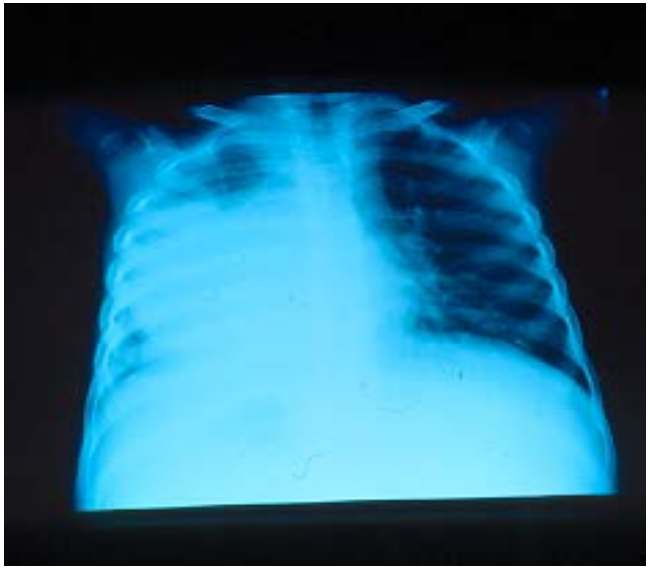
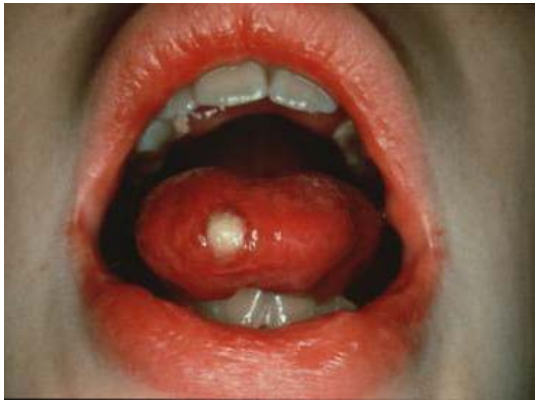
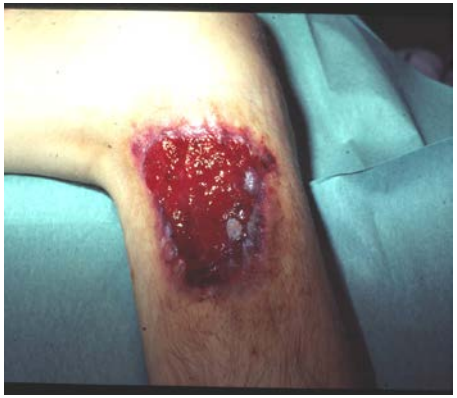
Infections in Patients with Congenital Neutropenia









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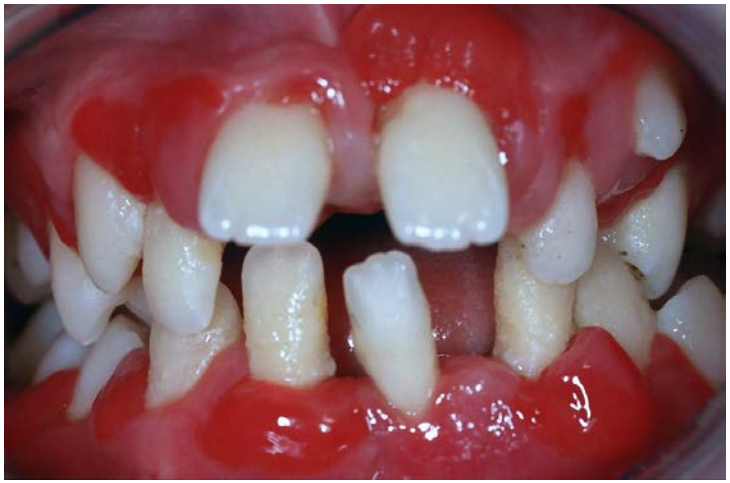
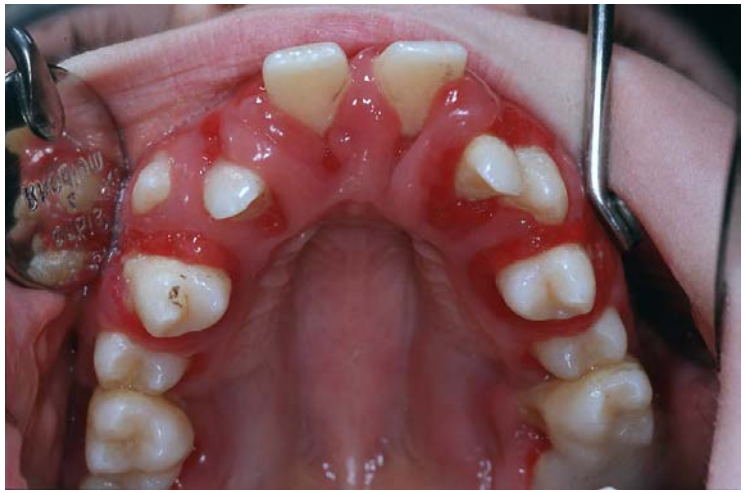
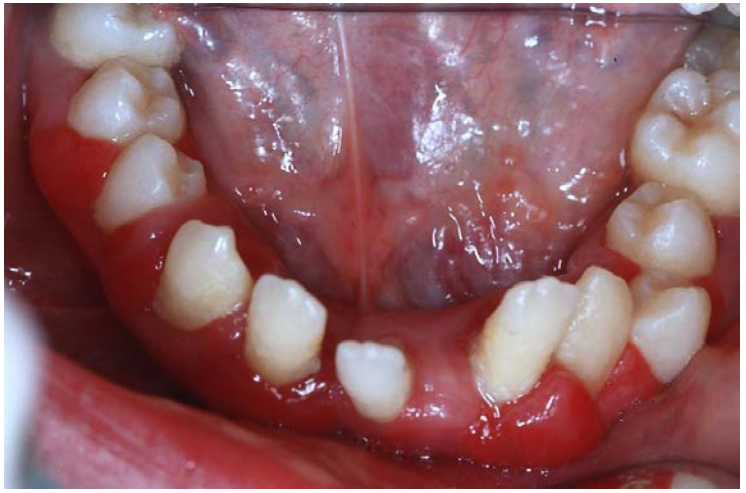
Congenital Neutropenia

Patient: A. P., 12 Years







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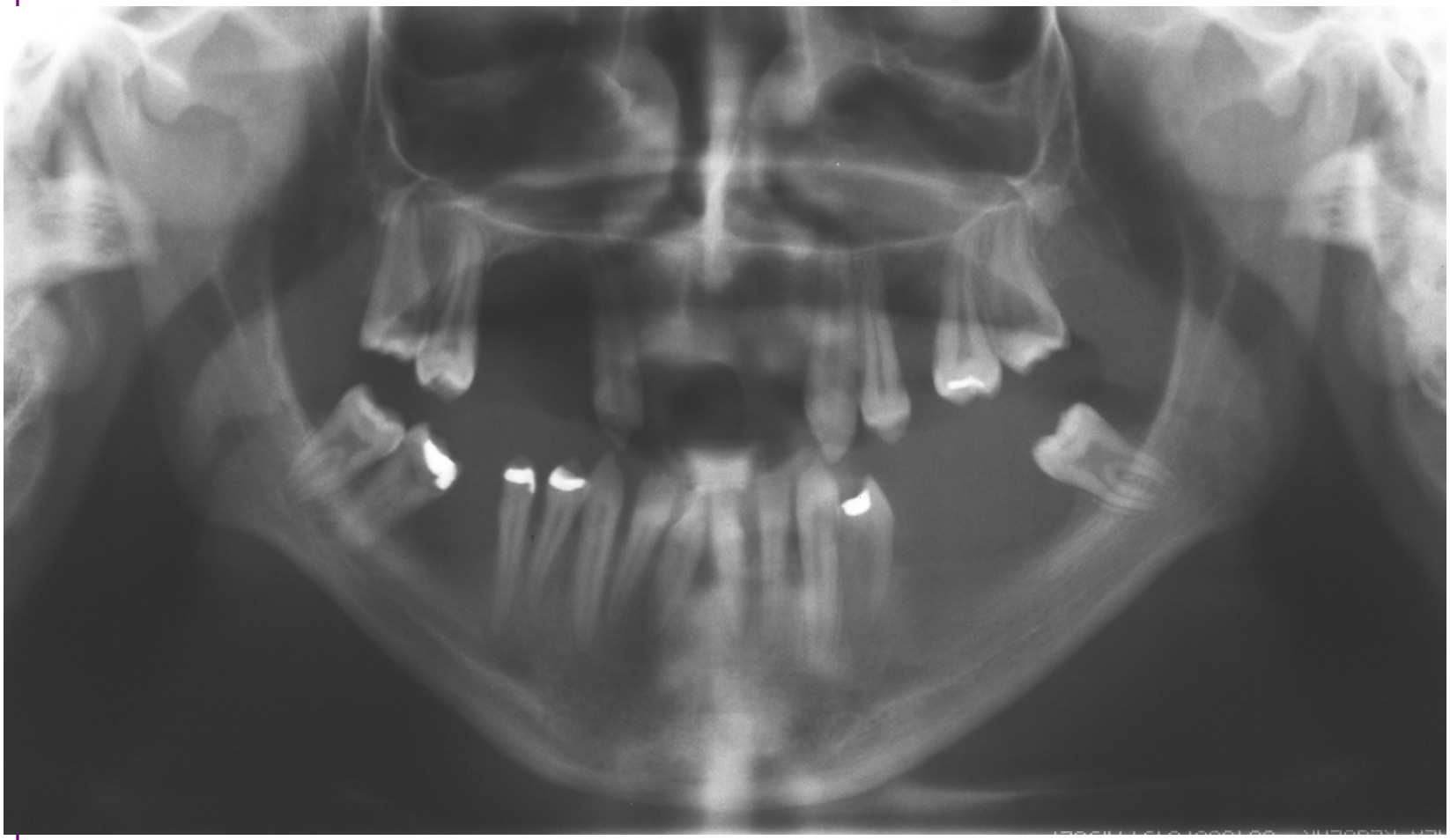
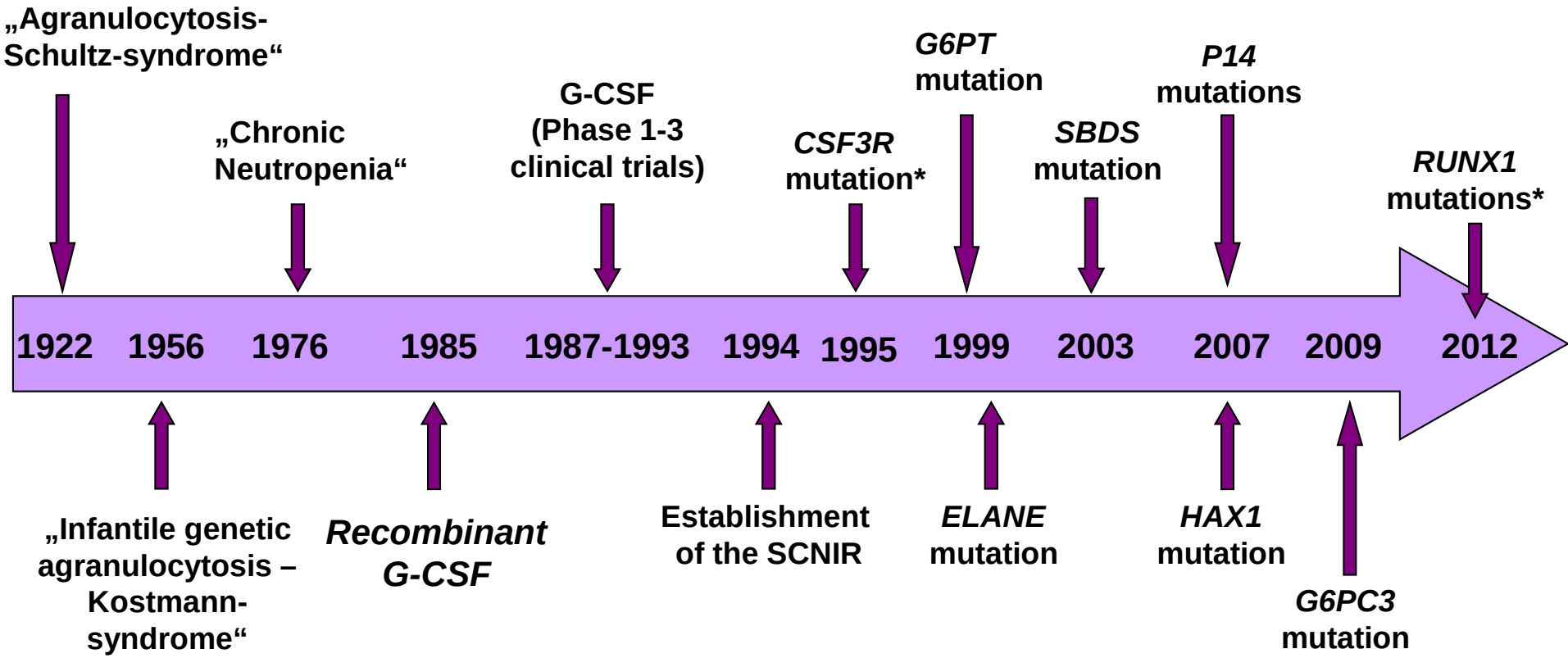
Congenital Neutropenia

Patient: A. P., 12 Years





* = acquired mutations

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Severe chronic neutropenia subtypes (9/2015)

Gene Mutation	Patients	Gene Mutation	Patients
Congenital neutropenia (CN) total	406	• Congenital White Cell Aplasia	1
• ELANE +	102	• Clericuzio Type Poikiloderma	1
• HAX1 +	47	• Cohen Syndrome	3
• G6PC3 +	9	• Pearson Syndrome	1
• Digenic mutations	4		
• JAGN1	2		
• CN not tested/ negative	117	Cyclic neutropenia	82
		• ELANE + 40	
Shwachman Diamond Syndrome	70	• ELANE - 9	
SBDS not tested 15		• ELANE not tested 33	
SBDS + 54			
SBDS - 1		Idiopathic neutropenia	87
		Autoimmune neutropenia	86
• Glycogen storage disease Ib	28		
• Myelokathexis	4	Others	18
• Barth Syndrome (TAZ+)	6	• Hyper IGM Syndrome 4	
• WAS mutation	7	• LGL 5	
• P 14 mutation	4	• diagnosis not approved 9	
• WHIM Syndrome (CXCR4+)	2		
		TOTAL	681

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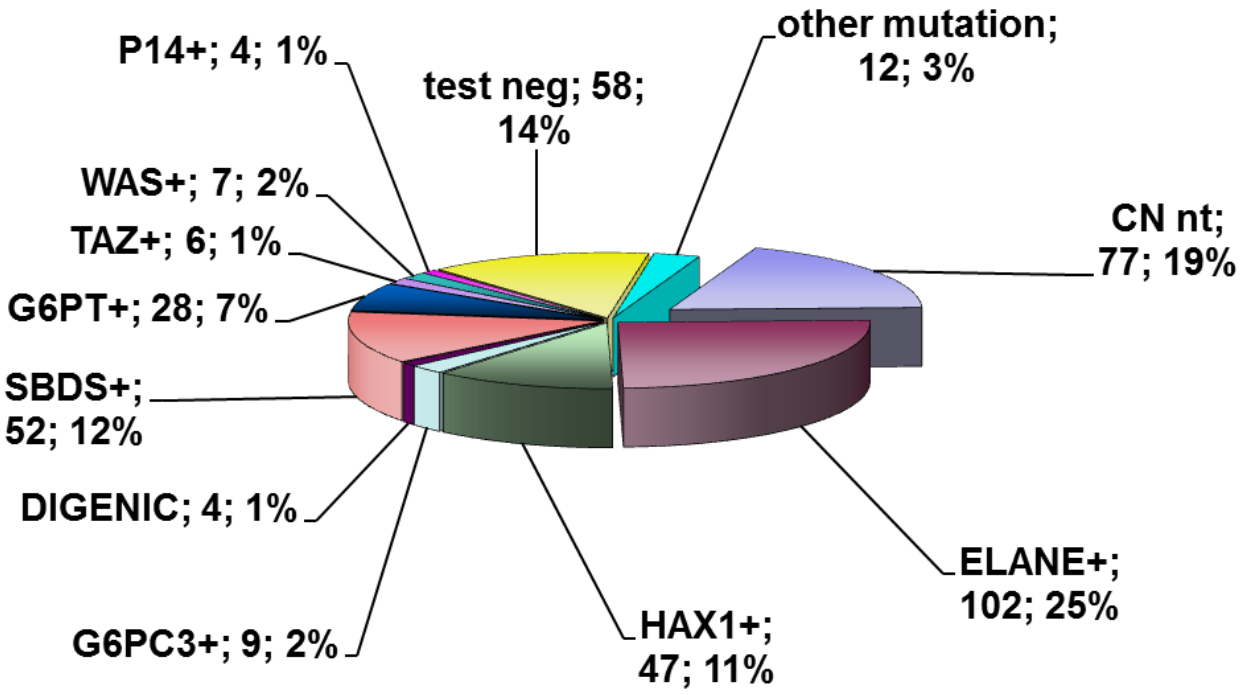
Genetic Distribution of Congenital Neutropenia in the SCNIR 09/2015



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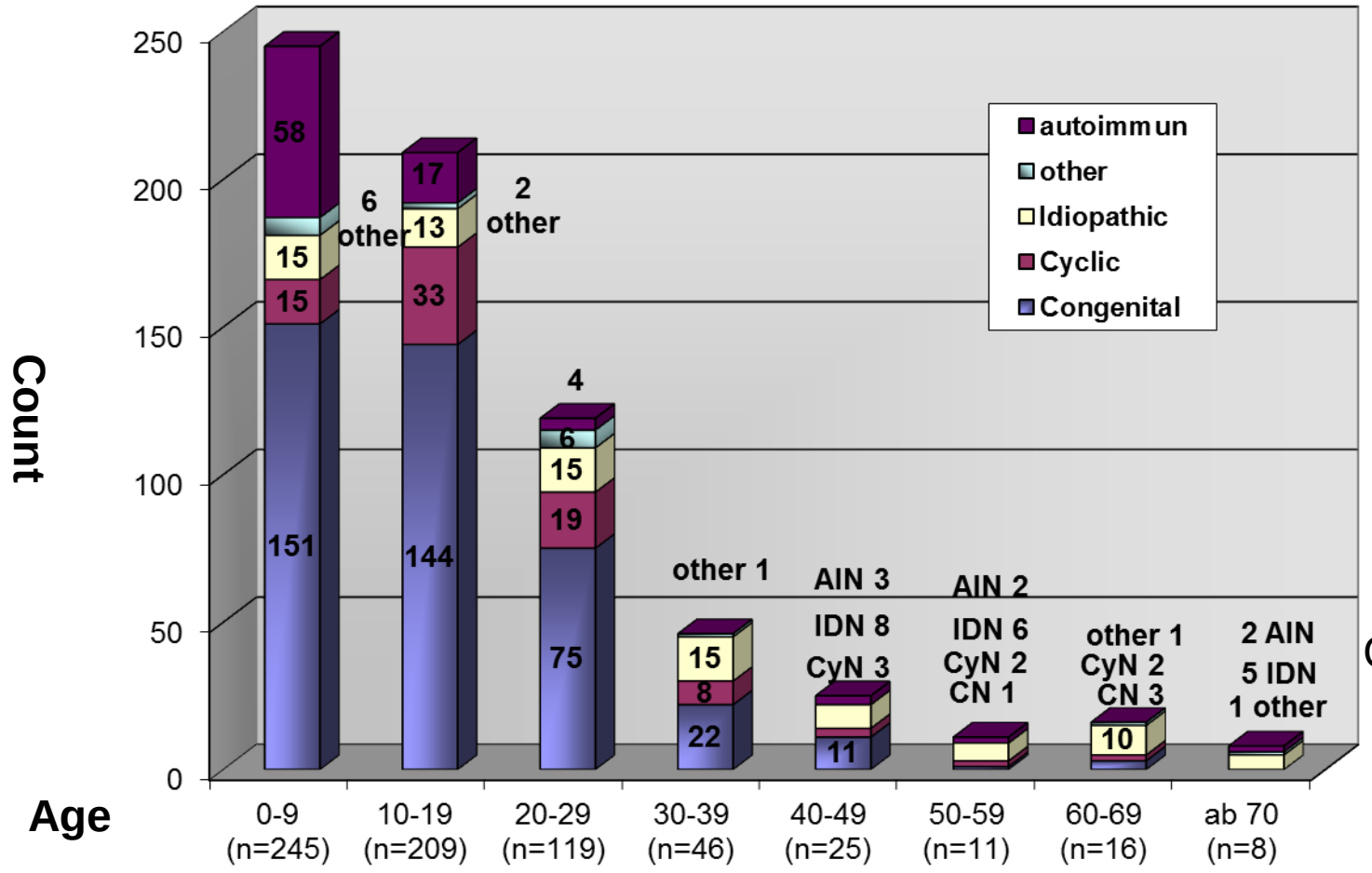
Age Distribution 09/2015



Median Age

CN=13 y

CyN=18 y

IDN=33 y

AIN= 6 y

Other=21 y

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Haematologica. 2014 Aug;99(8):1395-402.

Outcome and management of pregnancies in severe chronic neutropenia patients by the European Branch of the Severe Chronic Neutropenia International Registry

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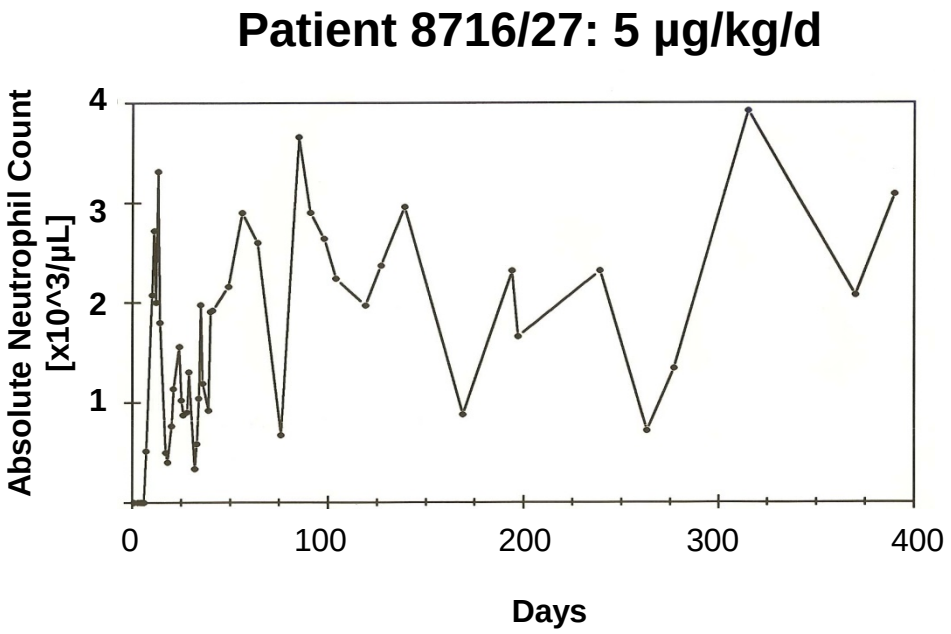
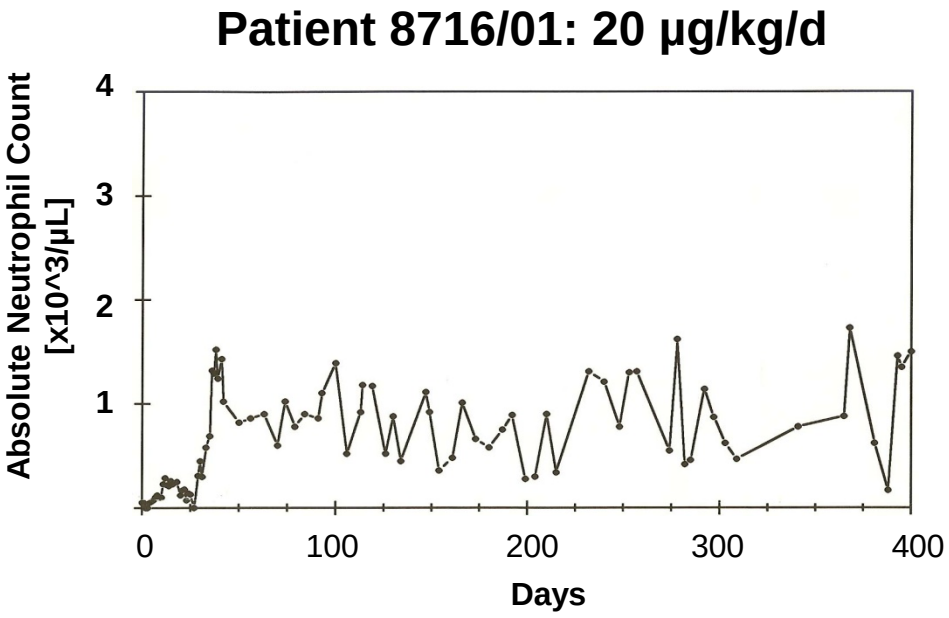
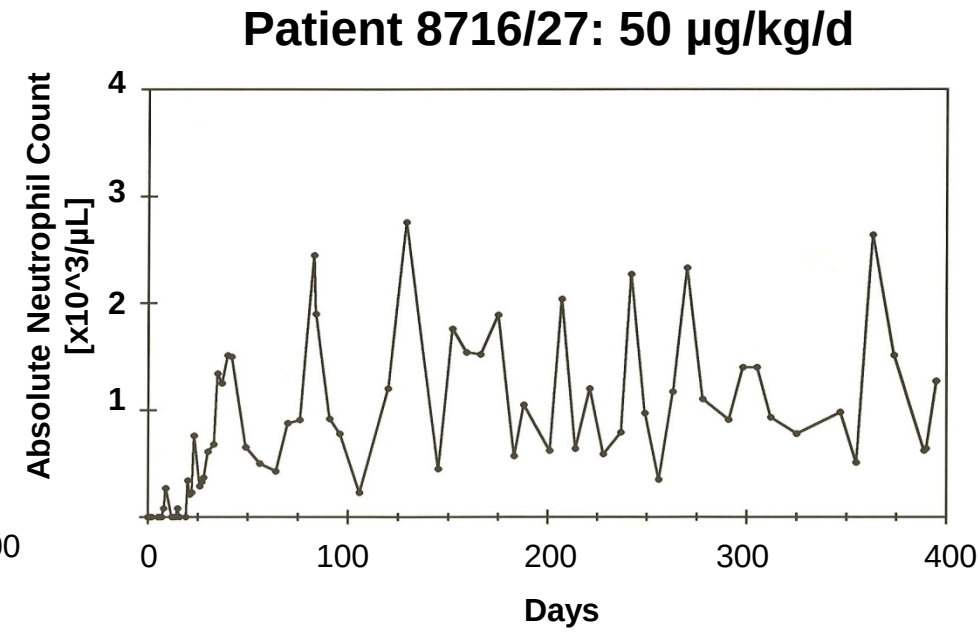
Severe Congenital Neutropenia

G-CSF Treatment
Phase I/II clinical trial 8716
Starting in 1987 in Europe







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Adverse Events

- **Osteopenia/Osteoporosis**
  - Osteopenia pre-existing to G-CSF treatment (Phase I/II/III clinical trials)
  - Approximately 50% of CN patients reveal osteopenia as judged by bone density measurement (Yakisan et al,. 1997, SCNIR 2013),
  - Vertebral fracture in 1 patient only
- **Splenomegaly/Splenectomy**

  Median spleen measurement 2 cm below costal margin
  - Frequently present at pre-treatment in CN (18%) and less common in CyN (13%)
  - Increased incidence during G-CSF treatment, mainly in CN (26 to 44 % through fup years)
  - Splenectomy was required in 1 IDN patient only
- **Hepatomegaly**

  Median liver measurement 2 cm below costal margin
  - Frequently present at pre-treatment in CN (21%) and less common in CyN (10%)
  - Increased incidence during G-CSF treatment, mainly in CN (22 to 28 % through fup years)
- **Vasculitis**
  - in 3% of CN and CyN patients, respectively
  - Mainly reversible after G-CSF reduction

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Congenital Neutropenia

- **Prior to G-CSF availability in the late 1980s more than 50 percent of patients died within the first years of life due to infections**

- **Typical infections include:**
  - **omphalitis**
  - **skin or liver abscesses**
  - **pneumonia**
  - **gingivitis or aphthous stomatitis**
  - **otitis media**

G-CSF leads to:

- Statistically reduced number of bacterial infections
- No requirement of intravenous antibiotics anymore

- **Improved quality of life**

Reference:

Bonilla, M., et al., N Engl J Med 1989
Welte, K., et al., Blood 1990
Dale, D., et al., Blood 1993
Zeidler C., et al., British Journal of Haematology 2008

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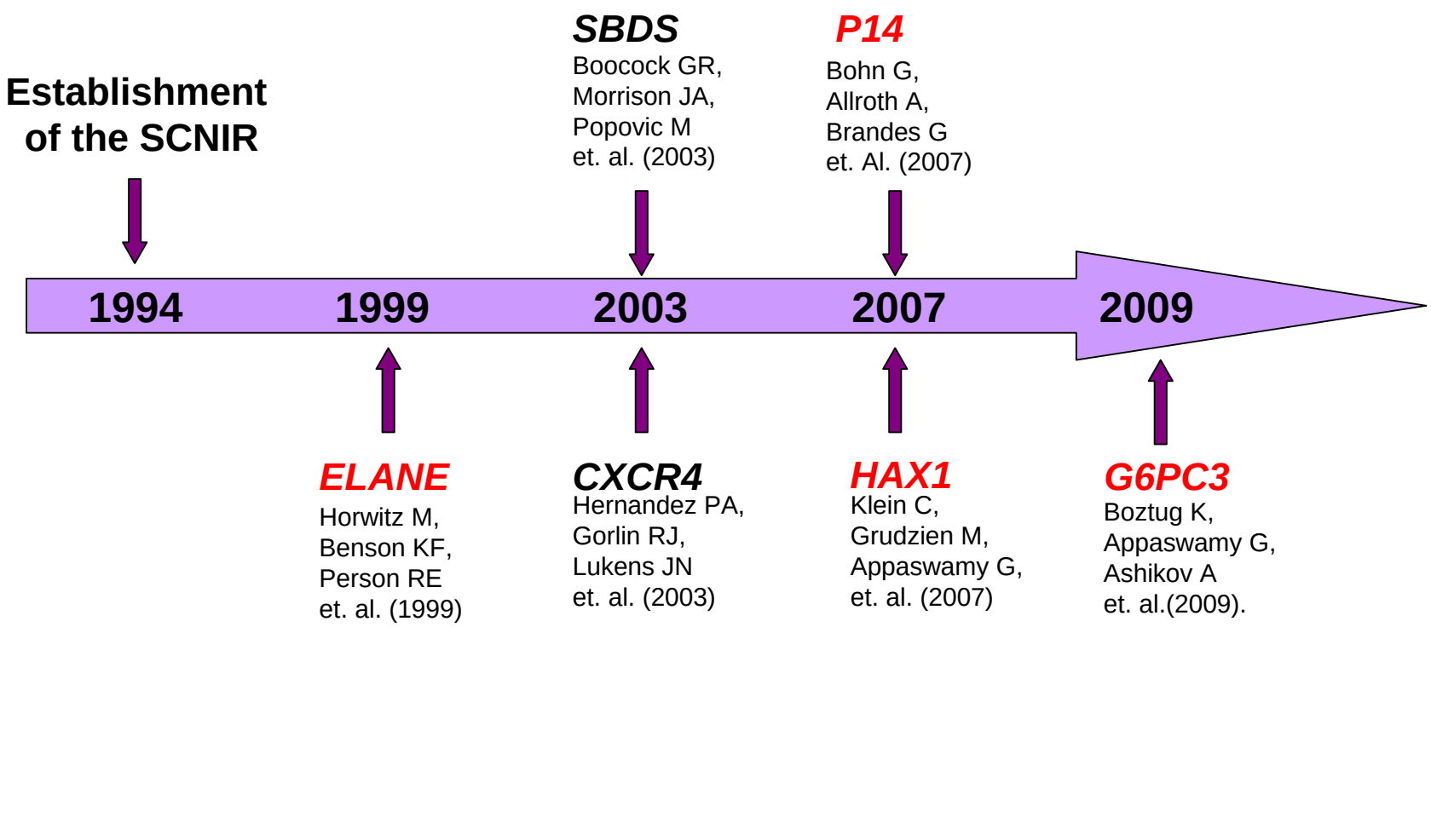
Identification of Neutropenia causing gene defects



Severe congenital neutropenia:

Gene Mutations

Autosomal dominant: ELANE mutations

Autosomal recessive: HAX1 mutations

Severe Chronic Neutropenia International Registry (SCNIR)

ELANE Mutations in Cyclic and Congenital Neutropenia

Linear Localization

Congenital Neutropenia (CN)
189 patients, 29 AML/MDS

Cyclic Neutropenia (CyN)
118 patients,
0 MDS/AML

5' UTR	Exon 1	Exon 2	Exon 3	Intron III	Exon 4	Intron IV	Exon 5
1 patient	*3 patients*	*29 patients*	*29 patients*	*4 patients*	*63 patients*	*11 patients*	*49 patients*
	1 MDS/AML	*4 MDS/AML*	*4 MDS/AML*	*1 MDS/AML*	*7 MDS/AML*	*2 MDS/AML*	*10 MDS/AML*
c. -9 A>G	M1R[1]	F43L	A79fs[1]	IVS3 -8 C>A[1]	L123H	IVS4 +1 G>A[1]	D201fs[1]
	M1T	V45M	R81P	IVS3 +2100 C>T	S126L[1]	IVS4 +1 G>T	S202fs[1]
		S46F	V83D		S126W	IVS4 +5 G>A	G203R
		C55S	L84P		A127D	IVS4 +6 3bp ins[1]	L206fs[1]
		G56R[1]	G85E[1]		T128del		V207D
		A57T	G85R		I129del		C208G
		A57V[1]	V98_Q102del		P139L		C208ter[1]
		I60M	V101M[1]		C151S		G210V
		I60T[1]			C151Y[3]		G210W
		A61G	R103L		L152P[1]		G214E
		A61V	R103P		A153P		G214R[3]
		V65D[1]	I118N		M154R		G214ter
		M66R	I120F		W156G		V219I
		S67W	I120N[1]		W156R		R220Q
		C71F	L121F		V174_C181del [1]		G221ter
		C71R	L121H		C181fs		C223fs
		C71S			V186I		C223ter[1]
		C71Y			V190fs[1]		S225ter
					R191S		G226R
					R193Q		Y228ter[1]
					Q194ter		D230fs[1]
					V197fs		F232fs
					F199fs		A233fs
							Q237fs
							N240del
		10 patients	*3 patients*	*1 patient*	*16 patients*	*49 patients*	*39 patients*
		F43L	Q97L	IVS3 -2 A>C	S126L	IVS4 +1 G>A	L206F
		A61V	V101M		S126W	IVS4 +3 A>T	G214ter
			D117V		P139L	IVS4 +5 G>A	R220Q
					D174ins		Y228ter
					V186_D201del		W241G
					Q194ter		W241L

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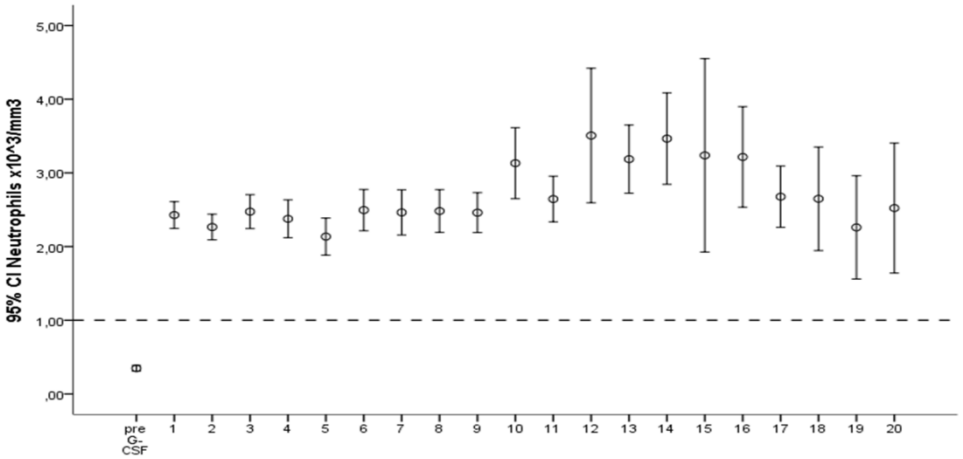
Long-term G-CSF Treatment

G-CSF can be administered daily s.c. for more than 20 years

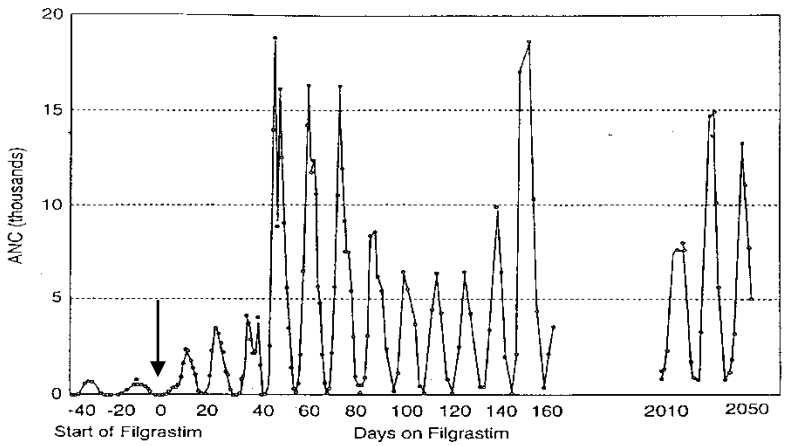
a) without exhaustion of hematopoiesis

b) without antibody production against G-CSF



Course of ANC under G-CSF in Congenital Neutropenia

Course of ANC under G-CSF in Cyclic Neutropenia



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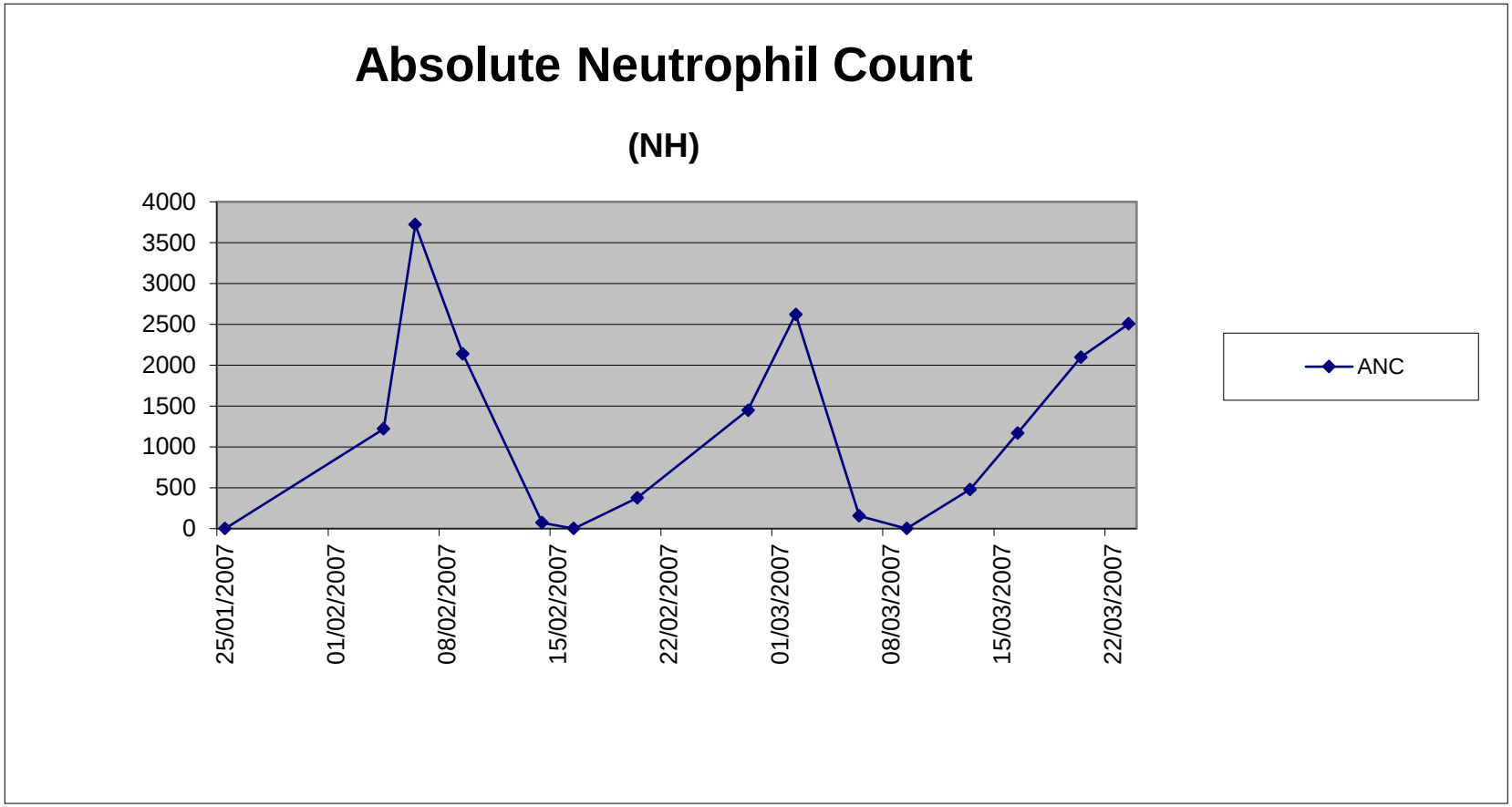
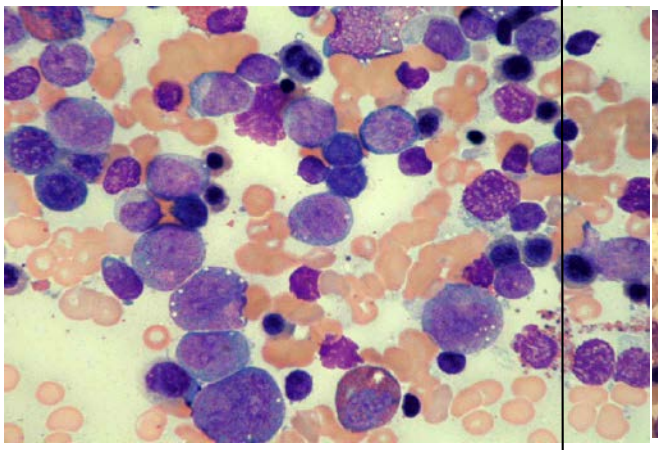
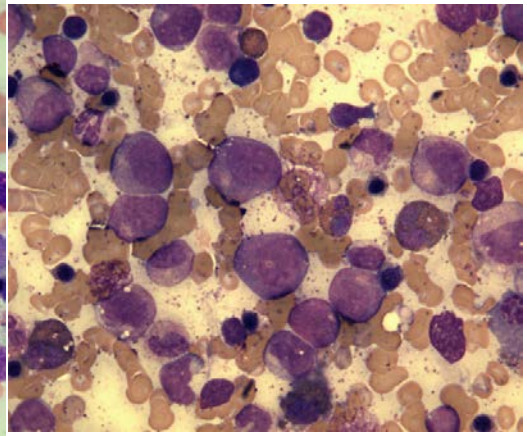
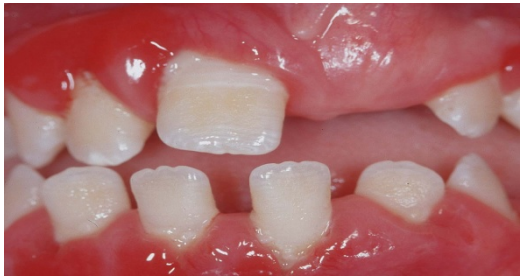
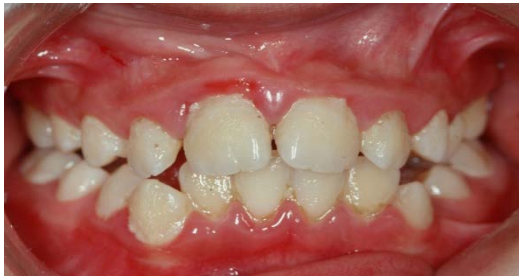
Cyclic Neutropenia

Pt. NH
ANC Course, no G-CSF



The clinical phenotype of ELANE- or HAX1-CN

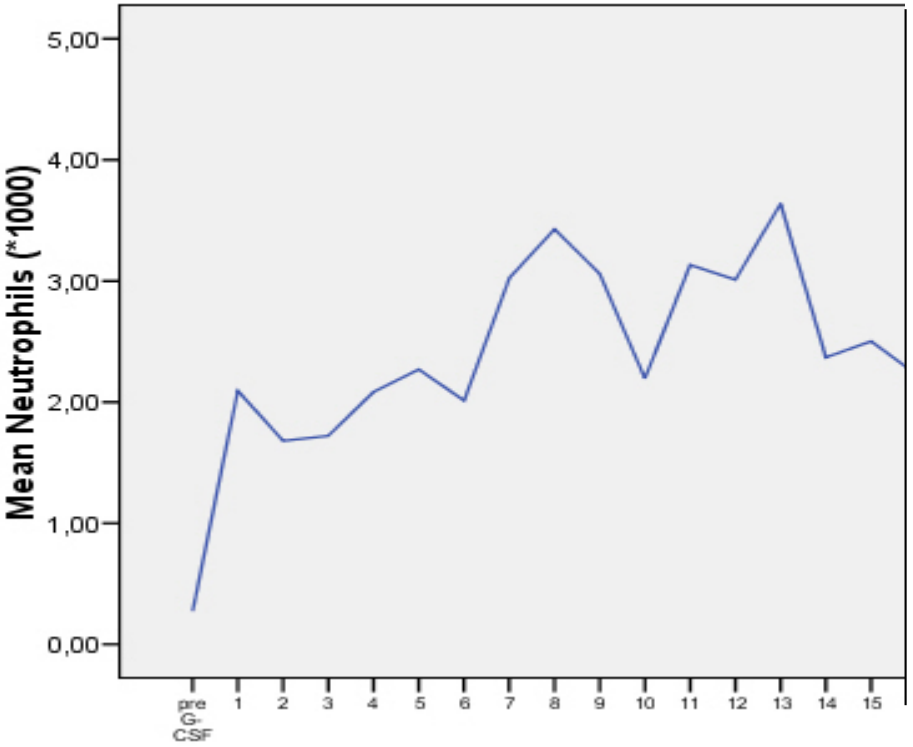
is independent of the mutational status

Mutation:	*ELA2*	*HAX1*
Age:	12 years	11 years
Bone marrow morphology at diagnosis: Maturation arrest at the promyelocyte/ myelocyte stage		
Gingiva and dental status: Hyperplasia of gingiva and gingivitis		

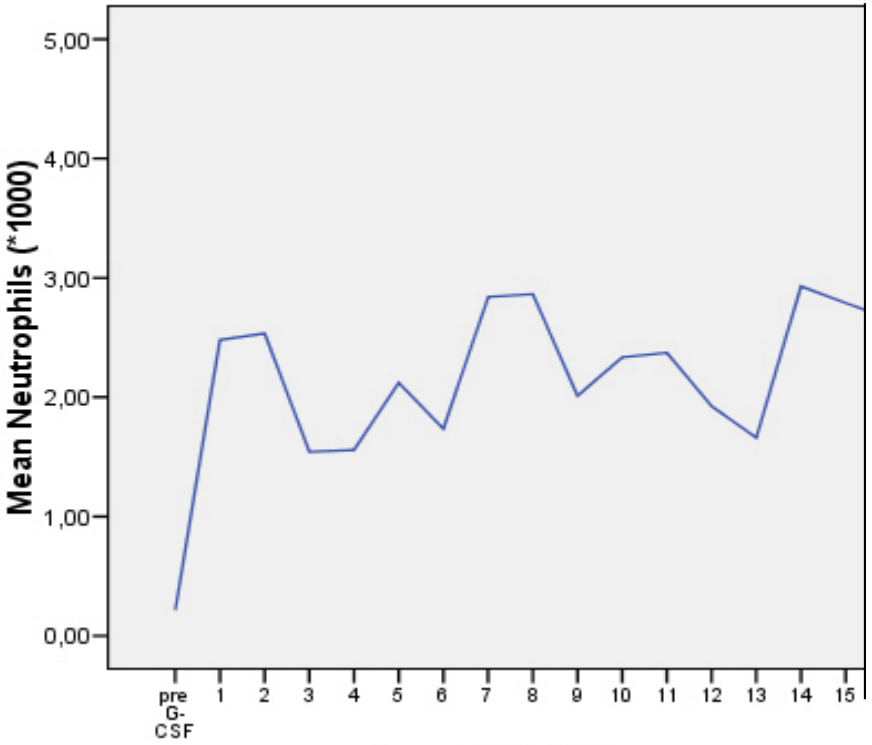
Zeidler et al., Br J Haematology 2008

Course of mean neutrophil counts in patients with *ELA2* or *HAX1* mutations

***ELA2* patients**
n = 50



***HAX1* patients**
n = 14



Years on G-CSF treatment

Zeidler et al., Br J Haematology 2008

Digenic Mutations in Congenital Neutropenia

Patient (current age in years/sex)	gene mutations	Inheritance	hematological findings	other findings
#1 (24 / f)	ELANE: **p.Ala166Thr (Exon 4)** (het) G6PC3: **p.Met116Lys (Exon 3)** (hom)	mother mother / father	Neutropenia no eosinophils Thrombocytopenia	constitutional developmental delay; hypogonadotropic hypogonadism; type II atrial septal defect; mild mitral and tricuspid insufficiency; prominent superficial venous pattern
#2 (0.5 / f)	ELANE: **p.Ala25Val (Exon 2)** (het) HAX1: p.Val144GlyfsX5 (Exon 3) (hom)	father mother / father	neutropenia	recurrent infections; no signs of neurodevelopmental delay yet
#3 (20 / m)	G6PC3: p.Gly260Arg (Exon 6) (hom) HAX1: **p. Val172Ile (Exon 4)** (het)	mother / father mother	Neutropenia no eosinophils, thrombocytopenia	height and weight below 3rd percentile; cryptorchism; genital dysplasia; microcephaly; inner-ear hearing loss; hypogammaglobulinemia; type II atrial septal defect; prominent superficial venous pattern
#4 (5 / m)	HAX1: p.Val144GlyfsX5 (Exon 3) **p.Leu130Arg (Exon 3)** (compound het) G6PC3: **p.Arg189Gln (Exon 5)** (het)	father mother father	Neutropenia	neurodevelopmental abnormalities

M. Germeshausen, C. Zeidler, M. Stuhrmann et al, Haematologica 2010; 95 (7)

Neutropenia associated with metabolic syndrome				
Shwachman Diamond syndrome	SBDS	+	-	Exocrine pancreas insufficiency, short stature, bone anomalies, anemia, thrombocytopenia, leukemic transformation
Barth syndrome	Taz 1	X-linked	-	Dilatative cardiomyopathy, skeletalmyopathy, short stature, 3-Methylglutaconicaciduria
GSD 1b	Glucose-6-Phosphat-Translocase	+	-	Hypoglycemia, lactic acidosis
G6PC3 CN	G6PC3	+	-	Short stature, cardiac or urogenital anomalies, visibility of subcutaneous veins

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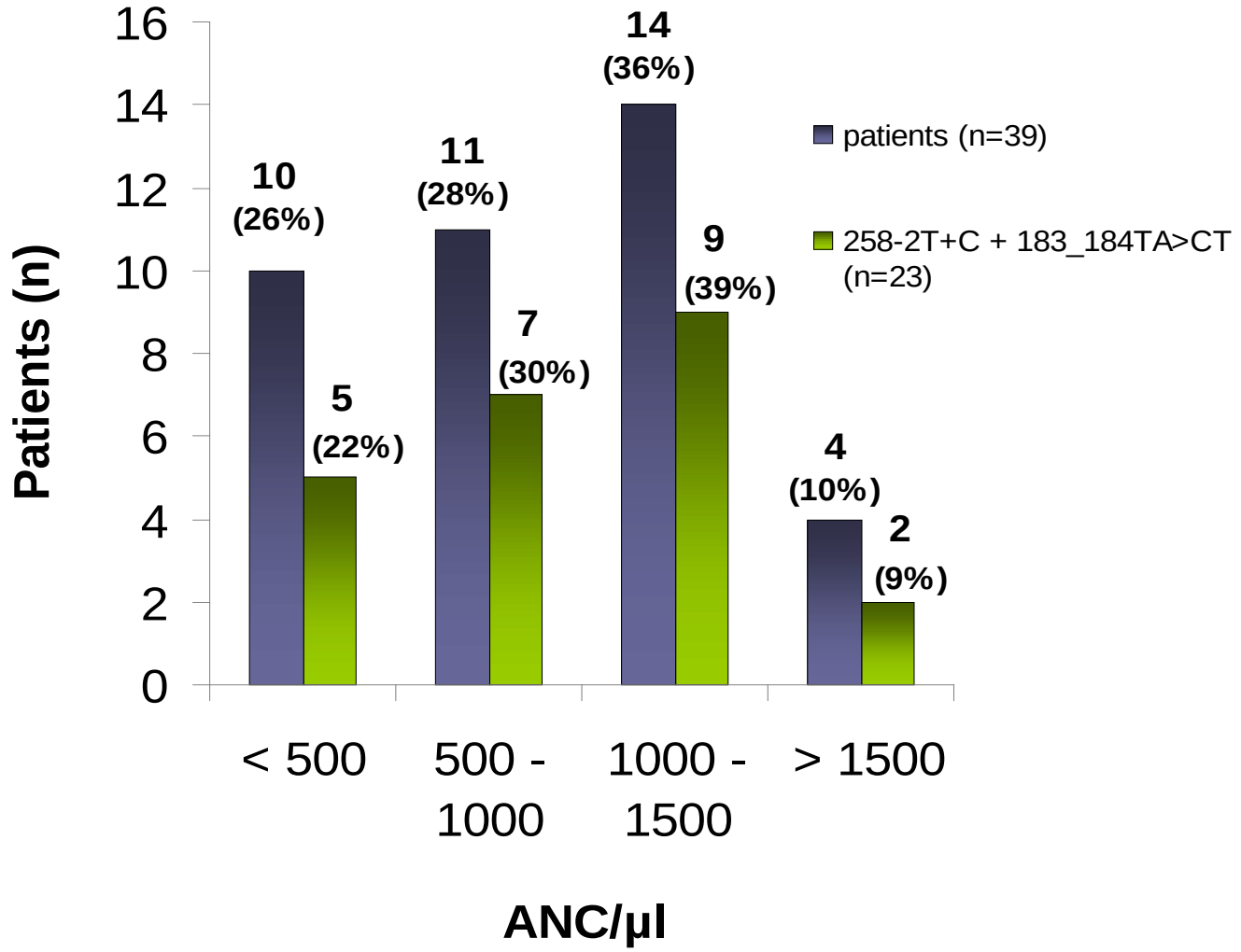
SDS
First reported ANC



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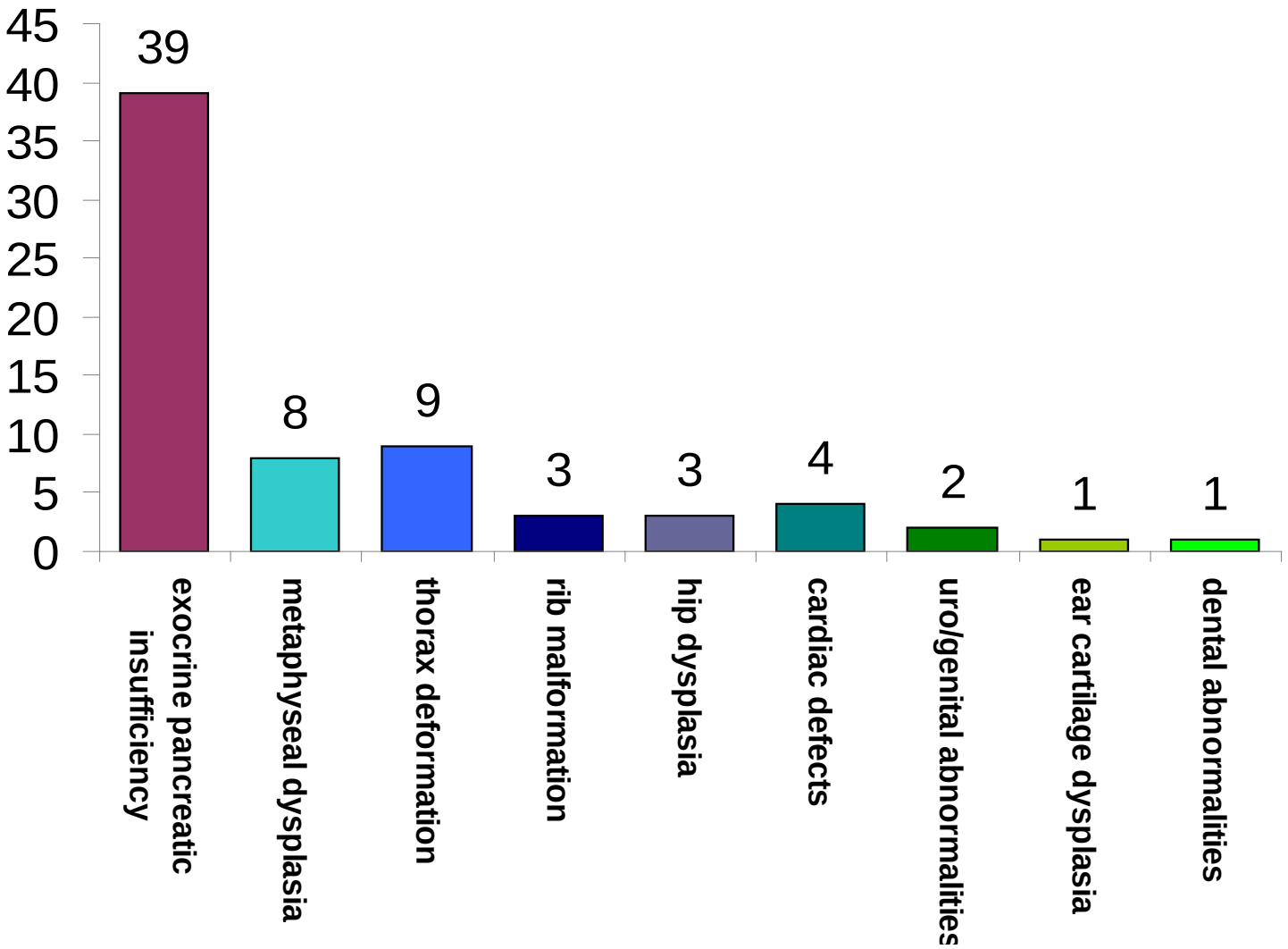
SDS-Clinical Symptoms at Diagnosis (n=40)



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Clinical Symptoms in the Course of Disease (n=40)

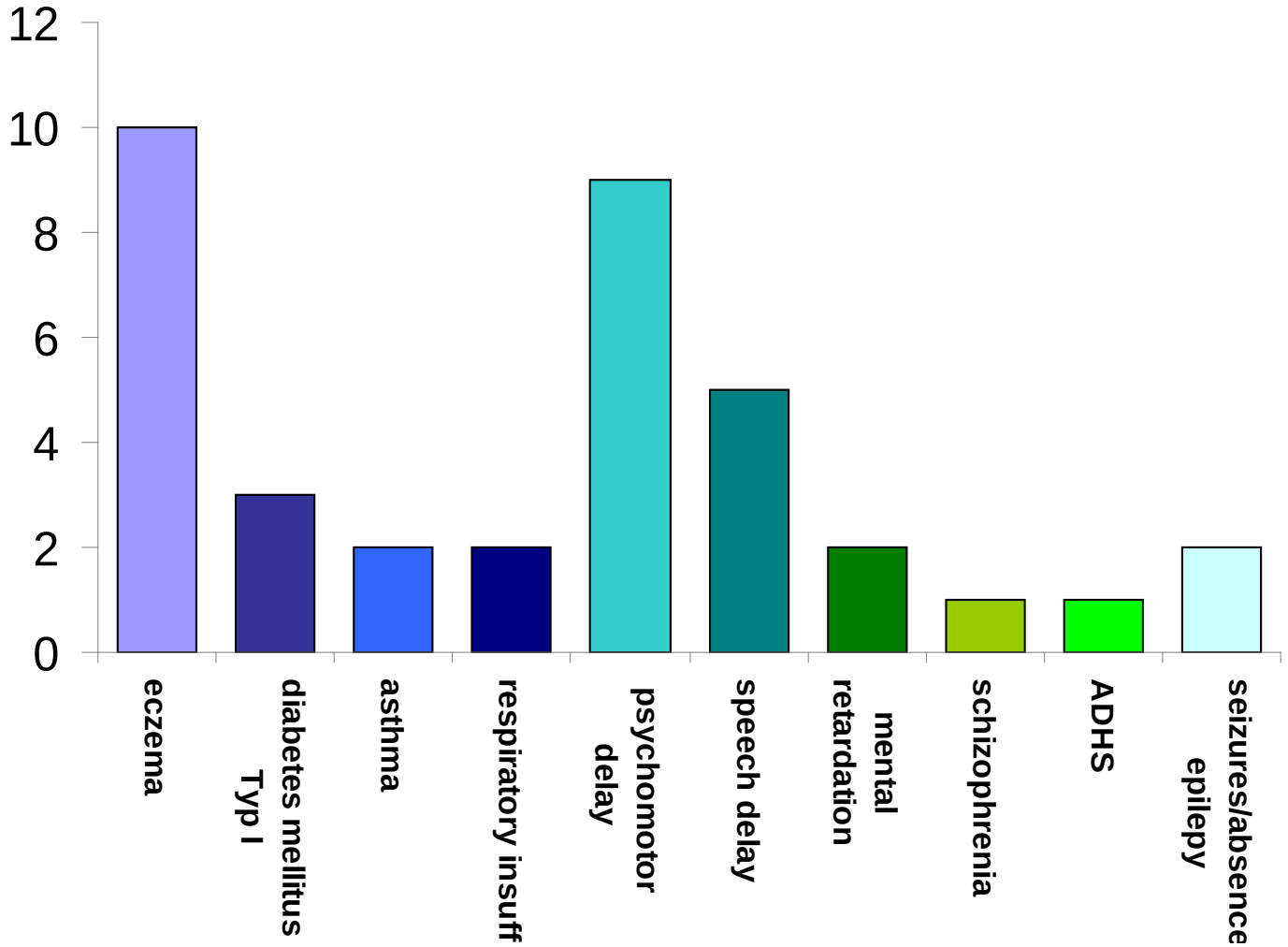
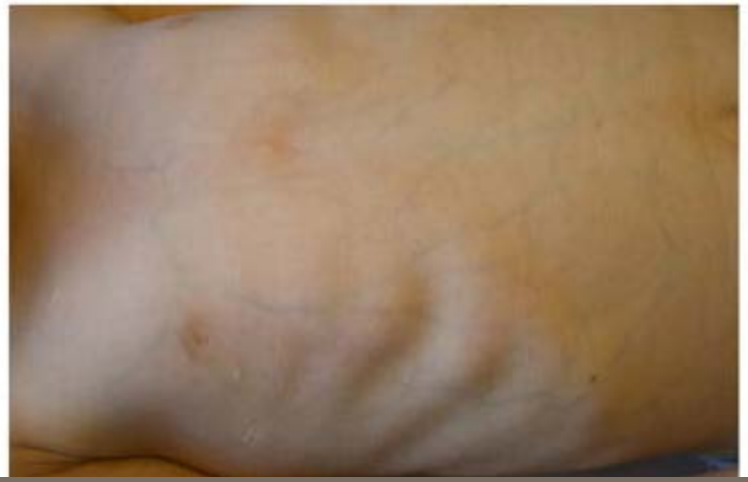


Table I. Summary of selected clinical features of the 16 patients with G6PC3 deficiency

Clinical feature	Frequency (percent)
Congenital heart defect	16 (100%)
Increased visibility of superficial veins	14 (87.5%)
Abnormal facial appearance	12 (75%)
Urogenital abnormalities	11 (68.8%)
Thrombocyopenia (intermittent)	10 (62.5%)
Failure to thrive	7 (43.8%)
Endocrine abnormalities	4 (25%)
Inner ear hearing loss	2 (12.5%)
Cutis laxa/hyperelasticity of the skin	2 (12.5%)



Boztug K, et al., NEJM 2009
Boztug K, et al., J Pediatr. 2012

Neutropenia with pigmentation defects				
Griscelli syndrome	Rab27a	+	-	Partial albinism, IgG deficiency despite normal lymphocyte numbers, hemophagocytosis
Chediak-Higashi syndrome	CHS gene	+	-	Albinism, T/NK + chemotaxis defect
Hermansky-Pudlack-syndrome	AP3B1	+	-	Partial albinism, short stature, IgG deficiency, hemorragh. diathesis
Hermansky-Pudlack- like-syndrome	p14	+	-	Partial albinism, short stature, IgG deficiency

p14 (*LAMTOR2, MAPBPIP)*

- **Consanguinous family with 15 children**
- **Recurrent bronchopulmonary infections**
- **Growth failure**
- **Partial albinism**

Severe congenital neutropenia:

Incidence of Leukemia and leukemogenesis

SEVERE CHRONIC NEUTROPENIA International Registry

Secondary Leukemias by Genotype 09/2015

Diagnosis	Total patient number (n)	MDS/Leukemia (n/%)
Congenital Neutropenia	**353 (without SDS)**	**39 (11,05 %)**
•*ELANE-CN pos.*	102	14 (12,74 %)
•*HAX1-CN pos.*	47	6 (12,76 %)
•*WAS pos.*	21 (incl 14 non-registered)	3 (14,28%)
•*G6PT pos* (GSD1b)	28	1 (3,57%)
•*Other (G6PC3, TAZ, P14, CXCR4 etc.)*	36	0
• *unclassified*	119	15 (12,6%)
SDS	**68**	**6 (8,82%)**
- *SBDS* not tested	15	1 (6,66%)
- *SBDS* positive	52	5 (9,61 %)
- *SBDS* negative	1	0
Cyclic Neutropenia	**82**	**2 (2,43%)**
- *ELANE*-positive	40	1 (2,5%)
- *ELANE* negative	9	0
- *ELANE* not tested	33	1 (3,03%)

Leukemia in IDN 2, LGL 1

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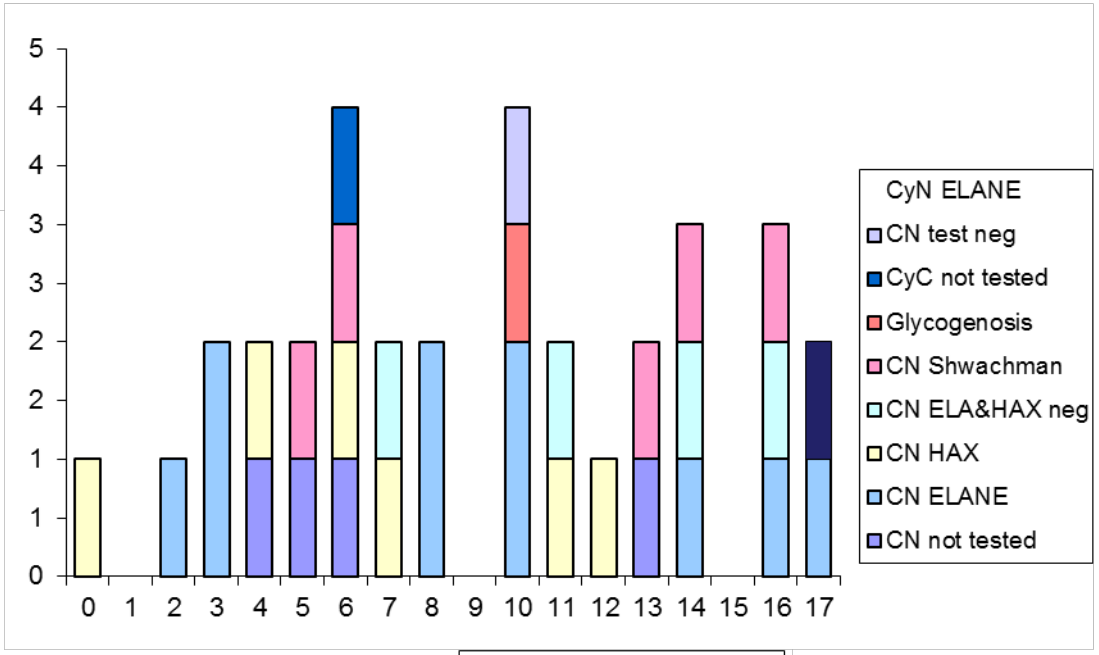
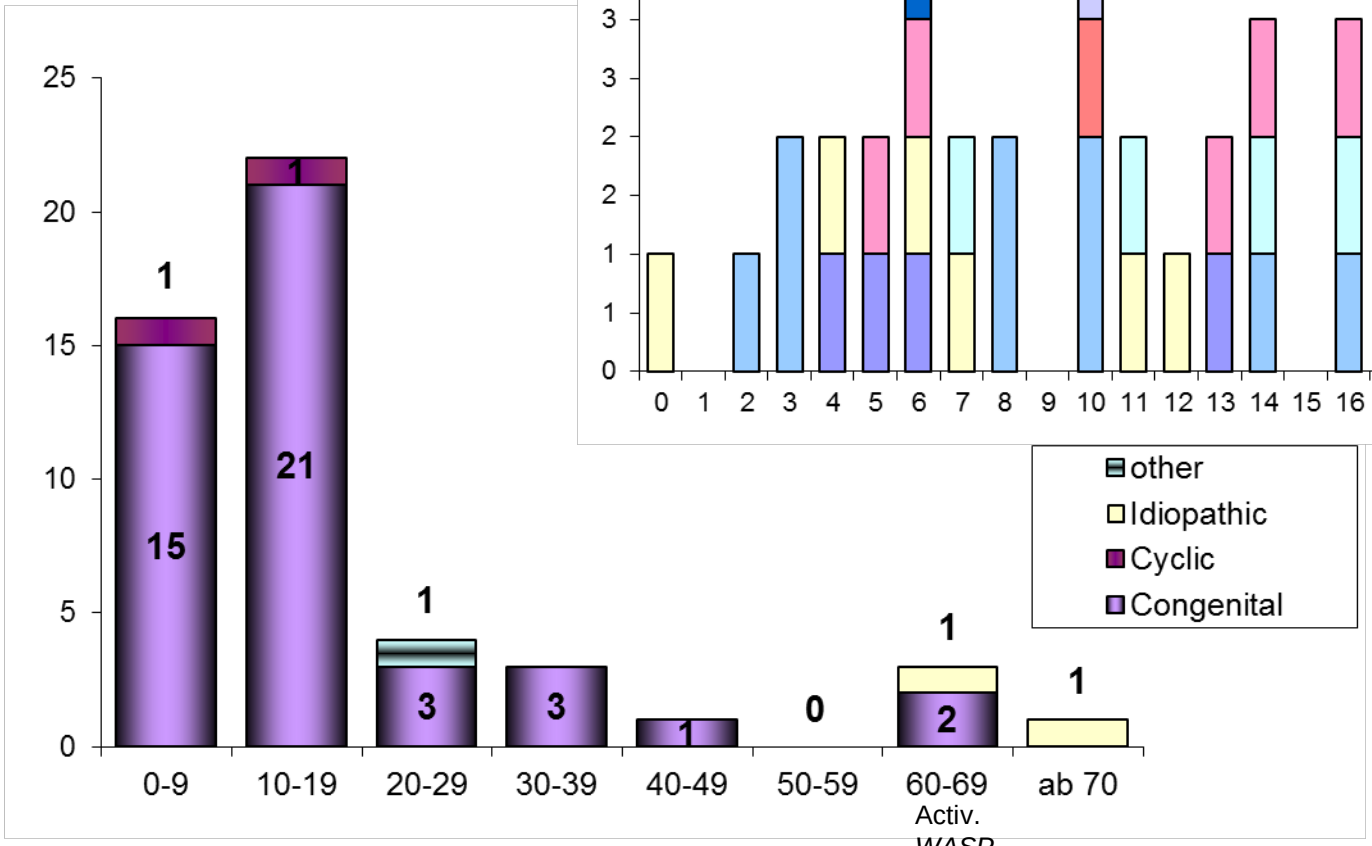
Onset of Leukemia by Age of Patient 09/2015





Activ. *WASP* mutation

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G-CSF Treatment by Neutropenia-Genotype

Neutropenia Code	No Leukemia (n)	Median G-CSF dose (µg/kg/d)	Leukemia (n)	Median G-CSF dose (µg/kg/d)
ELANE-CN	87	4,83	13	18,7
HAX1-CN	39	3,65	6	7,05
ELANEneg/HAX1neg	26	10,8	7	15,05
neg tested	20	4,43	1	4,86
WAS	4	1,57	2	3,09
SDS	58	1,72	5	4,3
CN not tested	57	5,35	7	4,95
GSD1B	26	3,0	1	3,0
CyC not tested	30	1,46	2	10,76

* Median G-CSF Dose for all Congenital Patients **4,7** µg/kg/d and for all Cyclic Patients **1,93** µg/kg/d

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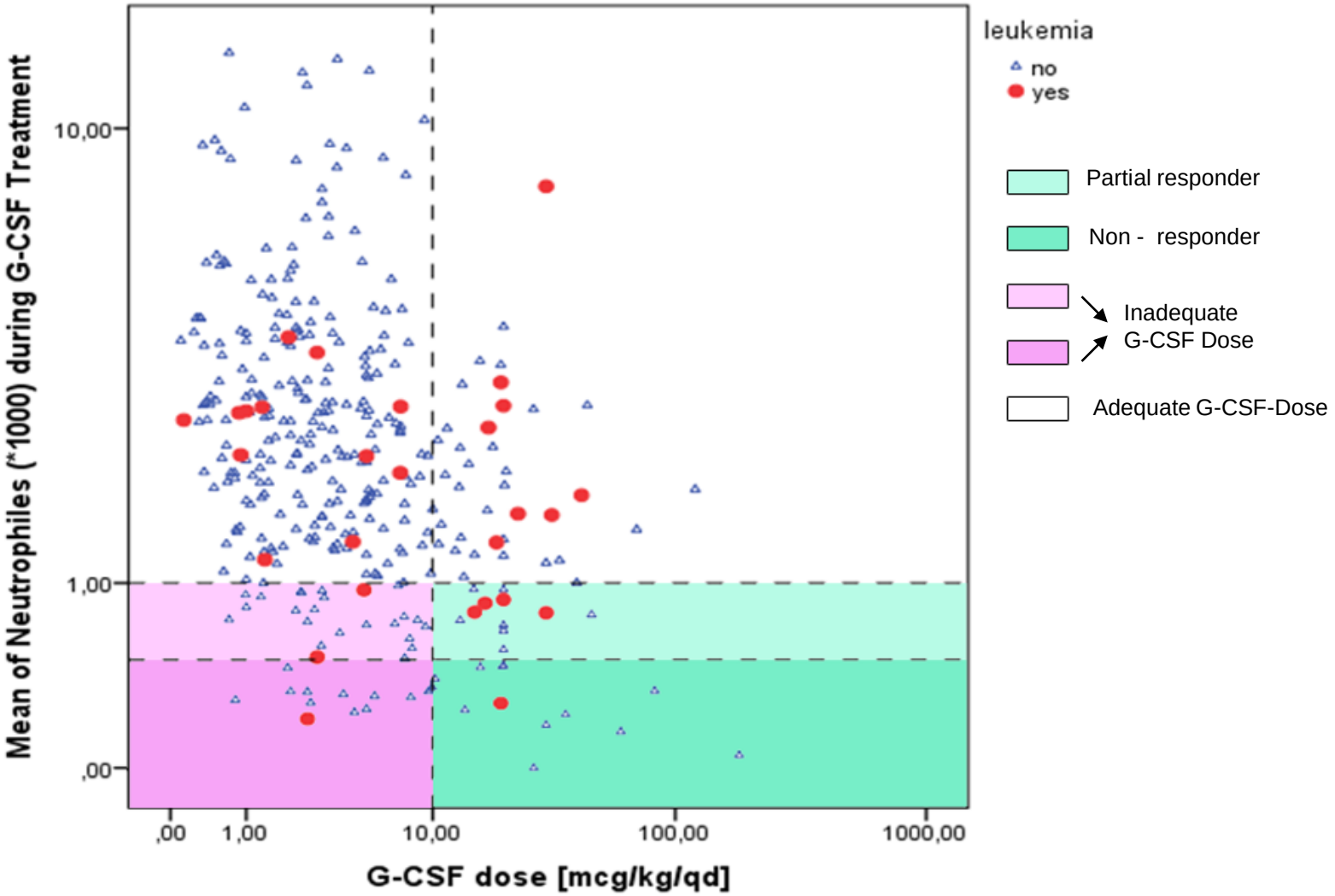
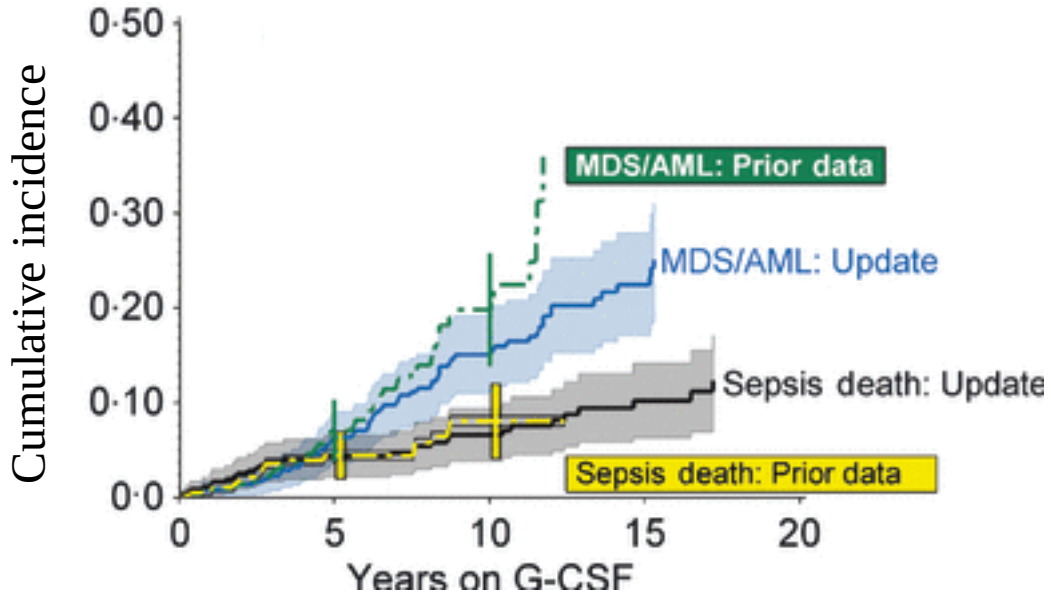
G-CSF Dose and Response to Therapy by absolute neutrophil count (ANC) (log. Skale)



Stable long-term risk of leukemia in CN patients



Rosenberg, et al., BJH 2010

Severe Adverse Events-
Reason for Stem Cell Transplantation

Reason for stem cell transplantation in 88 patients
Congenital 80 (12 SDS), CyN nt. 1, IDN 4, Autoimmun 1, LGL 2

Leukemia	N	Non – Leukemia	N
Leukemia/MDS	35	Non or partial response	19
MPS	1	No cytokine therapy available	2
Monosomy 7	1	G-CSF Receptor mutation	7
T-LGL	1	Pancytopenia	6
		Chronic infection, SAA	5
		Others	11
Total	**38**	**Total**	**50**

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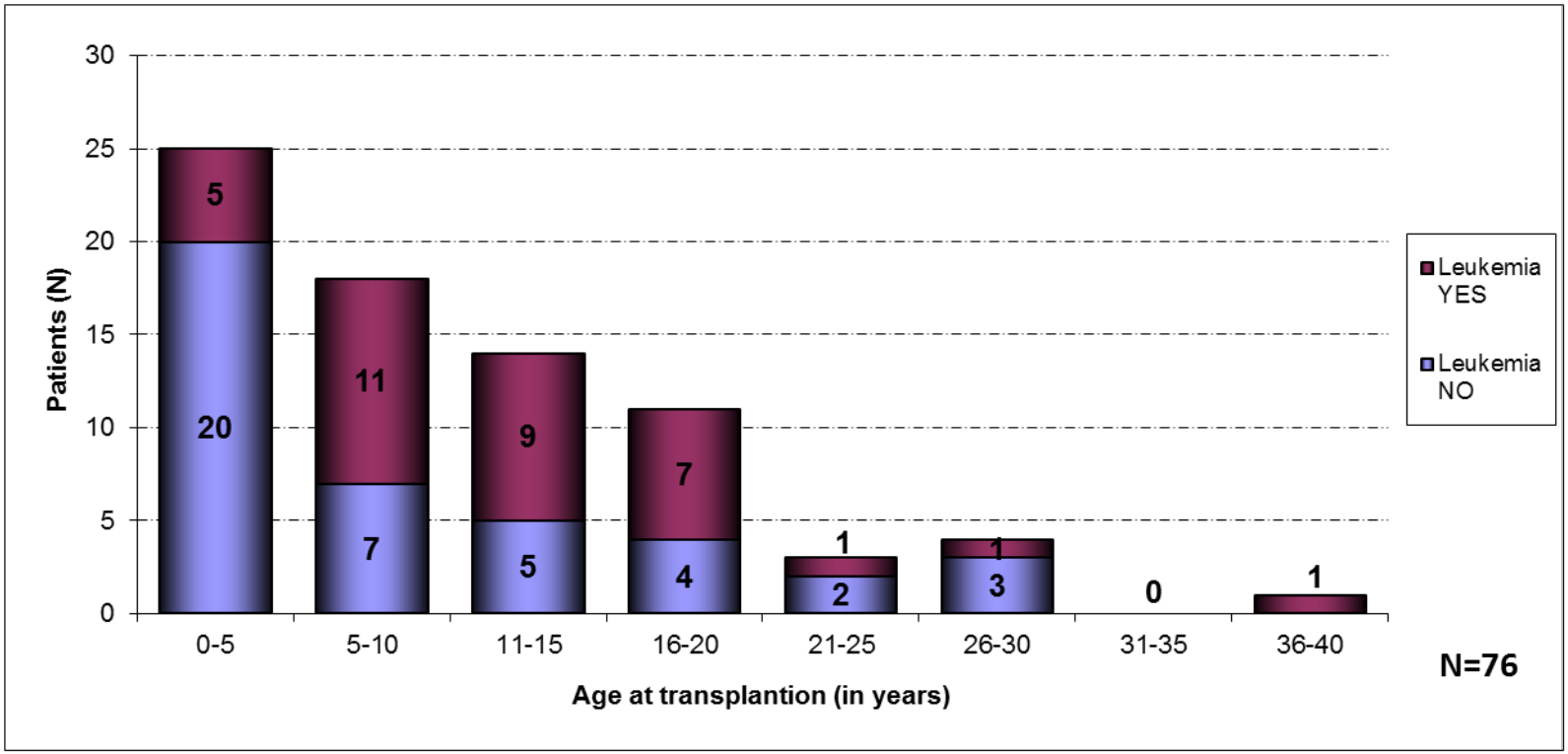
AGE AT SCT IN CONGENITAL (with SDS) AND CYCLIC NEUTROPENIA PATIENTS WITH/WITHOUT LEUKEMIA



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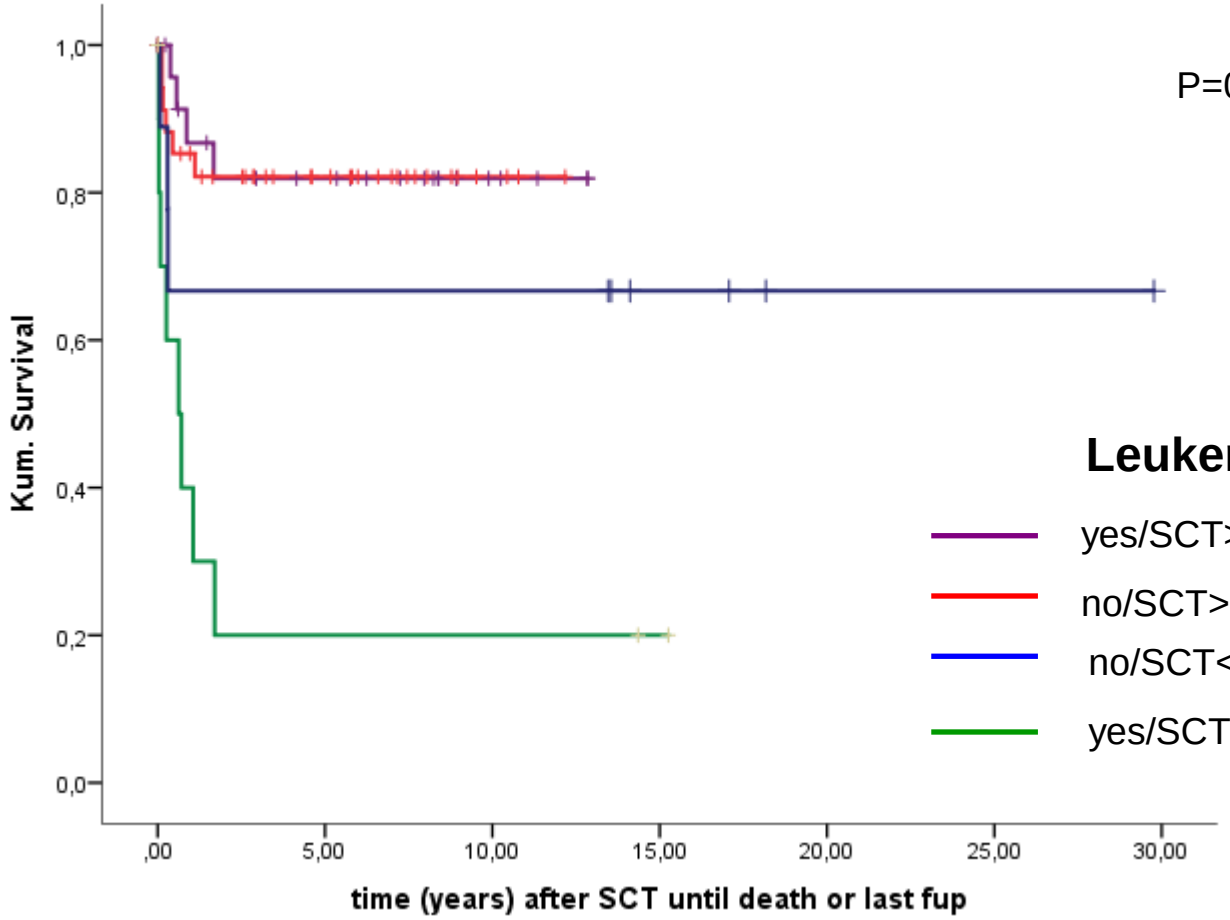
Survival after SCT by CN and CyN 09/2015



P=0,000 (Log Rank)

Leukemia and SCT

yes/SCT>=2001 **Events/N=4/26**

no/SCT>=2001 **Events/N=6/35**

no/SCT<2001 **Events/N=3/9**

yes/SCT<2001 **Events/N=8/11**

N=81

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SCT in CN and CyC (without SDS) Conditioning regimens since 2001

For leukemia Patients	Busulfan - based	Treosulfan - based	other
HLA ident	3	0	3
Matched unrelated	10	2	0
Haplo ident	2	0	2
Total *(missing 1)*	15	2	5

For non-leukemia Patients	Busulfan-based	Treosulfan-based	other
HLA ident	3	3	2
Matched unrelated	3	3	3
Haplo ident	3	3	2
Total *(missing 3)*	9	9	7

Busulfan Cyclophosphamide Fludarabin
Busulfan Cyclophosphamide Arabinosid C
Busulfan Fludarabin Campath
Busulfan Cyclophosphamide Melphalan
Busulfan Cyclophosphamide Thiotepa
Busulfan Melphalan VP-16
Cyclophosphamide Campath
Cyclophosphamide
Cyclophosphamide Fludarabin
Cyclophosphamide Thiotepa
Fludarabin Melphalan
Fludarabin Melphalan Thiotepa
Fludarabin Thiotepa
Fludarabin Melphalan VPIG
Treosulfan Fludarabin
Treosulfan Thiotepa Fludarabin
Treosulfan Fludarabin Melphalan
Treosulfan Campath Fludarabin
Treosulfan Melphalan Campath Fludarabin
Treosulfan Thiotepa Campath Fludarabin

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SOURCE OF STEM CELLS
CN and CyC w/o SDS since 2001

Leukemia Patients	BM	PBSC	Cord-blood
HLA ident	4	2	0
Matched unrelated	6	6	0
Haplo ident	1	4	0
Total	11	12	0

Non-leukemia Patients	BM	PBSC	Cord-blood
HLA ident	5	3	1
Matched unrelated	5	2	1
Haplo ident	2	2	1
Total (missing 6)	12	7	3

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Conclusions

- CN is a heterogeneous congenital disorder of myelpoiesis as judged by morphology, physical and metabolic abnormalities, pattern of inheritance, gene expression and gene mutations
- G-CSF is still the only effective treatment of severe congenital neutropenia (CN)
- Survival and quality of life have improved dramatically with G-CSF treatment
- Long term G-CSF treatment is capable to maintain sufficient neutrophil counts
- Congenital neutropenia is a pre-leukemic condition

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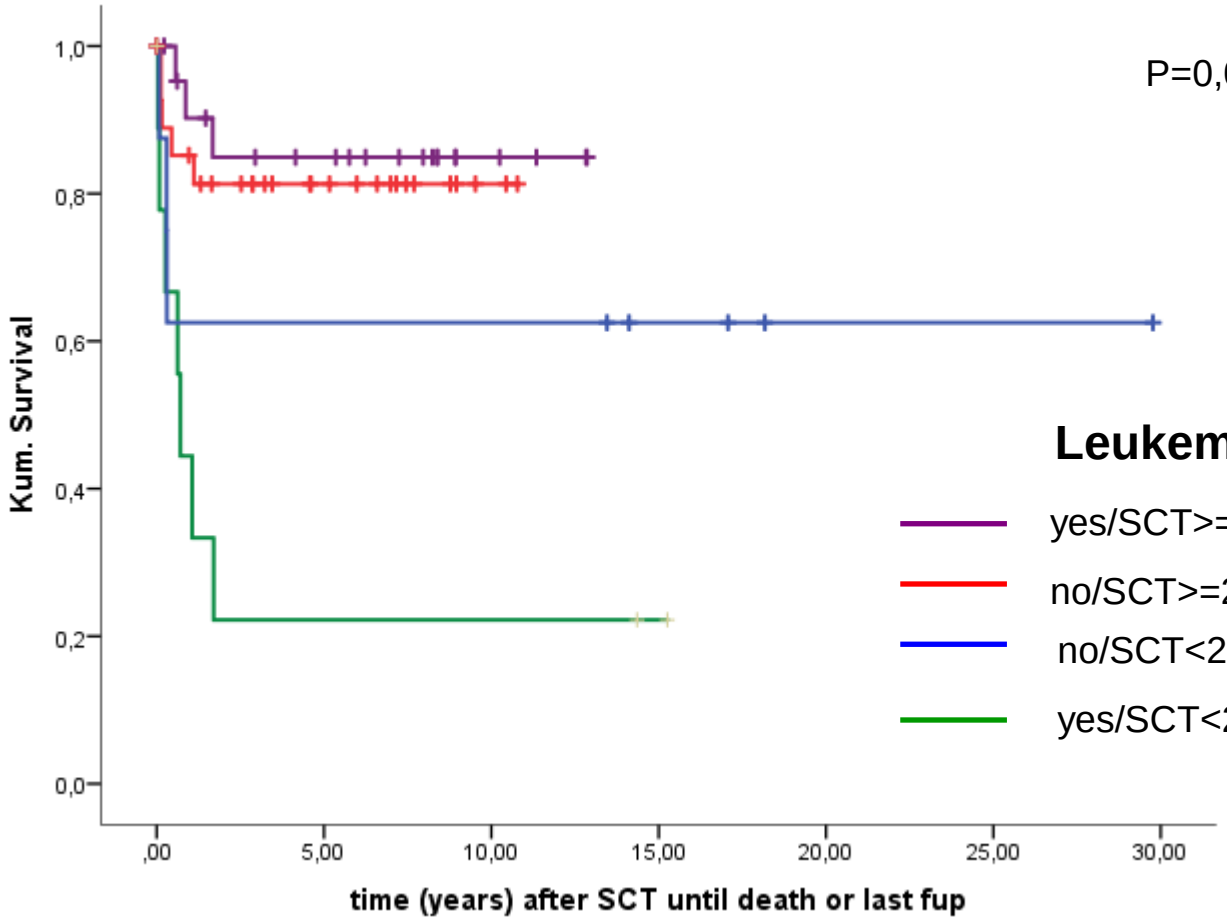
Survival after SCT by CN and CyN without SDS 09/2015



P=0,000 (Log Rank)

Leukemia and SCT

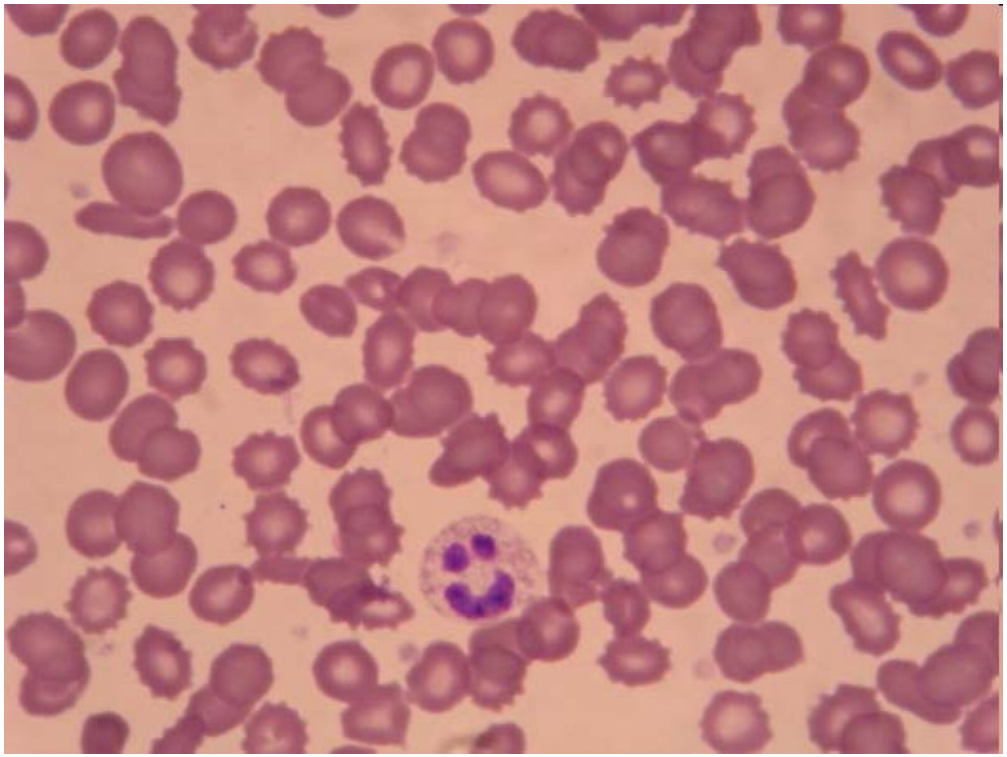
yes/SCT>=2001**Events/N=3/23**

no/SCT>=2001 **Events/N=5/28**

no/SCT<2001 **Events/N=3/8**

yes/SCT<2001 **Events/N=7/10**

N=69



SEVERE CHRONIC
NEUTROPENIA
International Registry

www.schwere-chronische-neutropenie.de
www.severe-chronic-neutropenia.org

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