



XLIX
CONGRESSO
NAZIONALE
AIEOP

HLH: i dati AIEOP

Elena Sieni

Oncoematologia Pediatrica

AOU Meyer IRCCS, Firenze

Bologna, 2 Ottobre 2024



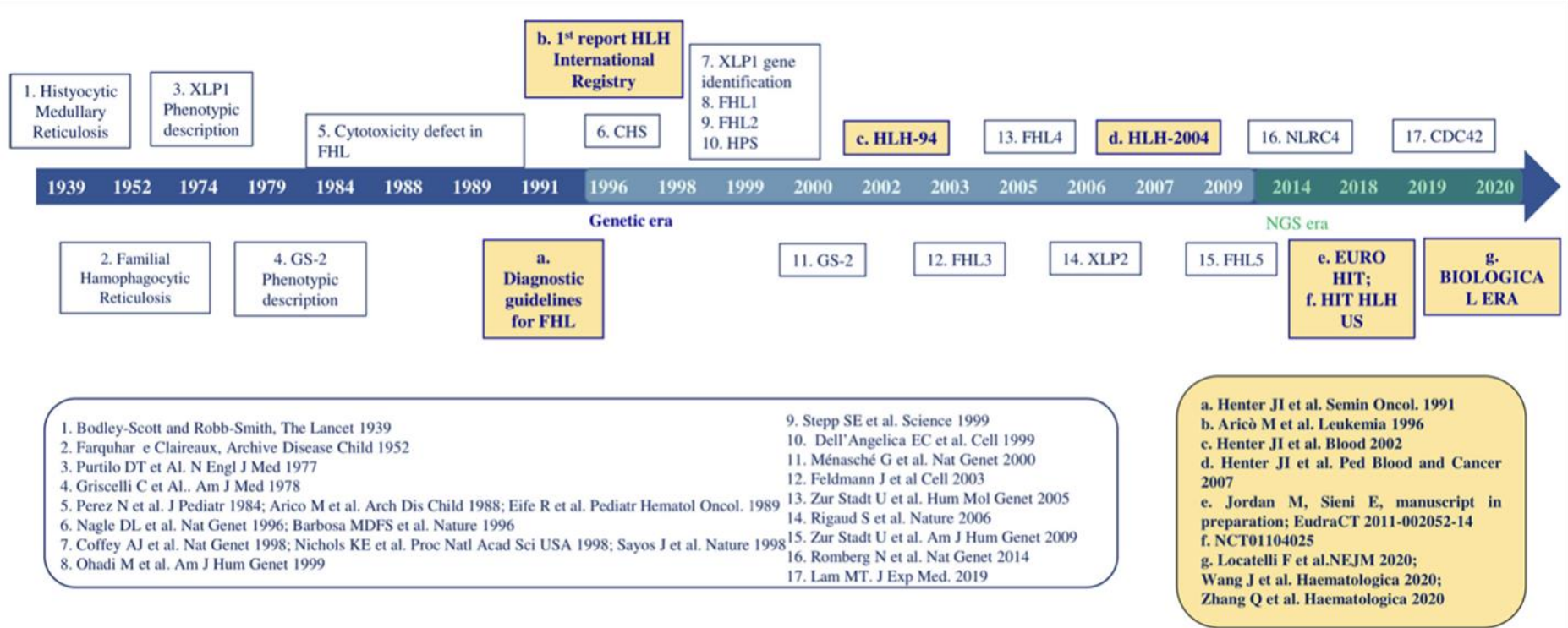
Il sottoscritto Elena Sieni

ai sensi dell'art. 3.3 sul Conflitto di Interessi, pag. 17 del Reg. Applicativo dell'Accordo Stato-Regione del 5 novembre 2009,

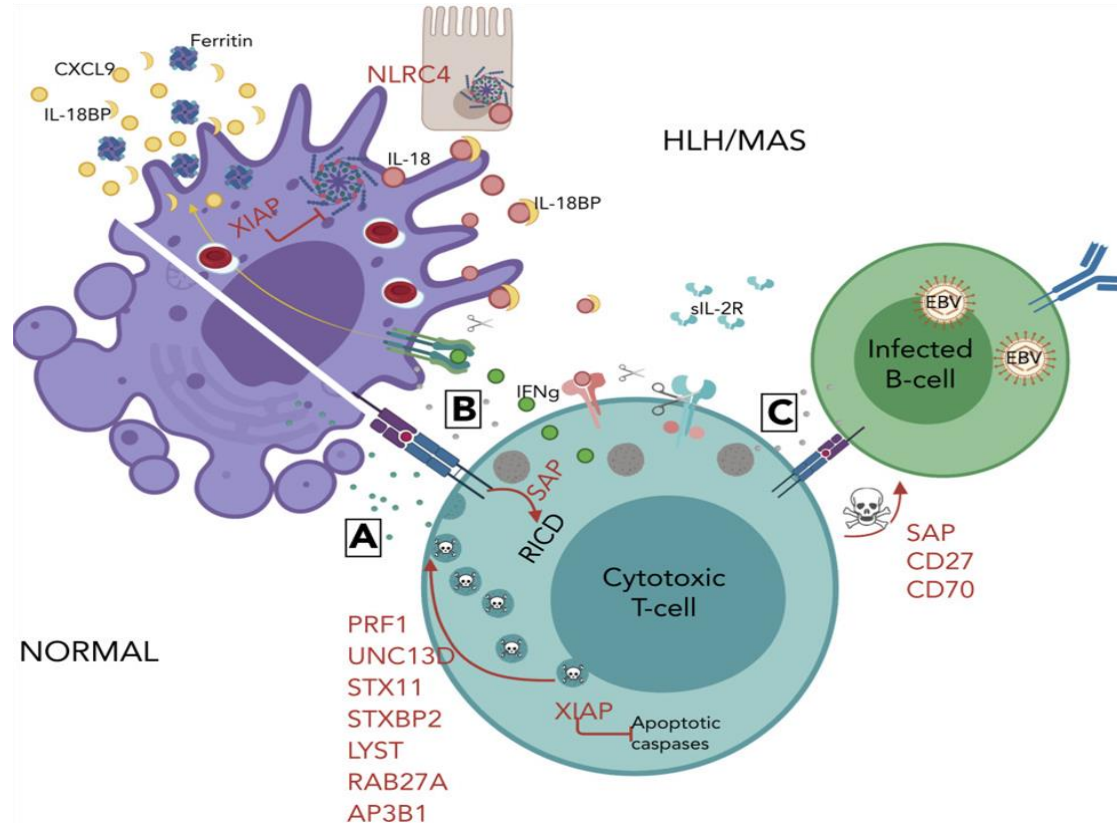
dichiara

che negli ultimi due anni NON ha avuto rapporti diretti di finanziamento con soggetti portatori di interessi commerciali in campo sanitario

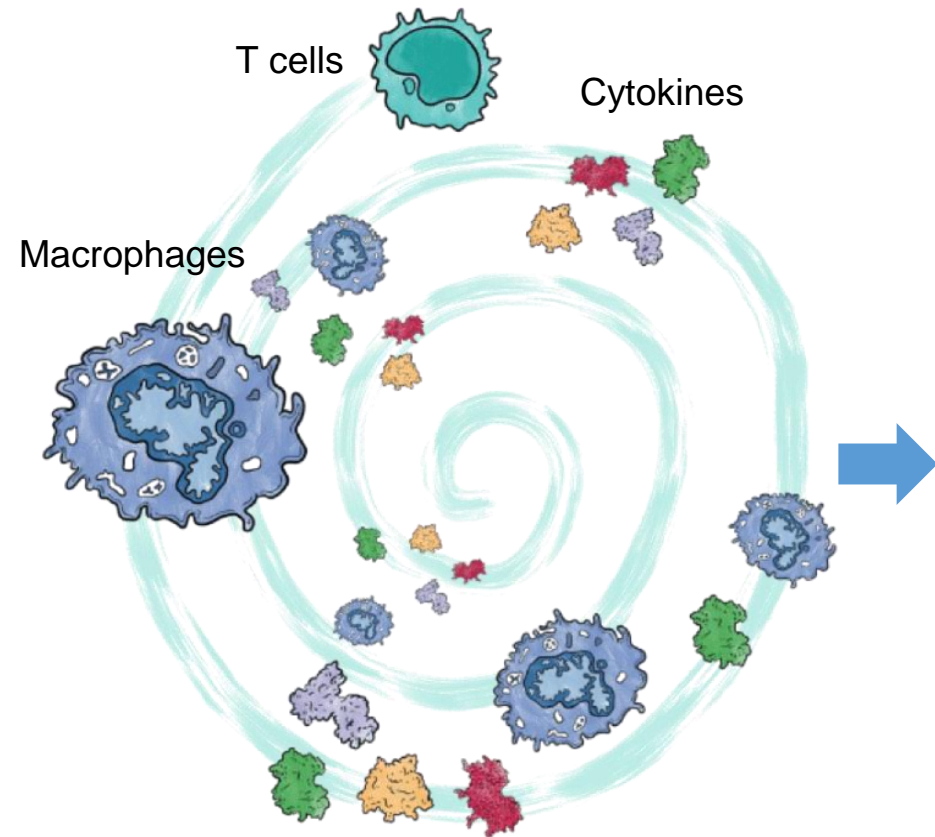
HLH discovery along the last 80 years



HLH is a life-threatening hyperinflammatory syndrome, caused by a highly stimulated but ineffective immune response

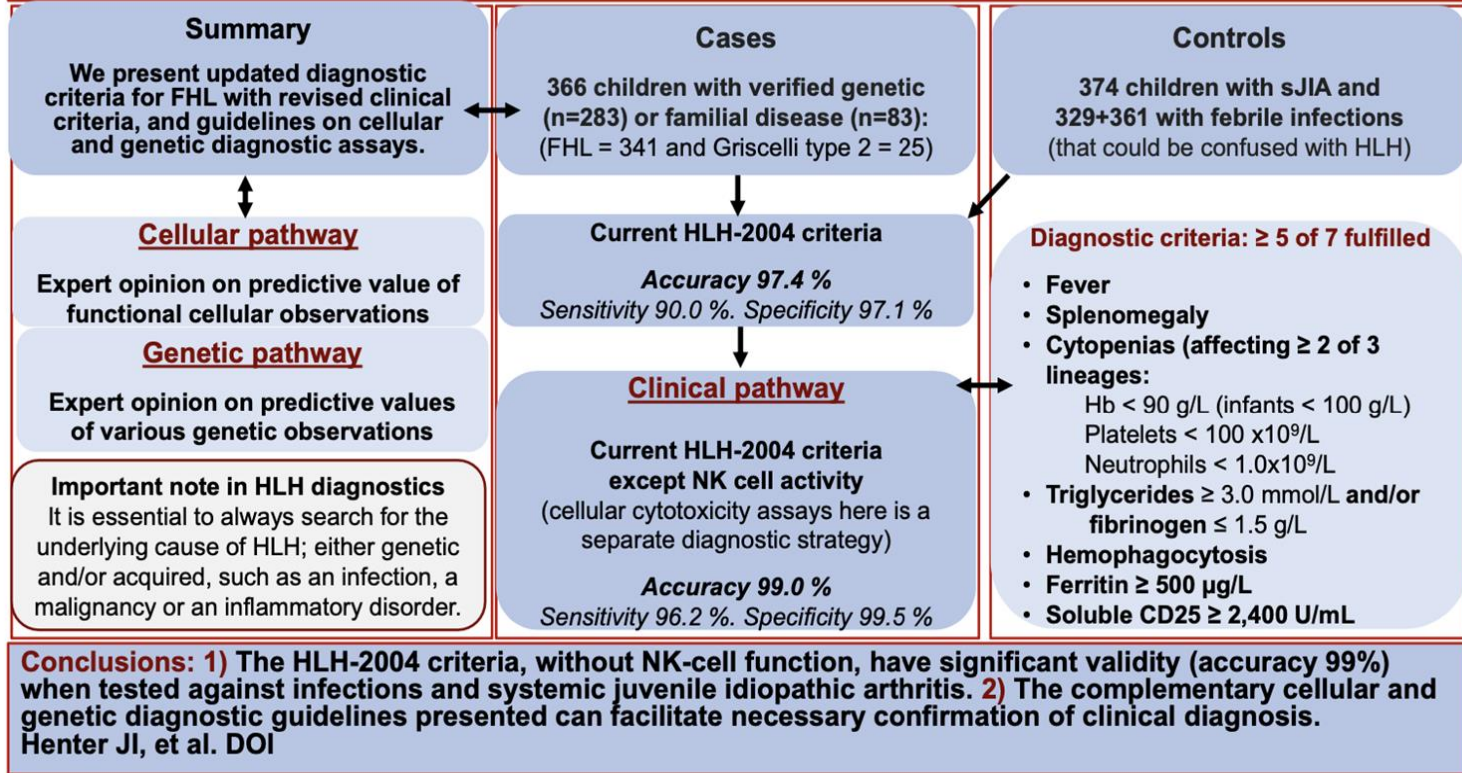


HLH clinical picture

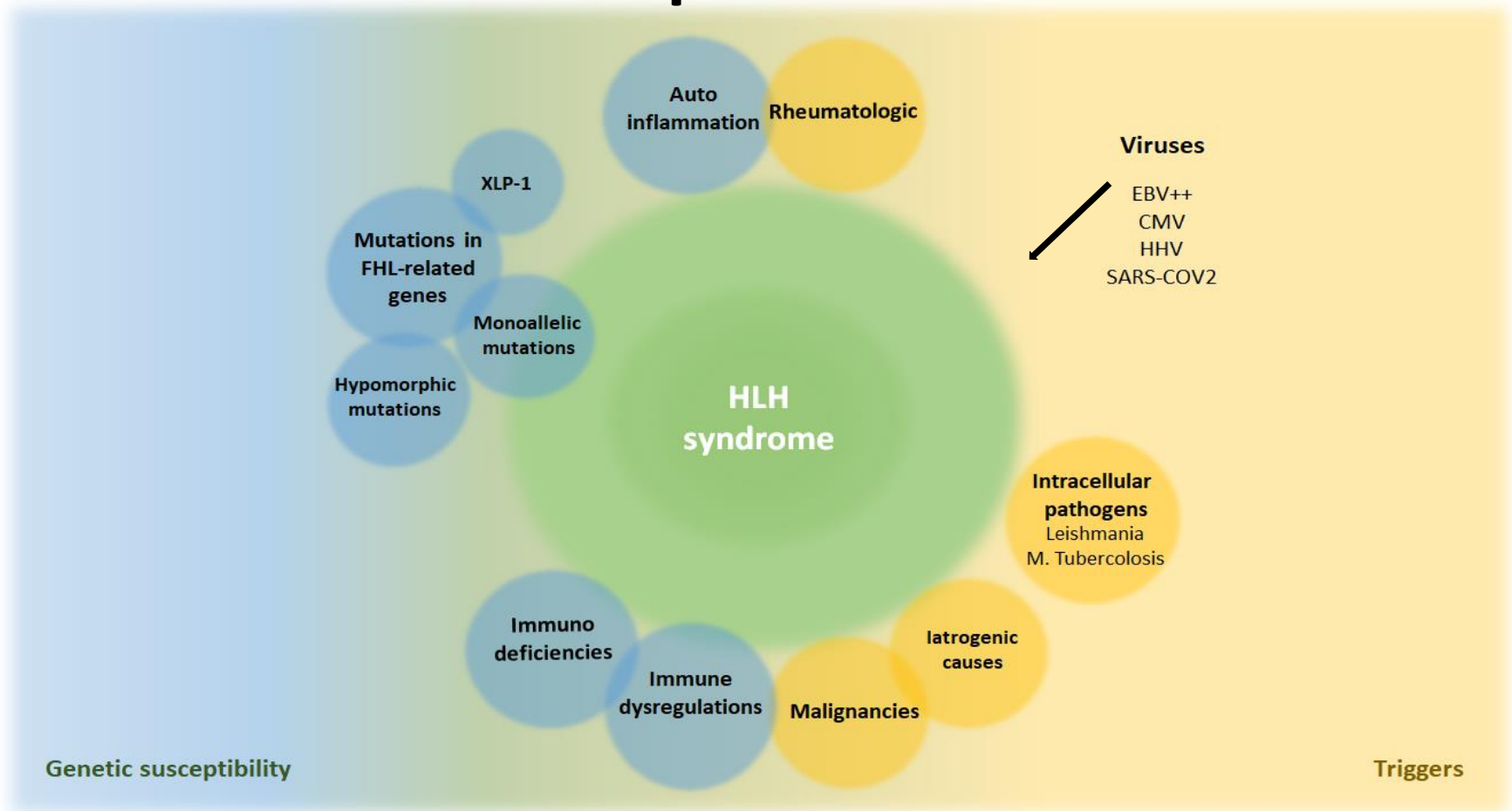


Unusual T cell activation	Innate/myeloid cell activation	Tissue injury/ infiltration
sCD25 > 2400 U/ML (or above age-specific normals)	Fever >38.5, likely recurrent or persistent	Hemophagocytosis in tissue biopsies
Elevated CXCL9	Ferritin >500 ng/mL	Hepatosplenomegaly Cytopenias in ≥2 lineages Fibrinogen <150 mg/dL Elevated ALT/AST CSF pleocytosis/ elevated protein or focal/global neurologic injury

Diagnostic Guidelines for Familial Hemophagocytic Lymphohistiocytosis Revisited

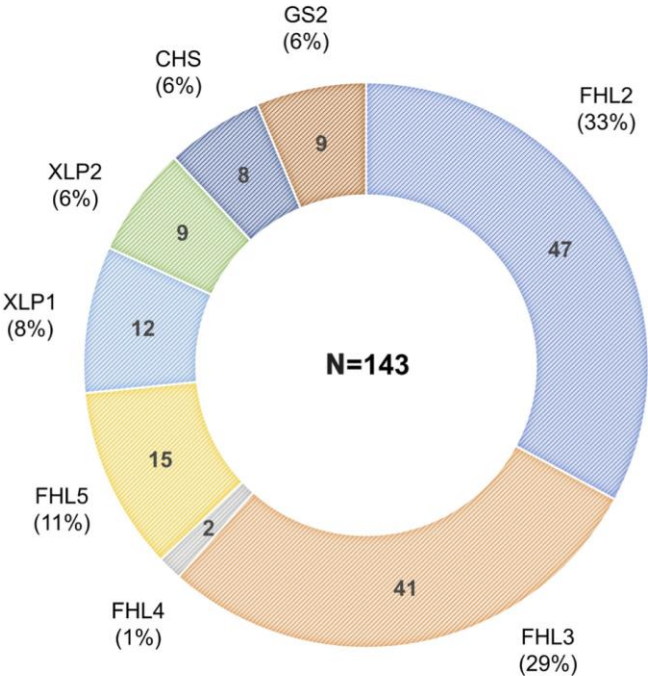


HLH spectrum



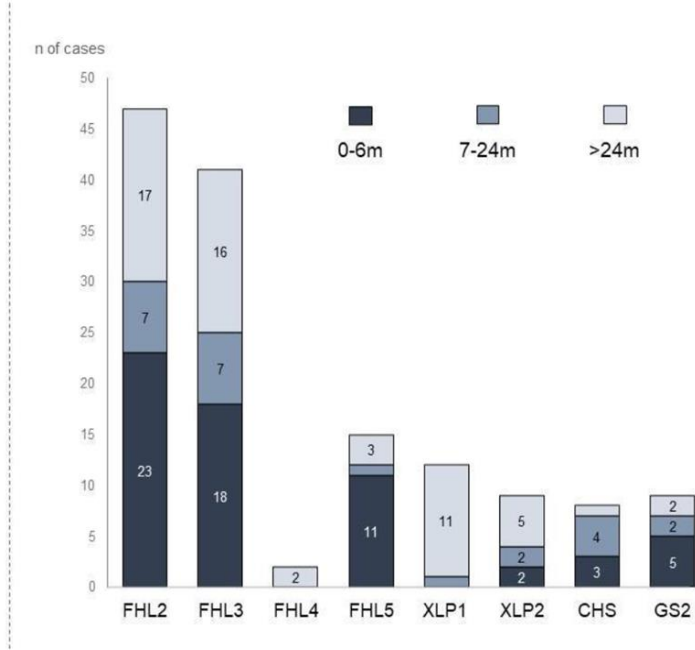
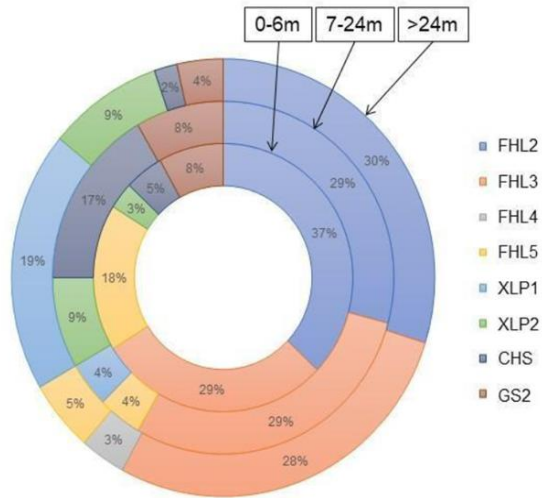
Outcome of primary hemophagocytic lymphohistiocytosis: a report on 143 patients from the Italian Registry

Francesco Pegoraro,^{1,2} Aurora Chinnici,^{2,3} Linda Beneforti,^{2,3} Michele Tanturli,⁴ Irene Trambusti,^{2,5} Carmela De Fusco,⁶ Concetta Micalizzi,⁷ Veronica Barat,⁸ Simone Cesaro,⁹ Stefania Gaspari,¹⁰ Fabiola Dell'Acqua,¹¹ Alessandra Todesco,¹² Fabio Timeus,¹³ Maurizio Aricò,¹⁴ Claudio Favre,² Annalisa Tondo,² Maria Luisa Coniglio² and Elena Sieni² for the AIEOP Histiocytosis Working Group[#]

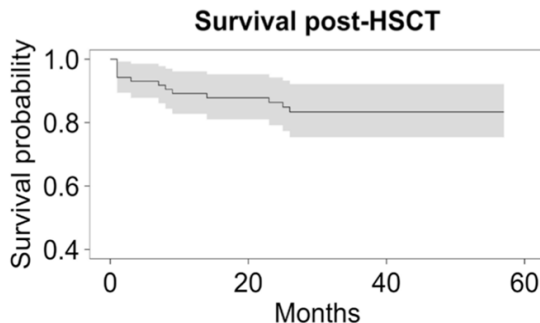
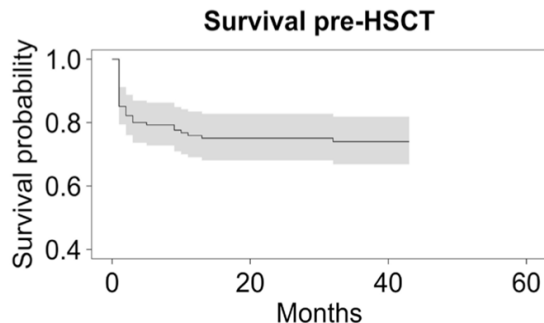
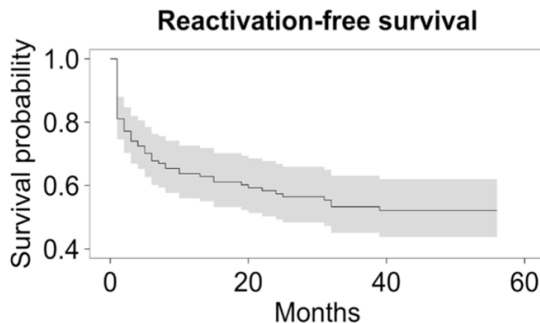
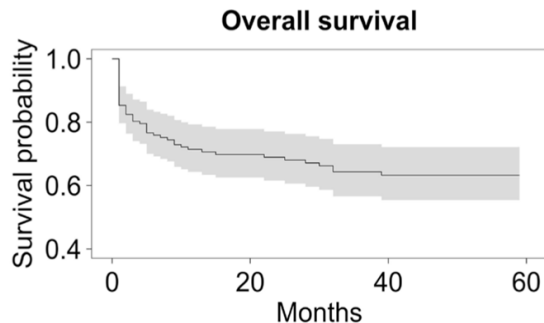


Characteristics	Included patients N=143
Age in months, median (IQR)	12 (2-81) 10% adults
Female sex, N (%)	55 (38)
Ethnic origin, N (%)	
Caucasian	113 (79)
Sub-Saharan African	3 (2)
North African	12 (8)
Middle East, Arabic	3 (2)
Indian subcontinent	9 (6)
Latin American	3 (2)
Familial disease, N (%)	38 (27)
Parental consanguinity, N (%)	30 (21)
Complete HLH-2004 criteria, N (%)	92 (64)

Age at onset in pHLH



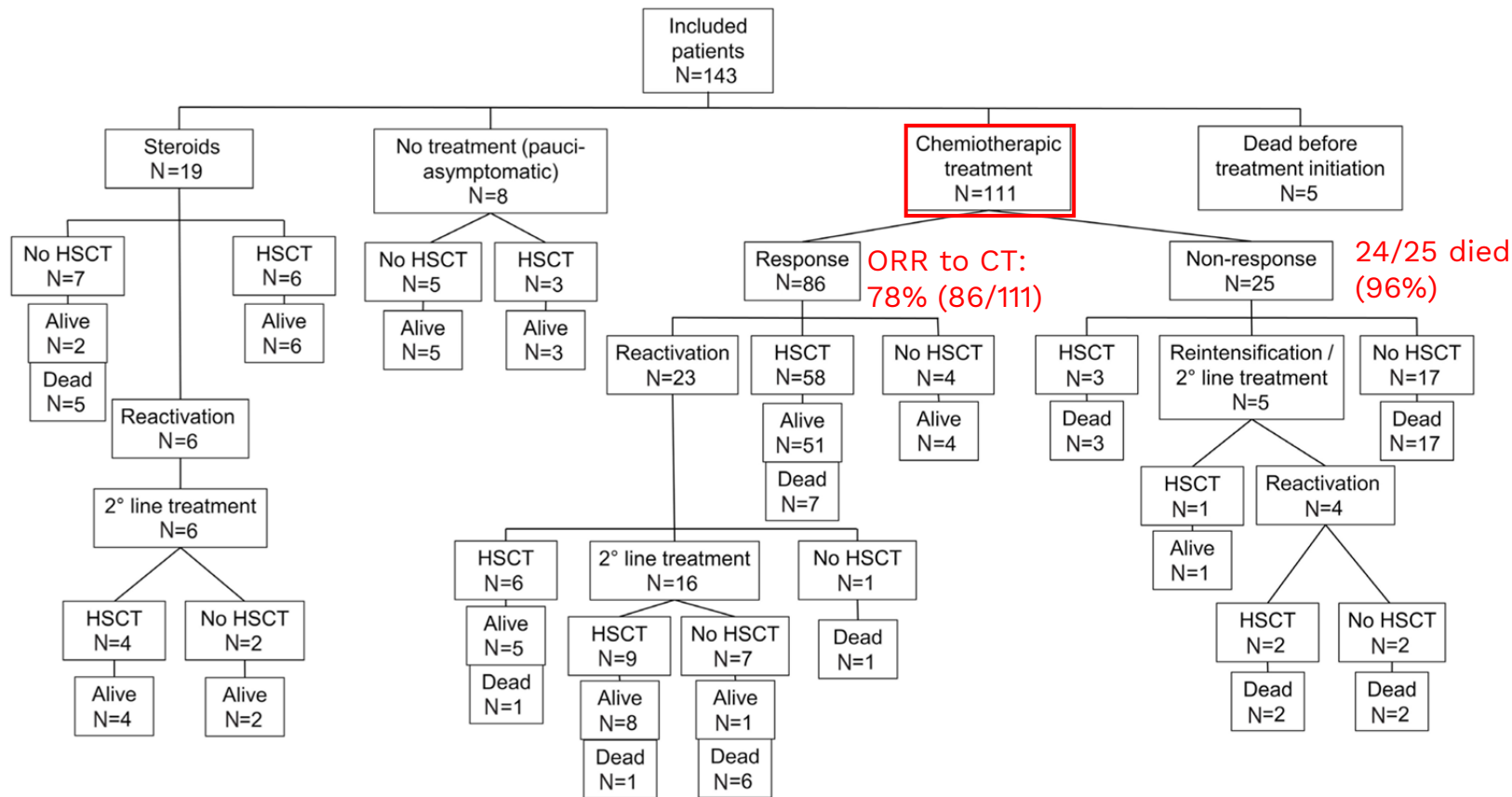
Treatment and outcome, pHLH



First line tx: 80% HLH-94/2004

- **OS at last follow-up: 65% (93/143)**
vs 48% HLH-94; 61% HLH-2004
- **Reac free survival: 86/111 (78%)**
- **Early mortality: 36/143 (25%)**
vs 27% HLH-94, 17% HLH-2004
- **Post-HSCT survival: 78/92 (85%)**
vs 66% HLH-94, 70% HLH-2004

Treatment response



Outcome FHL, Italian Registry 2007-2022

N=143

Multivariable analysis:

Non response

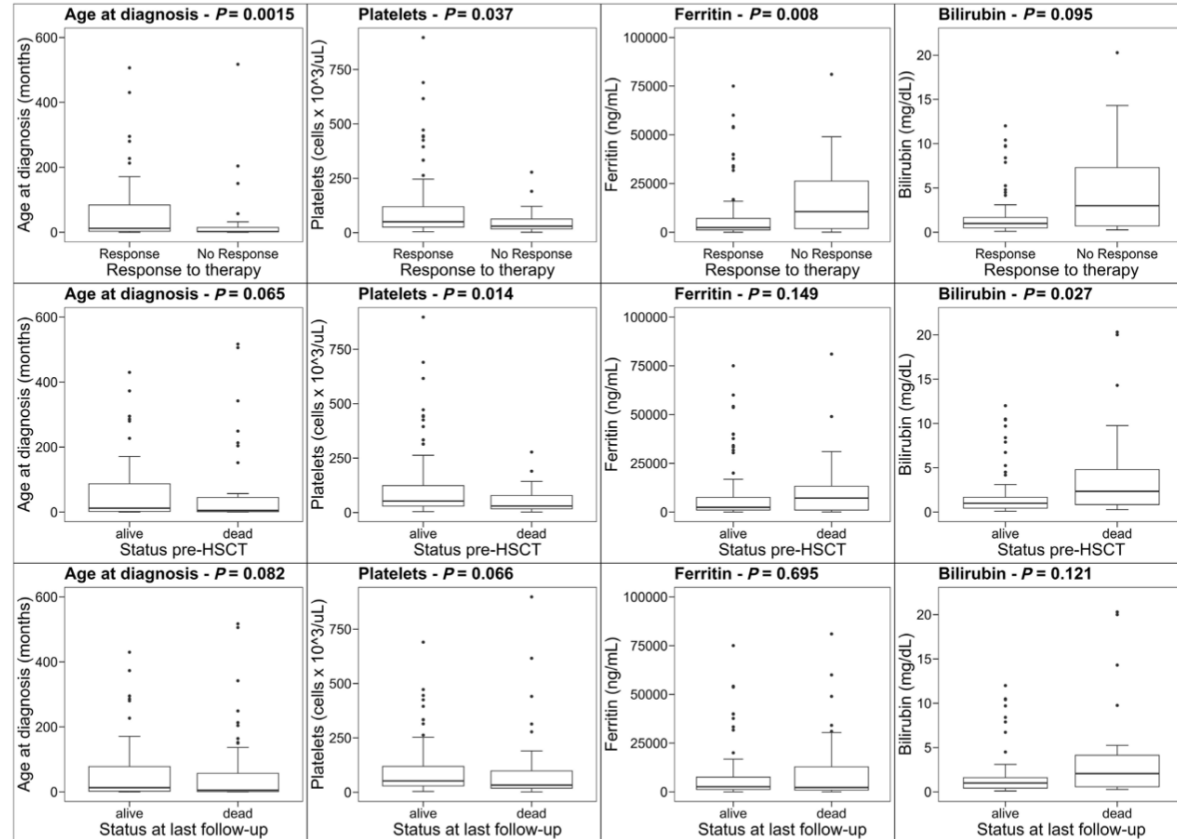
- Age at diagnosis <6m
- **Ferritin >5,000ng/dL**
- Bilirubin >2mg/dL

Pre-transplant mortality

- Ferritin >5,000ng/dL
- **Bilirubin >2mg/dL**

Overall mortality

- Ferritin >5,000ng/dL
- **Bilirubin >2mg/dL**

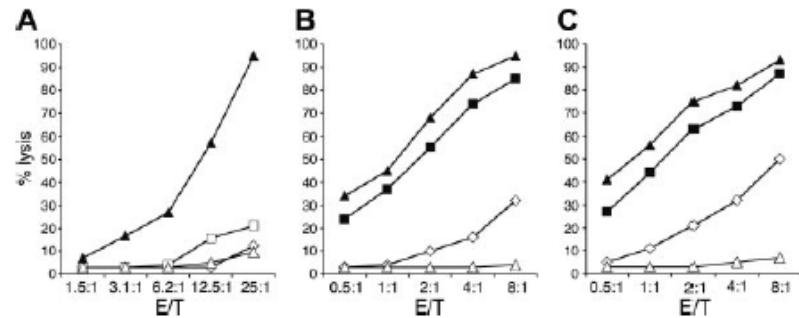
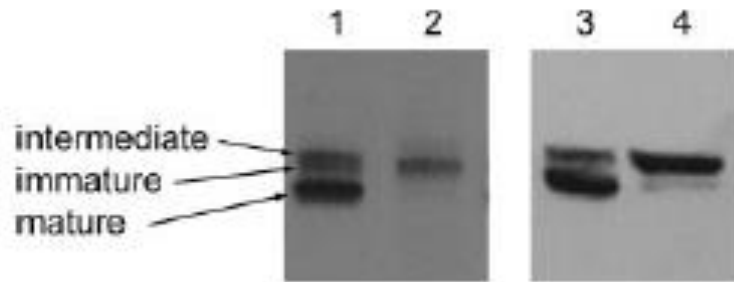


Outcome FHL, Italian Registry 2007-2022:

- 15/143 (10%) cases with milder disease were alive at a median follow-up of 34 months without receiving HSCT → **hypomorphic variants**
- 10 patients harboring homozygous or compound heterozygous A91V *PRF1* mutations, whose pathogenicity is still debated:
 - 4 were alive without HSCT
 - 3 received HSCT for active HLH
 - 3 died before being able to be transplanted

A single amino acid change, A91V, leads to conformational changes that can impair processing to the active form of perforin

Christina Trambas, Federico Gallo, Daniela Pende, Stefania Marcenaro, Lorenzo Moretta, Carmela De Fusco, Alessandra Santoro, Luigi Notarangelo, Maurizio Arico and Gillian M. Griffiths



A91V/A91V patients, Italian HLH Registry

	Included patients N=7
Age at HLH onset (years)	Median 9.4 IQR 1,9-30
M:F	5:2
Complete HLH 2004 criteria	1 (14%)
Fever	5/7 (71%)
Splenomegaly	5/7 (71%)
Bi-cytopenia	1/6 (17%)
Hypertriglyceridemia/hypofibrinogenemia	4/7 (57%)
Hyperferritinemia	5/7 (71%)
Hemophagocytosis	2/7 (29%)
CNS involvement	1/7 (14%)
Liver involvement	3/7 (43%)
PRF expression abnormal	4/6 (57%) (range: 3% - 60%)
Infectious Trigger	3/7 (43%)
Associated disease	4/7 (57%)
Death	1/7 (14%)
React	2/7 (29%)
HCST	2/7 (29%)

Additional factors are required in addition to A91V/A91V genotype to develop HLH

The hypomorphic Perforin A91V variant can become a risk allele *in trans* with loss-of-function *PRF1* mutations

(Germany, Italy, France, UK, Austria, Australia, USA)

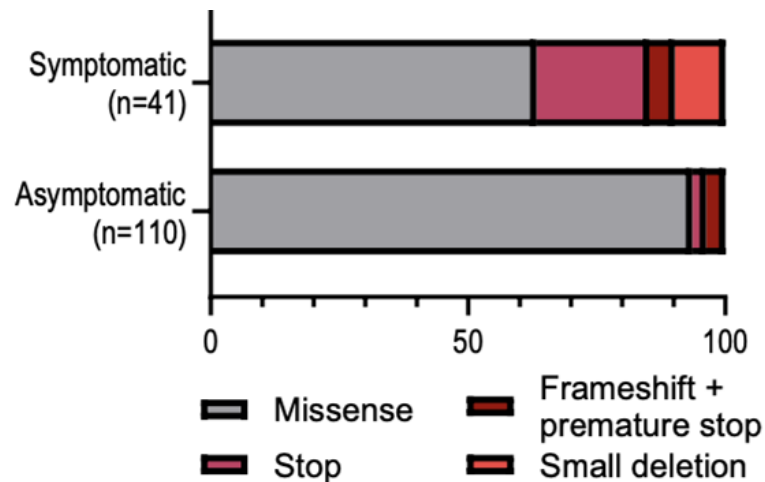
- ***A91V/pLOF predispose to HLH or FHL-2 related diseases?***
- Accurate risk assessment is crucial for genetic counseling, in particular for infants identified by newborn screening for early HSCT
- Preemptive HSCT in asymptomatic carriers proved to be safe and should be considered (*Lucchini G et al Blood 2018*)

A91V/pLOF population (UK biobank)

- 500,000 adults with genome sequencing and clinical history available
 - A91V/WT, 7.4%
 - A91V/pLOF, 0.1%
- 458 A91V/pLOF carriers:
 - splenomegaly/cytopenia (n=6)
 - neuroinflammation (n=4)
 - lymphoma (n=6)

A91V/pLOF:

low risk for FHL2-related manifestations



Symptomatic patients:

- deleterious variants: 15/41 (37%)
- missense variants: 7/110 (6%)

A91V/pLOF study: conclusions

- Overall low risk for A91V/pLOF individuals to develop FHL2-related disease manifestations.
- This risk justifies **regular monitoring**, but **HSCT should be reserved for symptomatic patients** and selected genotypes.

Monoallelic mutations in *PRF1* may predispose to cancer and HLH

Acute Lymphoblastic Leukemia

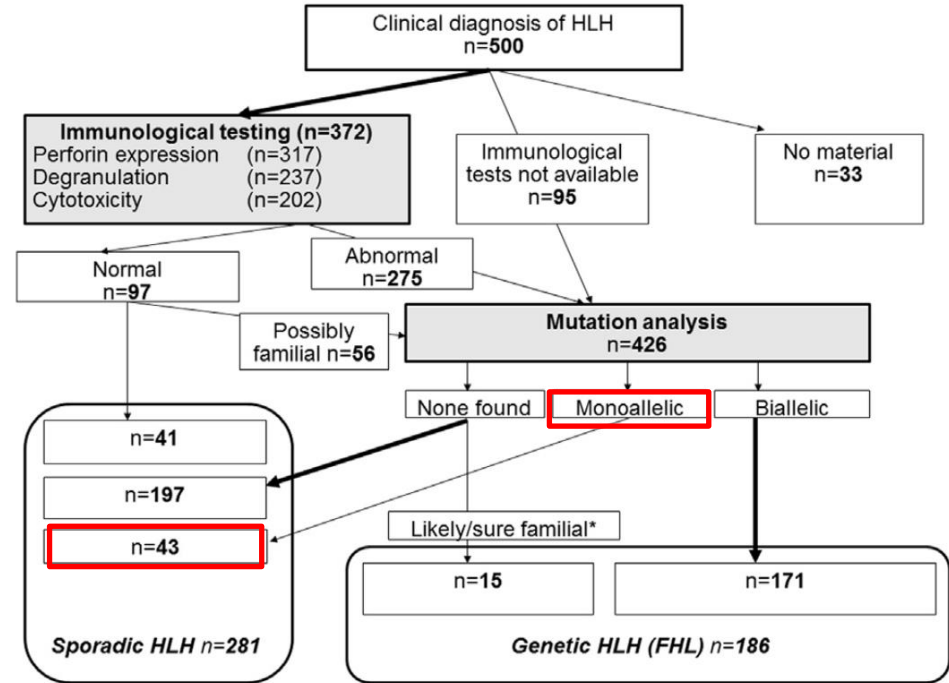
Clementi Blood 2005

A single amino acid change A91V in perforin: a novel, frequent predisposing factor to childhood acute lymphoblastic leukemia?

Ciambotti B et al JPHO 2013

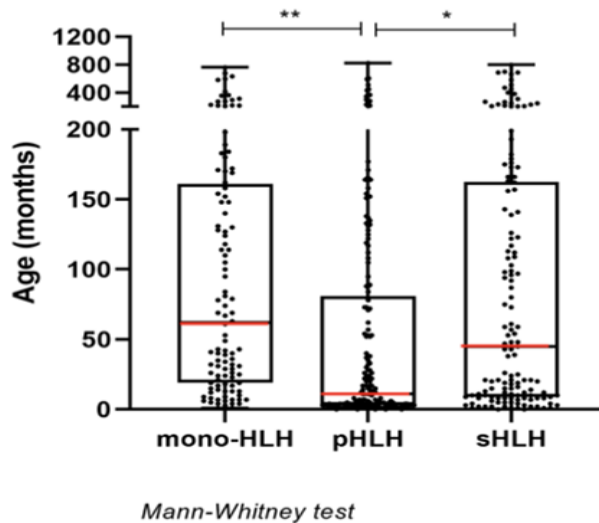
Monoallelic Mutations of the Perforin Gene may Represent a Predisposing Factor to Childhood Anaplastic Large Cell Lymphoma

Benedetta Ciambotti, DR,*† Lara Mussolin, PhD,‡§ Emanuele S.G. d'Amore, MD,||
Marta Pillon, MD,§ Elena Sieni, MD,* Maria L. Coniglio, DR,*† Martina D. Ros, DR,*†
Valentina Cetica, PhD,*† Maurizio Aricò, MD,*† and Angelo Rosolen, MD‡¶



Clinical presentation and outcome of 109 patients with HLH harboring monoallelic FHL mutations (Firenze, Genova, Padova, Torino, Monza, Ancona, Napoli, Cagliari)

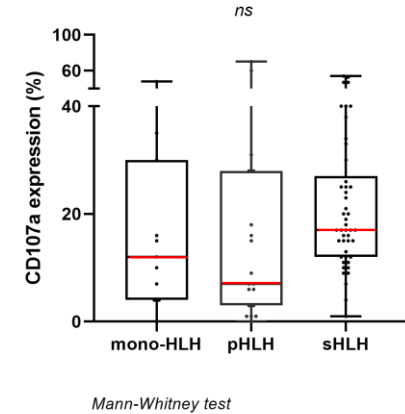
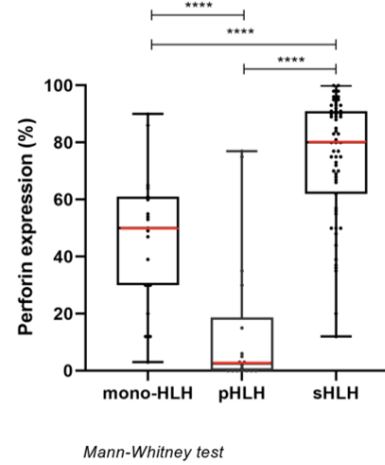
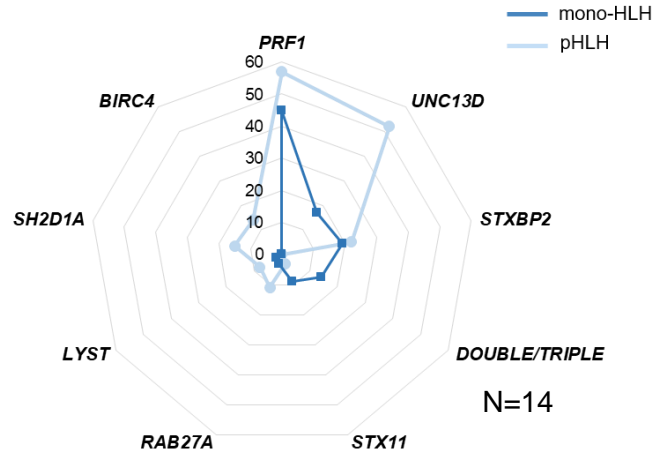
Baseline	mono-HLH (n=109)	pHLH (n=182)	p value Mono vs pHLH	sHLH (n=137)	p value Mono vs sHLH
Male sex, n (%)	57 (52)	105 (58)	0.3949	72 (53)	1
Age at onset, months - median (IQR)	62 (19-159)	11 (3-77)	0.0015[^]	44 (9-162)	0.8214 [^]
Consanguinity, n (%)	7 (6)	50 (27)	<0.0001	14 (10)	0.3612
Familiarity, n (%)	3 (3)	45 (25)	<0.0001	4 (3)	1
Complete HLH-2004 criteria n/n tot (%)	63 (57)	122 (67)	0.1023	137 (100)	
Fever	63/63 (100)	120/122 (98)	0.5484	129/137 (94)	0.0583
Splenomegaly	53/63 (84)	119/122 (97)	0.0014	122/137 (89)	0.3606
CNS symptoms	11/63 (17)	31/122 (25)	0.2683	25/137 (18)	1
Bi-Cytopenia	58/63 (92)	114/122 (93)	0.7658	123/137 (90)	0.7963
Hypertriglyceridemia or Hypofibrinogenemia	59/62 (95)	113/114 (99)	0.1260	128/131 (98)	0.3881
Hyperferritinemia	58/62 (93)	112/121 (93)	1	125/133 (94)	1
Hemophagocytosis	43/56 (77)	77/117 (66)	0.1615	87/120 (72)	0.5858
Associated disease, n (%)	47 (43)	20 (11)	<0.0001	51 (37)	0.3617
Rheumatic/Autoimmune	27 (25)	13 (7)	<0.0001	20 (15)	0.0507
Immunodeficiency	2 (2)	0 (0)	0.1395	11 (8)	0.0424
Neoplastic	14 (13)	5 (3)	0.0011	15 (11)	0.6933
Syndromic/Congenital	2 (2)	0 (0)	0.1395	4 (3)	0.6960
Metabolic	2 (2)	2 (1)	0.6319	1 (2)	0.5857



Coniglio M.L. et al. in preparation

Mono-HLH vs pHLH and sHLH: genetic and functional data

67 different mutations

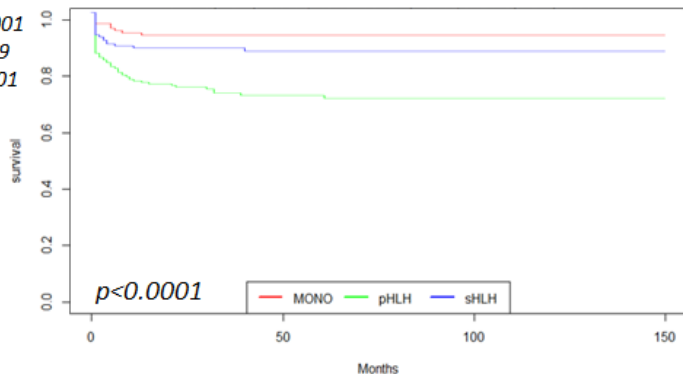


	monoHLH	pHLH	monoHLH vs pHLH	sHLH	monoHLH vs sHLH
Abnormal Functional n/n tot (%)	47/69 (68)	85/90 (94)	<0.0001	33/84 (39)	0.0006
Abnormal PRF	24/49 (49)	40/41 (96)	<0.0001	11/96 (11)	<0.0001
Abnormal CD107a	23/40 (57)	45/49 (92)	0.0003	22/88 (25)	0.0006
Type of mutation n/n tot (%)					
Missense	102 (94)	61/179 (34)	<0.0001	-	-
Deleterious	7 (6)	118/179 (66)	<0.0001	-	-

Mono-HLH vs pHLH and sHLH survival analysis

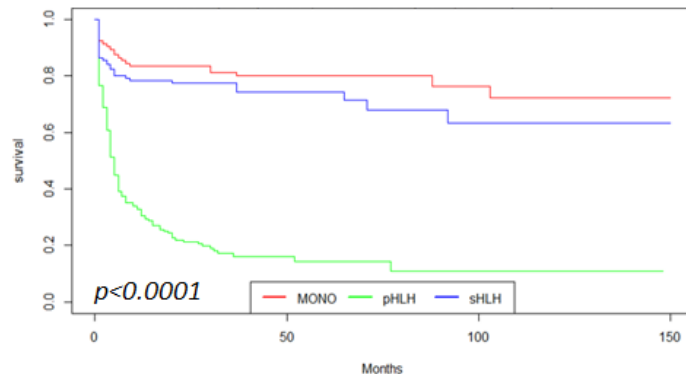
Overall survival

mono vs pHLH $p<0.0001$
mono vs sHLH $p=0.139$
sHLH vs pHLH $p<0.0001$



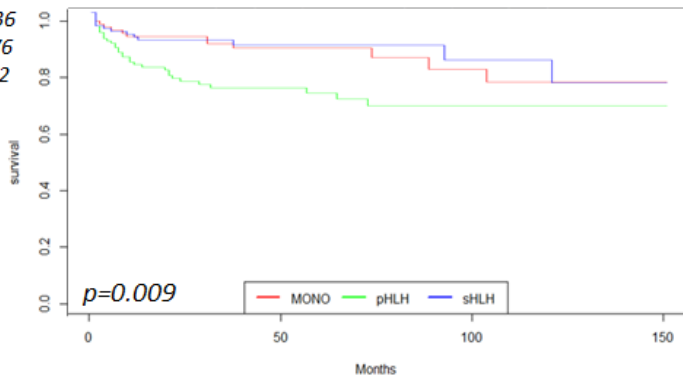
Any event

mono vs pHLH $p<0.0001$
mono vs sHLH $p=0.16$
sHLH vs pHLH $p<0.0001$



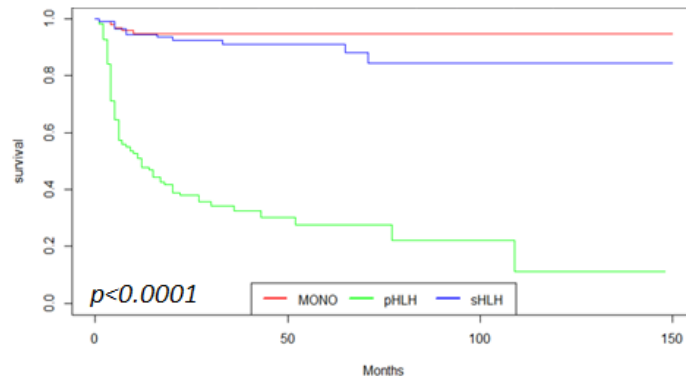
Reactivation

mono vs pHLH $p=0.036$
mono vs sHLH $p=0.876$
sHLH vs pHLH $p=0.032$



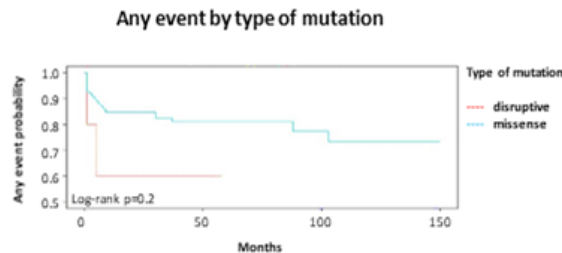
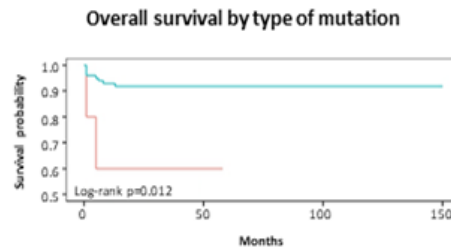
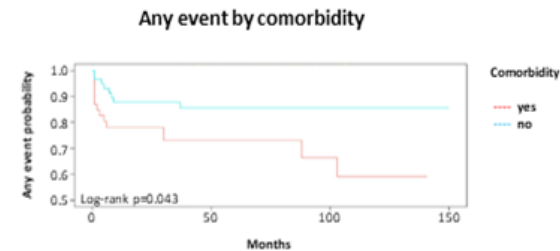
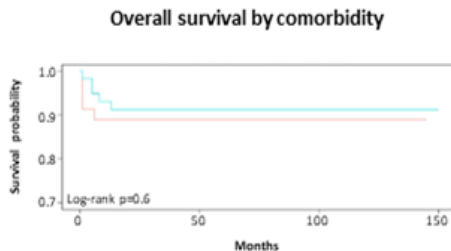
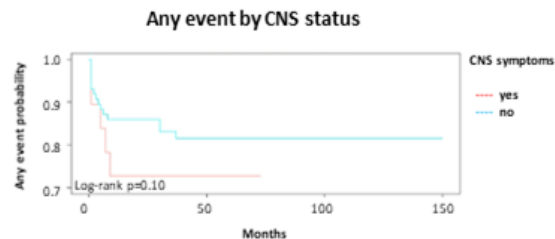
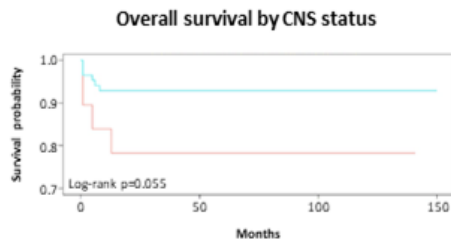
BMT

mono vs pHLH $p<0.0001$
mono vs sHLH $p=0.17$
sHLH vs pHLH $p<0.0001$



Predictors of death and any event (death or reactivation or HSCT) in mono-HLH

Mono HLH:
dead patients
n=14 /109 (13%)



Monoallelic mutations in FHL-genes: conclusions

- Despite partial functional defect, age at onset, overall survival, reactivation or HSCT were not different from sHLH
- **Aggressive treatment and HSCT are not justified by the presence of monoallelic mutations**
- Mono-HLH patients with disruptive mutations, CNS involvement and comorbidity should be strictly monitored
- **This study support the choice of parents carrying monoallelic mutations as donors for aplo-HSCT**



Genotype characteristics and immunological indicator evaluation of 311 hemophagocytic lymphohistiocytosis cases in China

Ja Zhang^{1†}, Yuan Sun^{2†}, Xiaodong Shi², Rui Zhang³, Yini Wang¹, Juan Xiao², Jing Cao², Zhuo Gao², Jinghui Wang¹, Lin Wu¹, Wei Wei³ and Zhao Wang^{1*}

Regular Article

PHAGOCYTES, GRANULOCYTES, AND MYELOPOIESIS

Genetic and mechanistic diversity in pediatric hemophagocytic lymphohistiocytosis

Ivan K. Chinn,^{1,2} Olive S. Edstein,^{1,2,3} Erin C. Poolham-Gregory,^{1,2} Baruch R. Goldberg,^{1,2} Lisa R. Forbes,^{1,2} Sarah K. Nicholas,^{1,2} Emily M. Mace,^{1,2} Tiphane P. Vogel,^{1,2} Harshal A. Abhyankar,^{1,2} Maria L. Diaz,^{1,2} Helen E. Haddig,^{1,2,3} Robert A. Krance,^{1,2,3} Candice A. Martinez,^{1,2,3} Trung C. Nguyen,^{1,2,3} Dalia A. Bashir,^{1,2,3} Jordana R. Goldstein,^{1,2} Aditya Singh-Pedersen,^{1,2} Luis A. Pedraza,^{1,2} M. Cecilia Pili,^{1,2,3} Juan C. Aldave-Becerra,^{1,2} Sean A. McQueen,^{1,2} Waleed Al-Herzi,^{1,2} Aghad Chandra,^{1,2} Zeynep H. Coban-Akdemir,^{1,2,3} Shalini N. Jhangiani,^{1,2,3} Dorra M. Muzny,^{1,2,3} Tian N. Cao,^{1,2} Diana N. Hong,^{1,2} Richard A. Gibbs,^{1,2,3,4} James R. Lupski,^{1,2,3,4} Jordan S. Orange,^{1,2} Kenneth L. McClain,^{1,2,3} and Carl E. Allen^{1,2,3}

REGULAR ARTICLE



Frequency and spectrum of disease-causing variants in 1892 patients with suspected genetic HLH disorders

Vanessa Gadoury-Levesque,¹ Lei Dong,² Rui Su,² Jianjun Chen,² Kejian Zhang,³ Kimberly A. Roma,¹ Rebecca A. Marsh,⁴ and Miao Sun⁵

¹Division of Allergy and Immunology, Cincinnati Children's Hospital Medical Center, University of Cincinnati, Cincinnati, OH; ²Department of Systems Biology, Sweden Research Institute of City of Hope, Monrovia, CA; ³Cytos BioScience, USA, San Jose, CA; and ⁴Division of Bone Marrow Transplant and Immune Deficiency and ⁵Division of Human Genetics, Cincinnati Children's Hospital Medical Center, University of Cincinnati, Cincinnati, OH



Article

Targeted NGS Yields Plentiful Ultra-Rare Variants in Inborn Errors of Immunity Patients

Alice Grossi^{1,2}, Maurizio Miano^{2,3,4}, Marina Lanciotti², Francesca Fioredda², Daniela Guardo², Elena Palmisani², Paola Terranova², Giuseppe Santamaria¹, Francesco Caroli^{1,5}, Roberta Caorsi², Stefano Volpi^{1,6}, Marco Gattorno^{2,4}, Carlo Dufour^{2,4} and Isabella Ceccherini^{1,4,6}

The Journal of Rheumatology 2022;49:1140–51
doi:10.1093/rheum/ckab330
First Release August 1, 2022



Hemophagocytic Lymphohistiocytosis Gene Variants in Childhood-Onset Systemic Lupus Erythematosus With Macrophage Activation Syndrome

Piya Labiry¹, Sergey Naumenko², Madeline Cousse², Fangming Liao³, Daniela Dominguez⁴, Andres Knight⁵, Deborah M. Levy⁶, Melissa Mizutani⁷, Lawrence W.K. Ng⁸, and Linda T. Hiraki⁹

Expanding spectrum of genetic predisposition to HLH

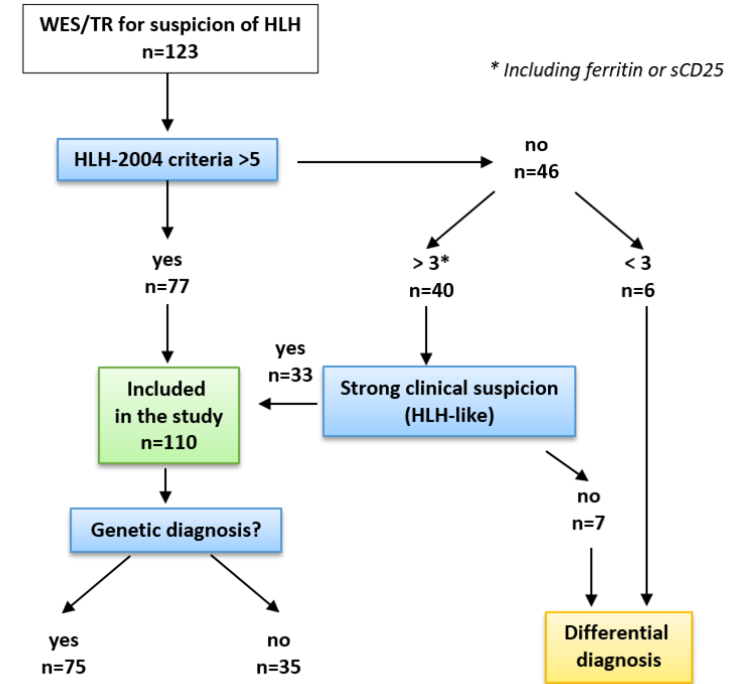
Available literature on NGS in HLH/MAS/PIDs:
2018-2022

Detection rate:

- Gene panels /target sequencing: 13% - 43%
- WES: 47 - 58% on small cohorts (max 48 patients)

Detection rate of extended genetic analysis in HLH: report from the Italian HLH Registry

- 110/123 patients with suspected HLH
- 2017 - 2024
- Median age: 4.4 (IQR 0.3, 12.6) y
- M:F=58:52



Genetic analysis was
informative
in 75/110 patients

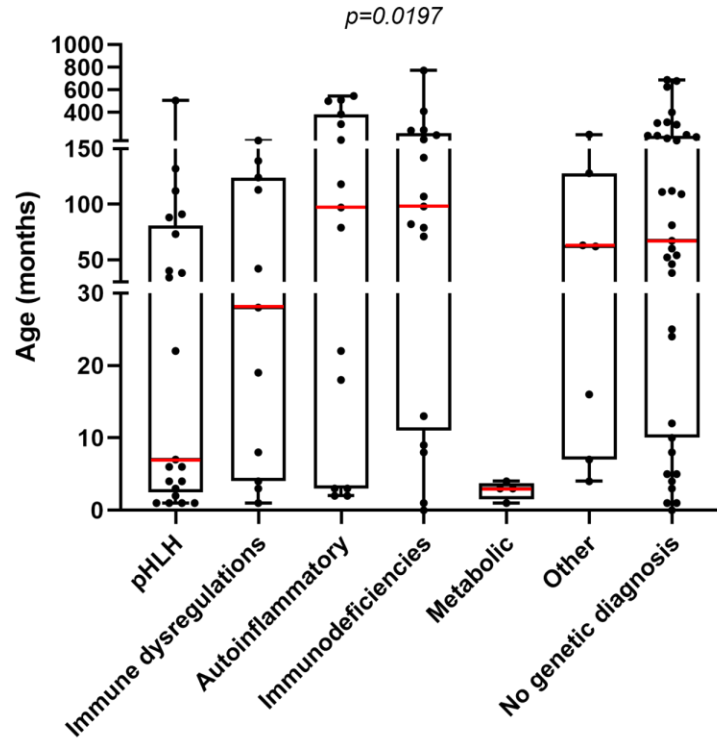
detection rate: 68%

103 variants in 43 genes

Disease group according IUIS Classification
(patients number)

	OMIM	Gene (patients number)
pHLH (21)	FHL3 FHL2 FHL5 CHS GS2 XLP1/2	<i>UNC13D</i> (10), <i>PRF1</i> (5), <i>STXBP2</i> (2), <i>LYST</i> (1), <i>RAB27A</i> (1), <i>SH2D1A</i> (1), <i>BIRC-4</i> (1)
Immune dysregulations (11)	ALPS/ALPS like APECED CVID IBD INFLAMMASOME	<i>FAS</i> (2), <i>FASL</i> (3), <i>CASP10</i> (2) <i>AIRE</i> (1) <i>LRBA</i> (1)
Autoinflammatory disorders (15)	NEMO Syndrome SPTCL Transport ER-Golgi	<i>IL10RA</i> (1), <i>NOD2</i> (1) <i>RIPK1</i> (1), <i>NLR4</i> (2), <i>NLRP12</i> (3), <i>NLRP3</i> (1), <i>TNFRSF1A</i> (4)
Immunodeficiencies (17)	BENTA CGD Congenital Neutropenia CVID GIDID IBD Infection susceptibility WHIM Syndrome SCID CID (NK deficiency)	<i>IKBKG</i> (2) <i>HAVCR2</i> (1) <i>COPA</i> (1) <i>NOD2</i> (1)
METABOLIC (4)	Wolman disease Niemann-Pick disease	<i>CARD11</i> (2), <i>CYBA</i> (2) <i>ELANE</i> (1), <i>GATA2</i> (2) <i>NFKB1</i> (1), <i>TNFRSF13B</i> (3) <i>TTC7A</i> <i>WAS</i> (1) <i>IFNGR1</i> (1) <i>CXCR4</i> (1) <i>JAK3</i> (1) <i>MCM4</i> (1)
OTHER candidate genes (7)	Thrombocythemia Complement deficiency Infection susceptibility, CNS involment Liver Involment Osteopetrosis Platelet disorder NEW	<i>LIPA</i> (3) <i>SMPD1</i> (1)
		<i>JAK2</i> (1) <i>C1S</i> (1) <i>RANBP2</i> (1)
		<i>ABCB11</i> (1) <i>CLCN7</i> (1) <i>PLAT</i> (1) <i>MBL2</i> (1)

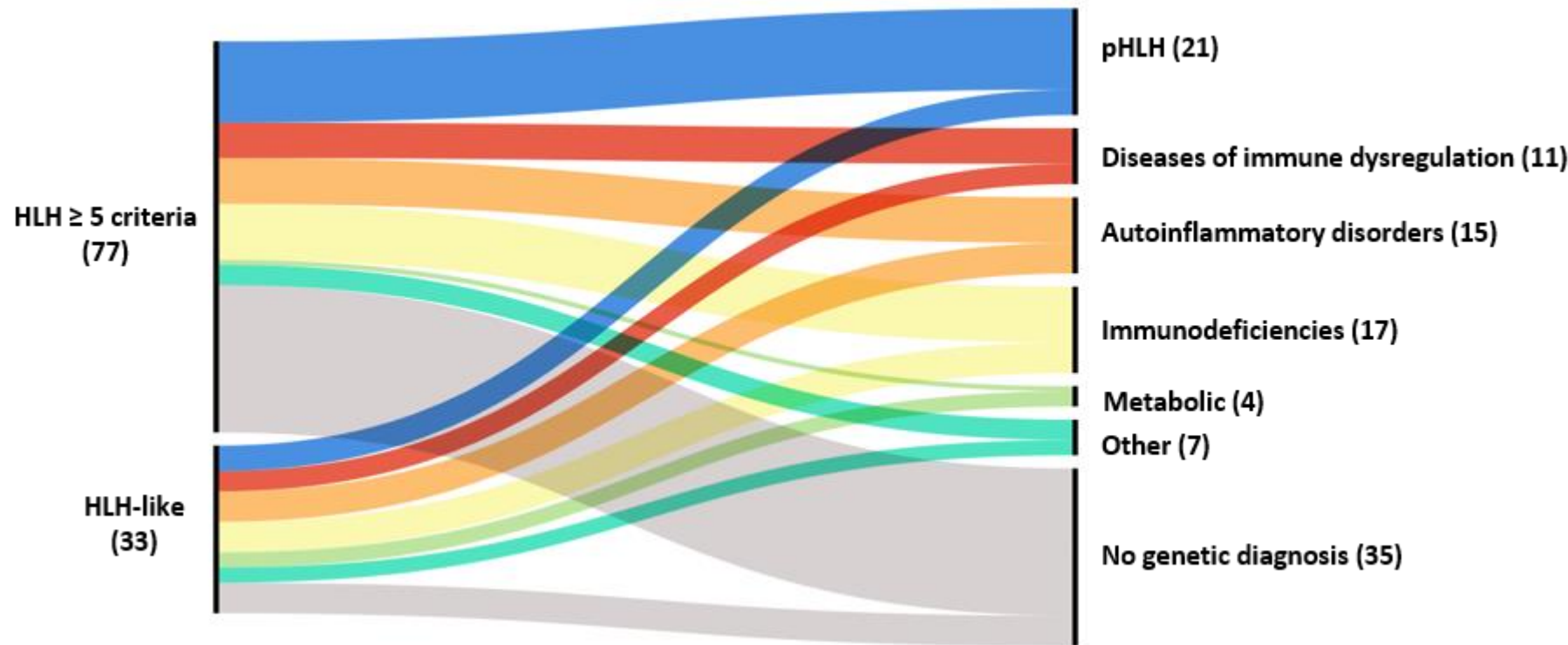
Age distribution among disease groups



Kruskal-Wallis test

Multiple comparison among groups: all ns

Disease group according to clinical presentation



Predictors of extending genetic analysis findings

	WT N=35	MUT N=75	p value
Age-years (IQR)	5.6 (0.8-16.2)	3.2 (0.3-10.7)	0.1202
Male sex (%)	16 (45.7)	42 (56.0)	0.412
Consanguinity (%)	4 (11.4)	27 (36.0)	0.011
Complete criteria (%)	29 (82.9)	48 (64.0)	0.074
Infection (%)	18 (51.4)	27 (38.6)	0.296

Characteristic	OR [†]	95% CI [†]	p-value
age	1.00	1.00, 1.00	0.4
consanguinity			
0	—	—	
1	5.49	1.68, 22.0	0.008
complete_criteria			
0	—	—	
1	0.68	0.19, 2.35	0.5
[†] OR = Odds Ratio, CI = Confidence Interval			

Extended genetic analysis: conclusions

- The detection rate of NGS in the Italian HLH Registry is higher than previously reported, suggesting an **accurate patient selection**
- Consanguinity is associated with higher probability to identify a genetic diagnosis
- **Patients with suspicion of HLH should undergo extensive sequencing regardless of complete criteria and age**
- Disease group varies according to age at onset with pHLH and metabolic diseases prevalent in children < 1 year

Malignancy-associated HLH, Italian HLH Registry

- 50% of all adult HLH
- Few reports in children:
Zhizhuo H. Hematology 2020, n=27
Lehmberg K et al. Br J Haematol 2015, n=29

Italian HLH Registry, **n=30 patients with MA-HLH**
(post-HSCT and CAR-T excluded)

Referral centres:

Torino, Padova, Firenze, Cagliari, Brescia, Bari, Ancona,
Napoli Paus, Palermo, Modena, Pescara

Median age: 6.6 y

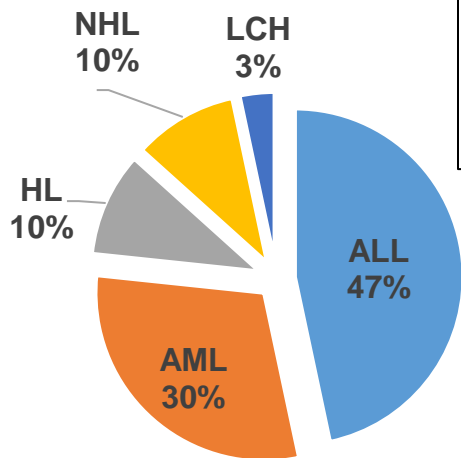
M: 21

Presenting features	N (%) median (range)
Fever	28 (93)
Splenomegaly	20 (67)
Bi-cytopenia	29 (97)
ANC/mm ³	470 (105-2290)
Hb (g/dl)	8 (6-9.9)
plt/mm ³	47 (23-74)
Hypertriglyceridemia /hypofibrinogenemia	14 (47)
Triglycerides	211 (100-400)
Fibrinogen	290 (237-414)
Hyperferritinemia	29 (97)
Ferritin	9986 (2805-23972)
Hemophagocytosis	12/25 (48)
Liver involvement	14 (47)
CNS involvement	4 (13)

Preliminary data

Malignancy-associated HLH, Italian HLH Registry

N=30 children



At malignancy onset/relapse, N=21 (70%)
During chemotherapy, N=9 (30%)

Adults:

- T and NK-cell lymphomas (35%)
- B cell lymphomas (32%)
- Leukemias (6%)
- Hodgkin lymphomas (6%)
- Other hematologic cancers (14%)
- Solid tumors (3%)
- Other malignancies (3%)

Genetic predisposition:

9/18 (50%)

7/18 monoallelic mutations in FHL- genes

1 XLP1

1/18 GATA2

Cytotoxicity defects:

7/14 (50%): 3/7 Prf; 4/7 degranulation

Infectious triggers:

15/50 (30%)

Preliminary data

Malignancy-associated HLH, Italian HLH Registry

Treatment and outcome

HLH specific treatment:

N=19/30 (63%)

- Steroids n=14
- HLH-2004 n=4
- Anti IL-1 n=1

Response rate: 21/30 (70%)

HLH reactivation: 3/30 (10%)

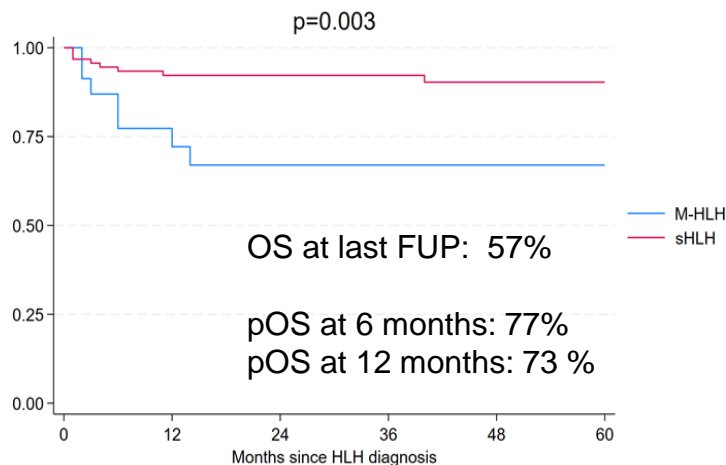
HSCT: 12/30 (40%)

92% for malignancies

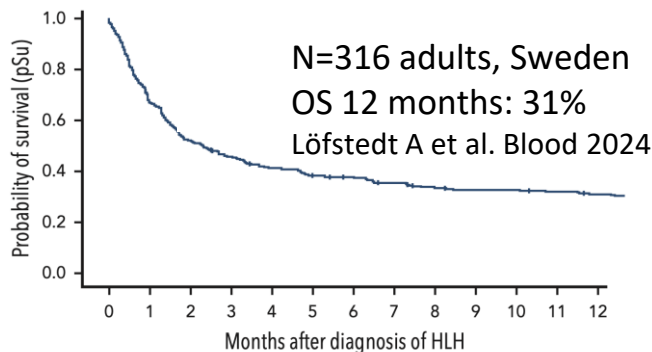
Mortality: 13/30 (43%)

- HLH n=4/13 (30%)
- Malignancy n=9/13

Median follow-up: 42 months (14-79)



Lehmberg K 2015
6 months OS: 67%

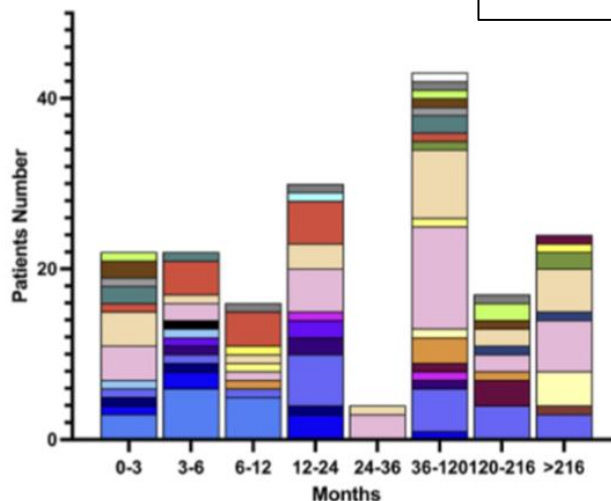
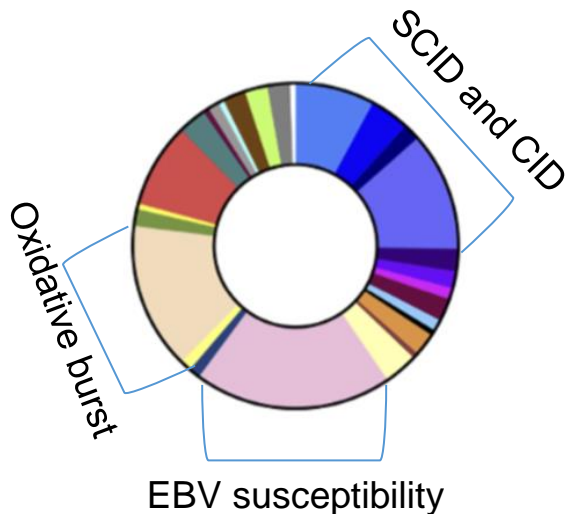


Preliminary data

HLH as an additional warning sign of inborn errors of immunity beyond familial-HLH in children: a systematic review

- 149/178 molecular diagnosis
- 29/178 clinical or functional diagnosis
- 46 IEI, 8 IUIS groups

- HLH preceded the IEI diagnosis in 75% of cases
- Liver and CNS involvement were less common than in FHL cases
- Limited data on treatment and outcome



HLH in patients with immunodeficiency, Italian HLH Registry and IPINET network

N=73 patients with HLH and clinical or molecular evidence of PID

Networks involved:

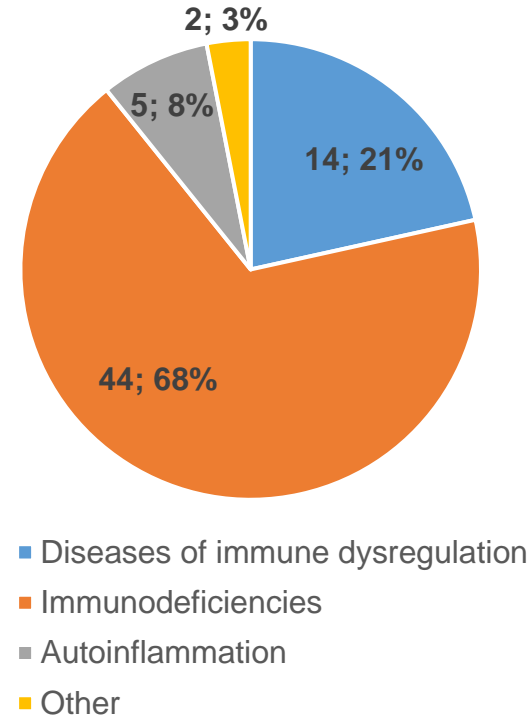
- AIEOP HLH Registry, n=48
- IPINET network, n=18
- Both, n=7

Median age HLH diagnosis (IQR): 3 (0.4-9) years

Infectious trigger in 23/52 (44%)

Genetic diagnosis in 65/68 (96%)

Cytotoxic function: abnormal in 20/34 (59%)



Ongoing study

Conclusions

- Data from the Italian HLH Registry and international collaborations provide further understanding of the HLH spectrum refining treatment indication in different HLH groups
- To date, most FHL patients can be cured from standard chemo and advanced HSCT techniques; however, no responders are at highest risk of fatal outcome and may benefit from alternative treatments
- Intensive treatments and HSCT are not justified in asymptomatic patients with hypomorphic mutations and in patients with monoallelic variants
- Deeper characterization of sporadic HLH may allow increase knowledge of hlh pathofisiology and improve patients outcome in these setting
- WES has expanded the spectrum of genetic predisposition to HLH providing the basis for target therapies



Gruppo di lavoro istiocitosi:

- Stefano Chiaravalli, INT Milano
 - Paola Corti, Monza
 - Carmen De Fusco, Napoli Pausillipon
 - Stefania Gaspari, OBG Roma
 - Concetta Micalizzi, Gaslini, Genova
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- S. Ehl, (Friburgh)
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European Consortium for
HistiOcytosis



Linda

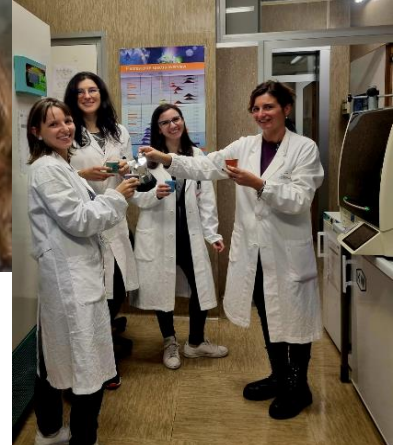
Aurora



Francesco



**Michele
Tanturli,
statistician**



Lab:

**Maria Luisa Coniglio
Aurora Chinnici
Linda Beneforti
Daniela Balasco**



Pediatric Hem-Onc:

**Irene Trambusti
Francesco Pegoraro**



Irene

Maria Luisa