ONCOEMATOLOGIA
TRA SOSTENIBILITÀ E ADERENZA
IL CASO DEL TRIVENETO

Importanza delle tecniche citogenetiche nella diagnosi del mieloma multiplo

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Cosa si intende per alto rischio e rischio citogenetico standard: classificazioni a confronto

R-ISS: HR t(4;14), t(14;16), 17p-

Standard Risk: absence of HR aberrations

Palumbo A, JCO 2015

IWMG: HR: t(4;14), t(14;16), t(14;20), 17p-, nonhyperdiploid karyotype.
Ultra HR ≥ 3CA (gain 1q/del1p Poor risk)
Standard Risk: (All other including) t(11;14), t(6;14)

Rev. 2016. Sonneveld P et al Blood

mSMART 2.0: HR t(14;16), t(14;20), 17p-

Intermediate Risk: t(4;14), gain1q

Standard Risk: Hyperdiploid, t(11;14), t(6;14)

http://www.msmart.gov

mSMART 3.0: HR t(4;14), t(14;16), t(14;20), 17p-, gain 1q

Standard Risk: Trisomies, t(11;14), t(6;14)

Rev August 2018

MAYO CLINIC

https://www.msmart.org/multiple-myeloma

mSMART 3.0: Classification of Active MM

High-Risk

- High Risk genetic Abnormalities [a,b]
  - t(4;14)
  - t(14;16)
  - t(14;20)
  - Del 17p
  - p53 mutation
  - Gain 1q
- RISS Stage 3
- High Plasma Cell S-phase[c]
- GEP: High risk signature

- Double Hit Myeloma: Any 2 high risk genetic abnormalities
- Triple Hit Myeloma: 3 or more high risk genetic abnormalities

Standard-Risk[a]

All others including:

- Trisomies
- t(11;14)[d]
- t(6;14)

[a] Trisomies may ameliorate
[b] By FISH or equivalent method
[c] Cut-offs vary
[d] t(11;14) may be associated with plasma cell leukemia

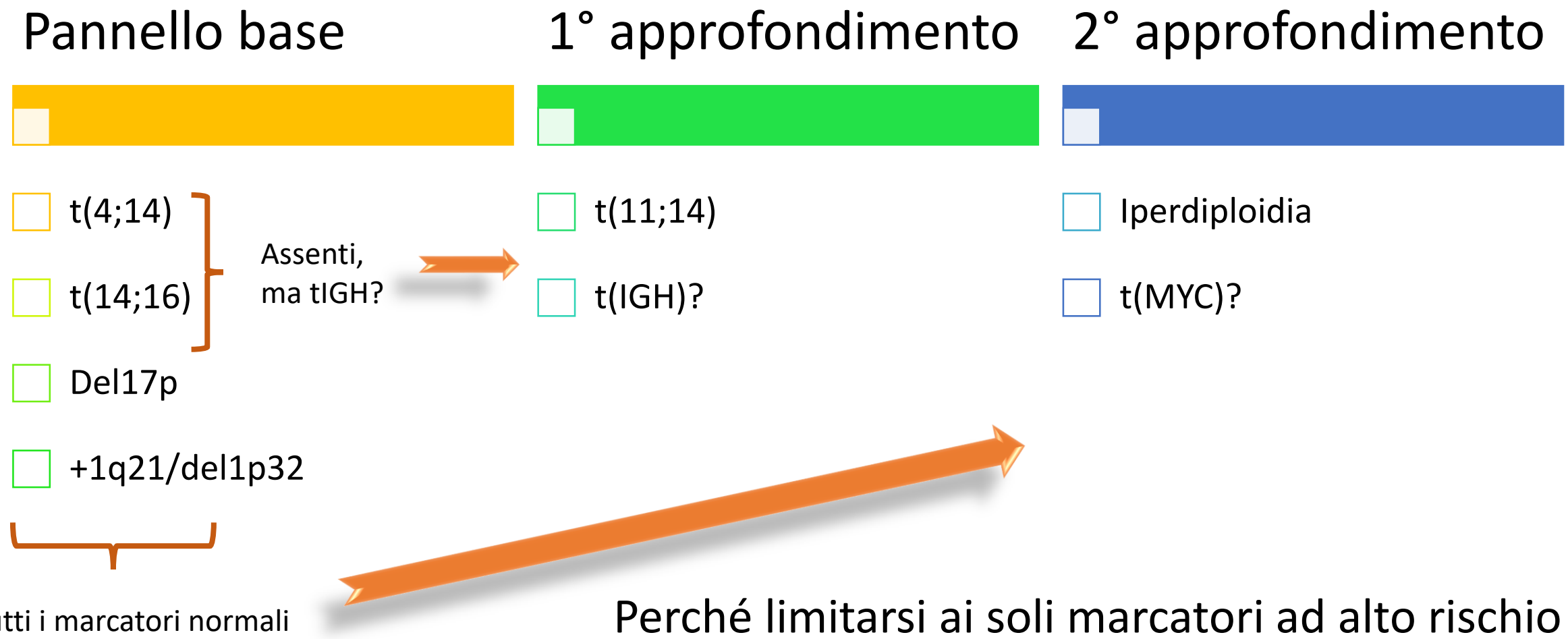
Dispenzieri et al. Mayo Clin Proc 2007;82:323-341; Kumar et al. Mayo Clin Proc 2009 84:1095-1110; Mikhael et al. Mayo Clin Proc 2013;88:360-376. v14 //last reviewed August 2018

European Myeloma Network 2018

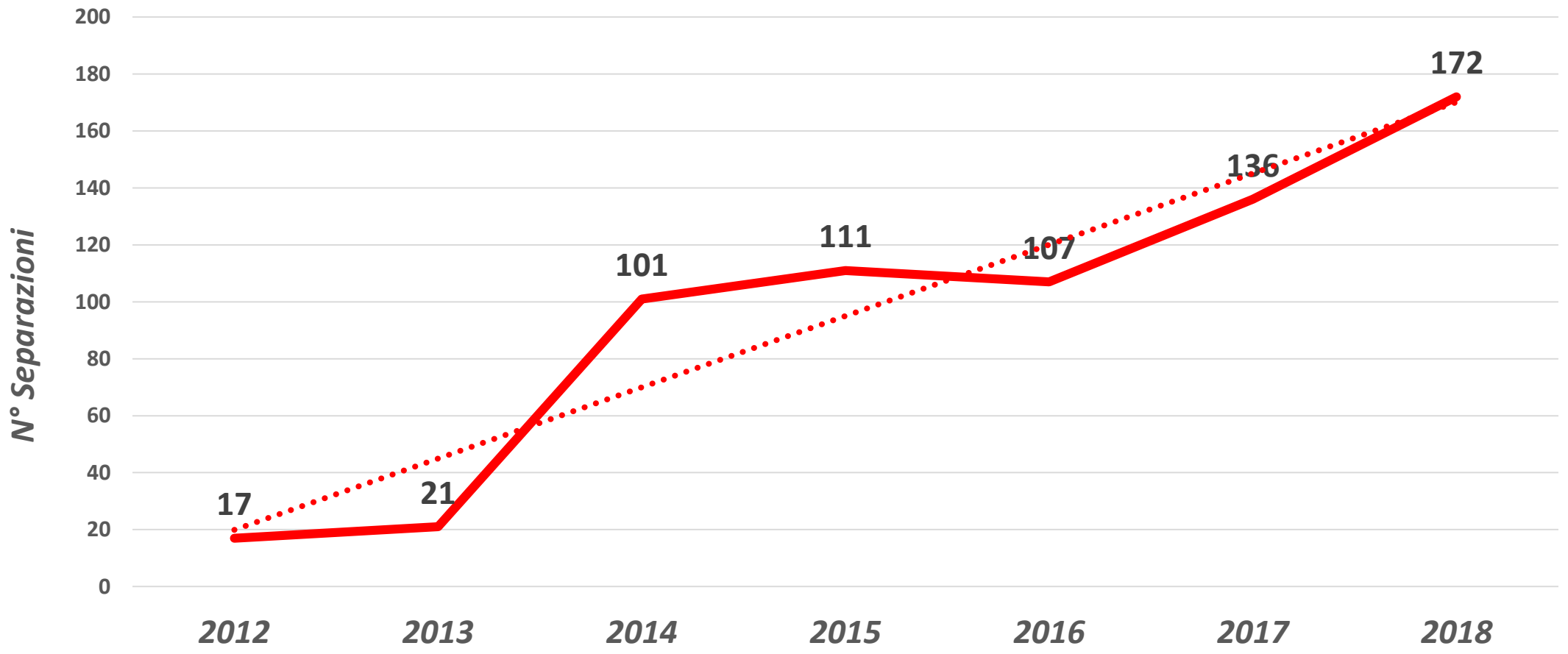
	Cytogenetics	*Genetic event*	Frequency	Prognosis	Response to PI	Response to IMiD	Remarks
Mandatory	Del17p13	*P53*	5 % to 15 %	Independent marker, with negative impact on PFS and OS	Negative prognostic factor	Negative prognostic factor Pomalidomide seems beneficial.	Most important prognostic factor,
Highly recommended	t(4;14)(p16.3;q32)	*FGR3 MMSET*	15%	Independent marker, with negative impact on PFS and OS	Improves survival compared to classic agents	Unfavourable for any IMiD	
Highly recommended	Gain 1q21	*CKS1B*	34 % to 40 %	Independent marker, with negative impact on PFS and OS	Negative prognostic factor	Negative prognostic factor	Might be directly implicated in bortezomib resistance
Highly recommended	Del 1p32, Del 1p22	*CDKN2C*	7 % to 17 %	Independent marker, with negative impact on PFS and OS	Negative prognostic factor		
Recommended	t(11;14)(q13;q32)	*CCND1*	20%	Good prognosis	Good prognosis	Good prognosis	Sensitive to venetoclax
Recommended	t(14;16)(q32;q23)	*CMAF*	2% to 3 %	Controversial			Considered as a negative prognostic factor, but not confirmed in IFM study
Recommended	Hyperdiploidy of odd chromosomes		60%	Standard prognosis, unless associated with other negative prognostic markers	Standard prognostic factor		May neutralize the negative prognostic impact of del17p or t(4;14)

Al least t(4;14) and del17p; also recommended t(14;16),+1q21/del1p32 Caers J et al, Haematologica 2018

Quali marcatori testiamo
L'esperienza del laboratorio di Padova

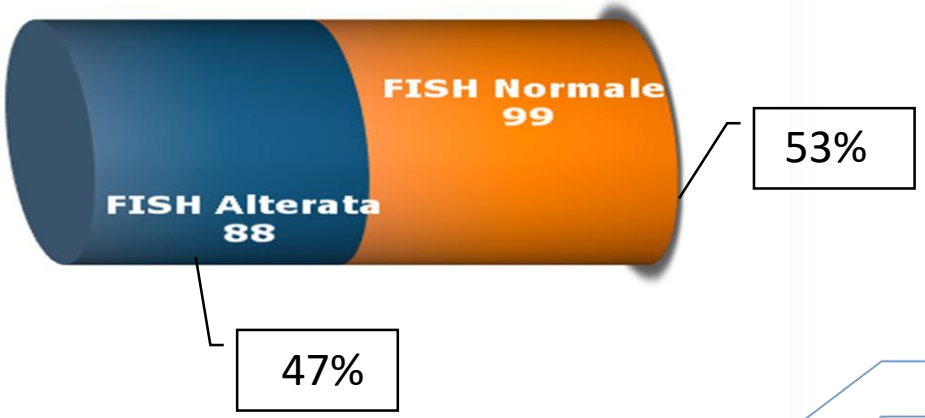


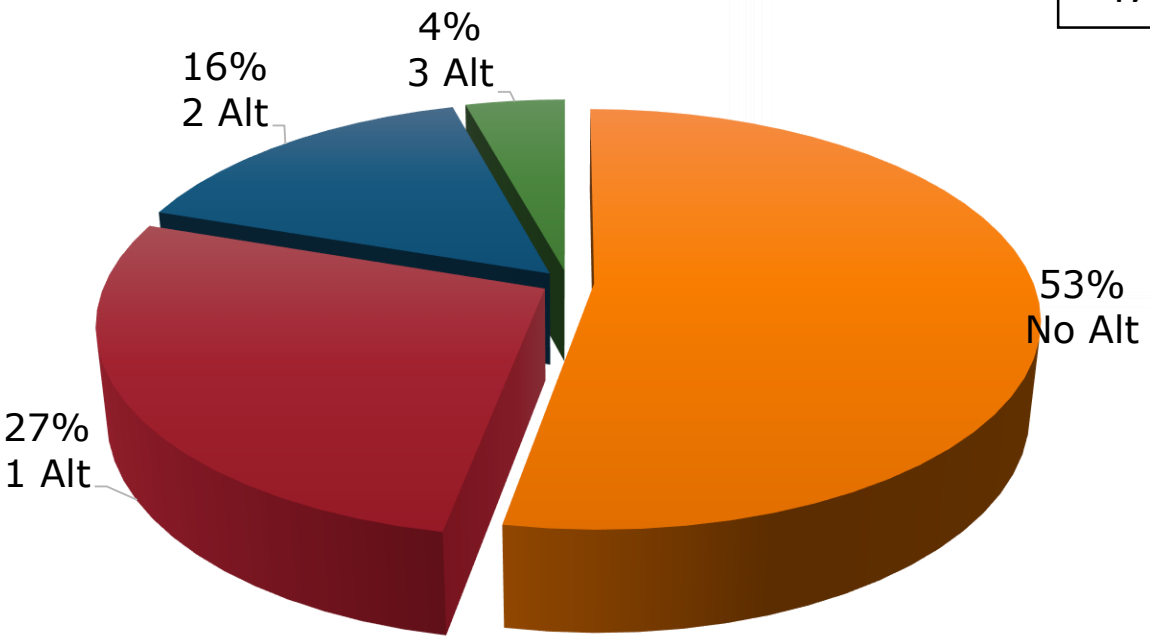
Attività diagnostica FISH su CD138+



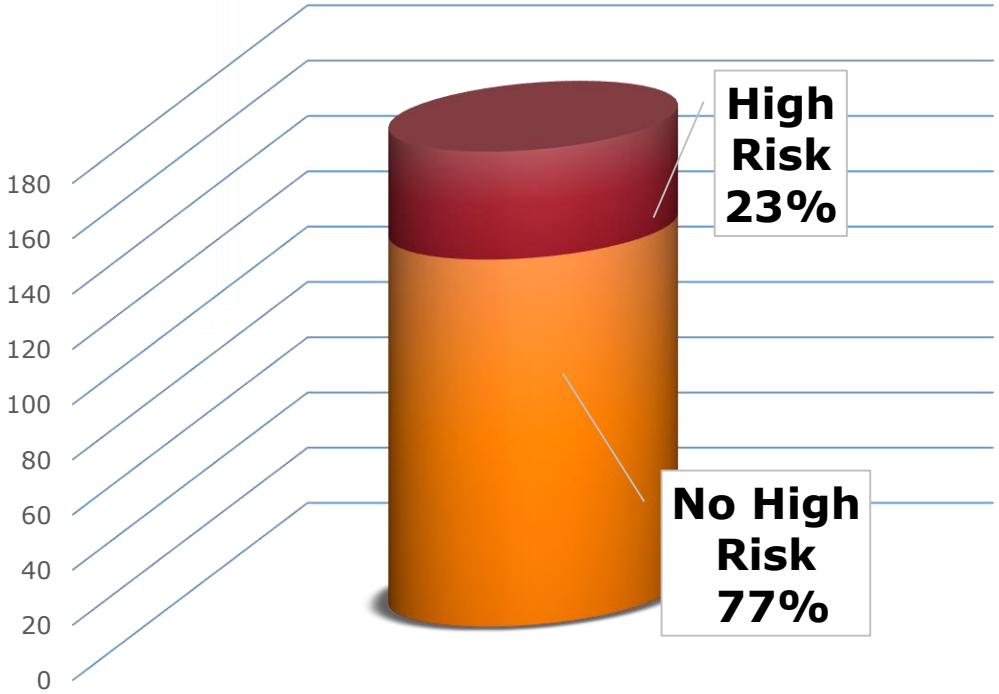
Diagnostica FISH Mieloma 2018

N= 187 casi (172 CD138+; 15 su intero)



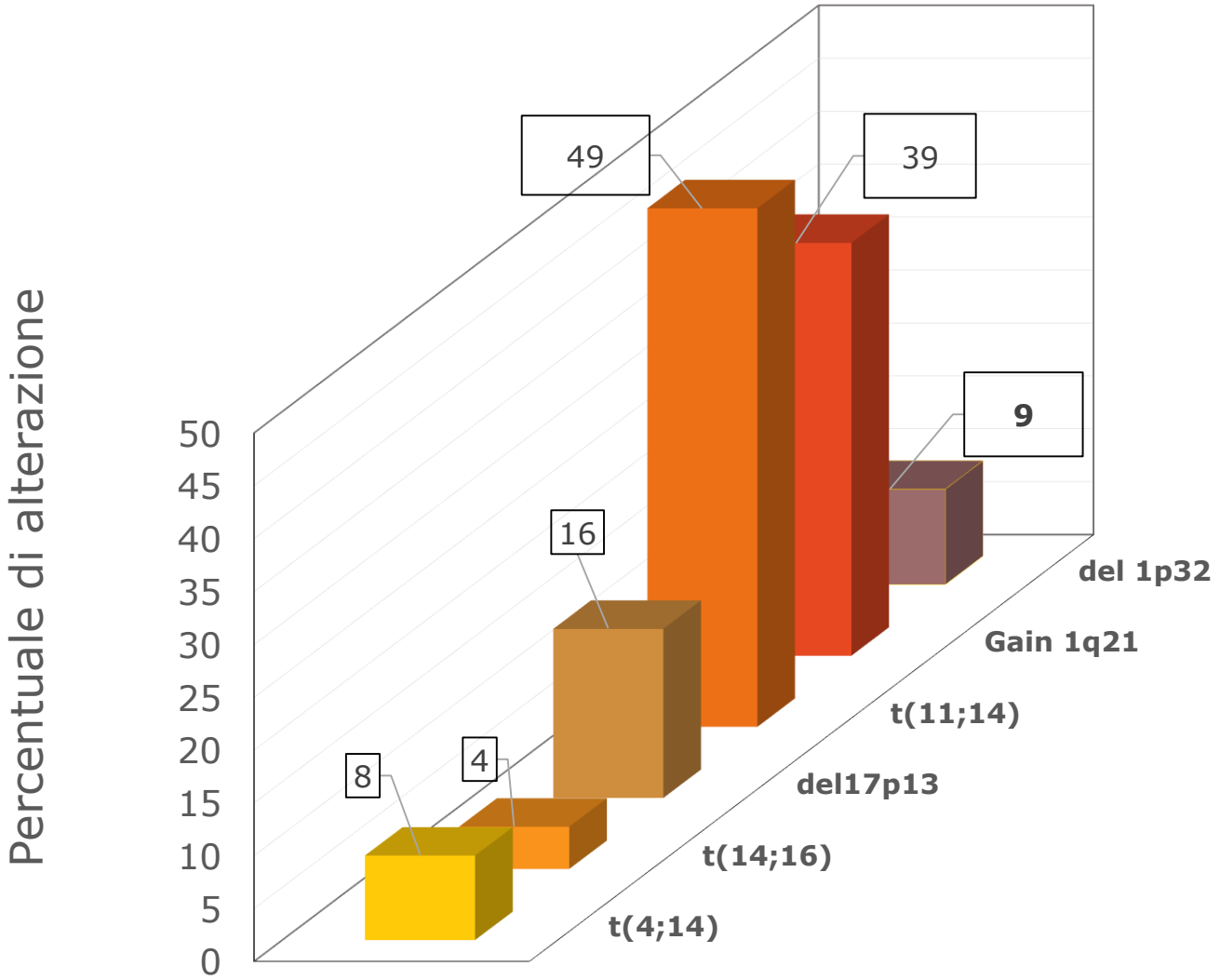


Numero di alterazione su 5 loci
t(4;14), t(14;16), 17p-, +1q21, 1p32-



N= 172 casi

Frequenza di alterazione per marcatore



Marcatore	N° alterati/totale casi analizzati
t(4;14)	14/174
t(14;16)	7/174
del17p13	29/179
t(11;14)	36/74
Gain 1q21	70/178
del 1p32	16/178

Pannello base

- t(4;14)
- t(14;16)
- Del17p
- +1q21/del1p32

Assenti, ma tIGH?

1° approfondimento

- t(11;14)
- t(IGH)?

✓ t(IGH) 41 casi: 27 (66%) IGH/CCND1

Costi: 164,55 €/ Ibridazione
Pannello base: 658,2 €
Se 1° approfondimento: 822,75 €

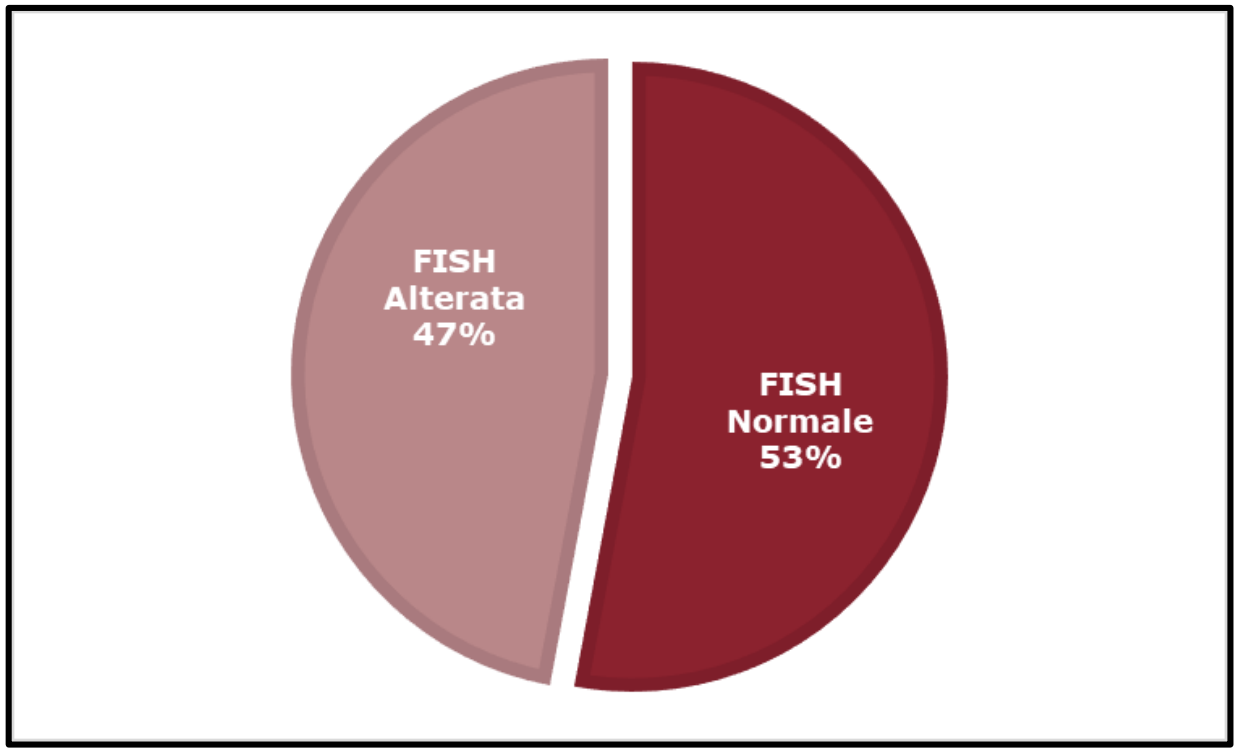
PANNELLO STANDARD: N°4 FISH

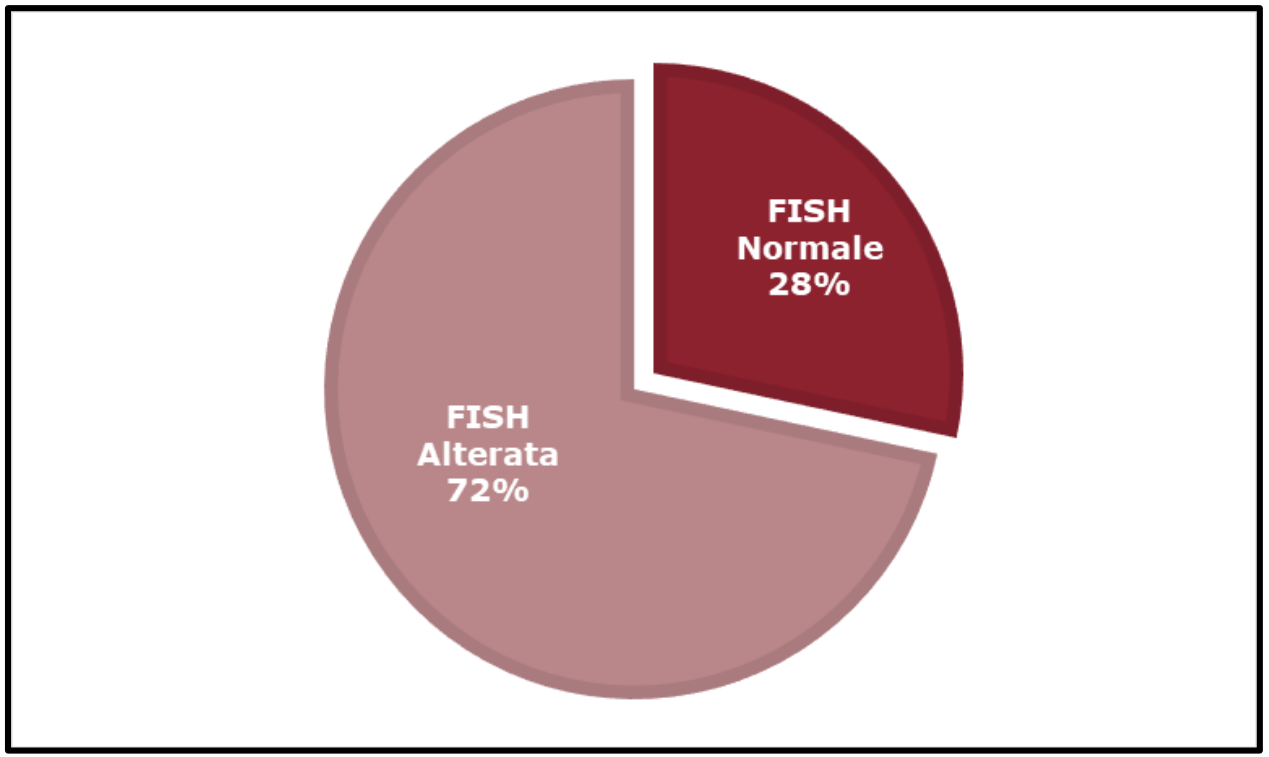
- t(4;14),
- t(14;16),
- del17p,
- gain1q21/del1p32

PANNELLO ESTESO: n° 5-7 FISH

- ✓ t(11;14),
- ✓ IGH,
- ✓ +5/+9/+15

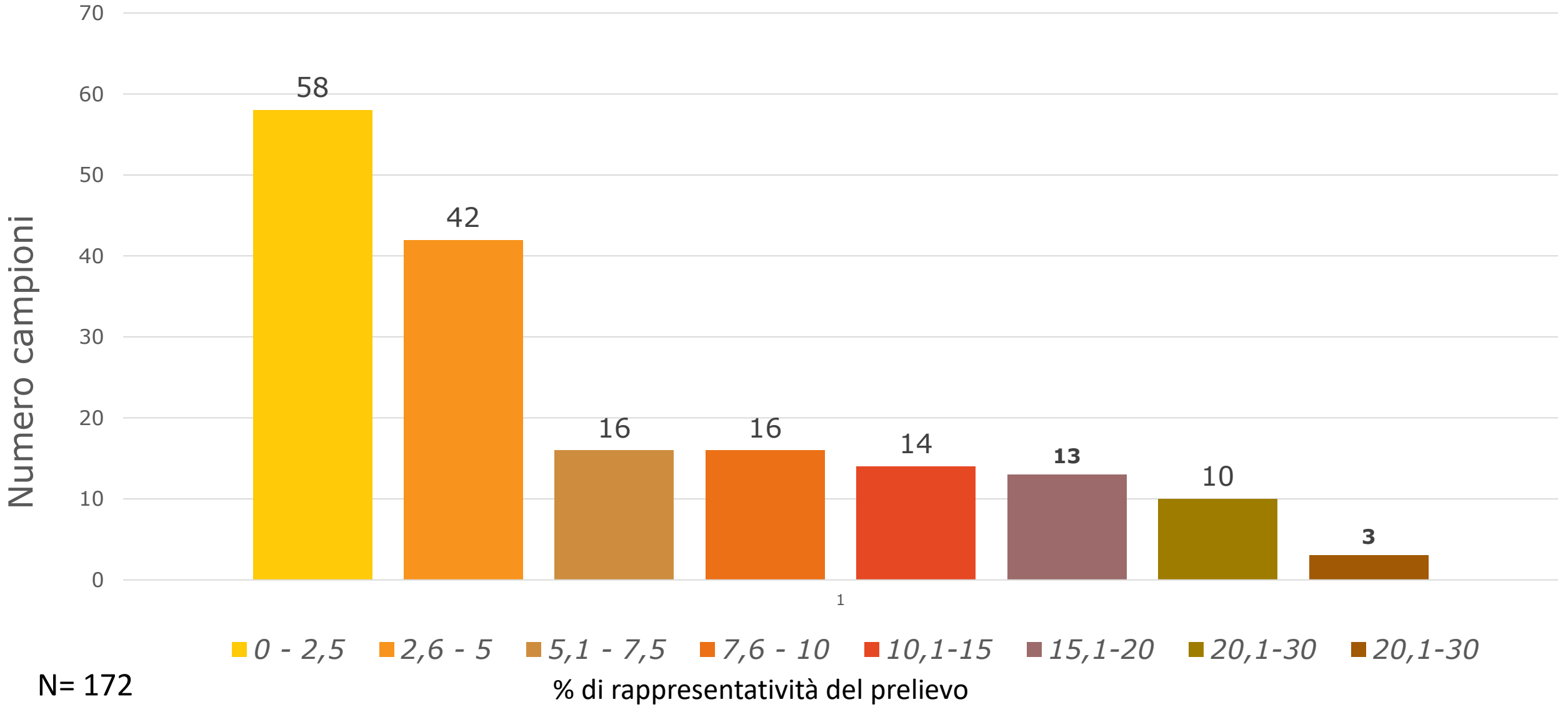
Δ =25%





N=187 casi

Rappresentatività dei prelievi sottoposti ad arricchimento in CD138



N= 172

Le sfide future per il laboratorio

1)La valutazione del rischio alla recidiva (Gay F, BJH 2019)

-Quanti pazienti cambiano il gruppo di rischio

-Quali marcatori analizzare

2)La sub-classificazione dei pazienti a rischio standard

- I pz classificati a rischio standard rappresentano un gruppo eterogeneo, 1/6 ha una malattia assimilabile all'HR)
- Alla dg il 75% dei pazienti presenta alterazioni a rischio standard o non ha alterazioni (SV RaJkumar, BJH 2019)

Le richieste del laboratorio

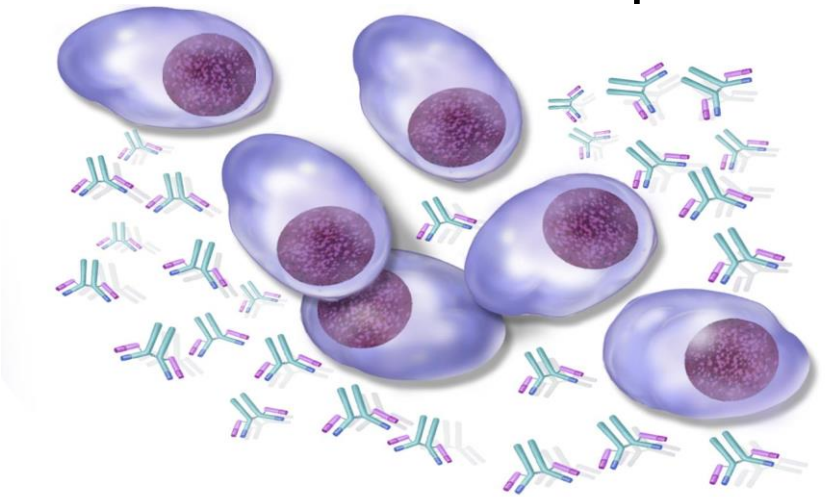
I)Bisogno di informazione/formazione patologia-specifica

2)Necessità di creare un tavolo di lavoro *ad hoc* all'interno della REV

3)Coinvolgimento nel PDTA

4)Aggiornamento del tariffario per includere i costi relativi alla separazione delle cellule CD138+

……..ma soprattutto tante plasmacellule!!

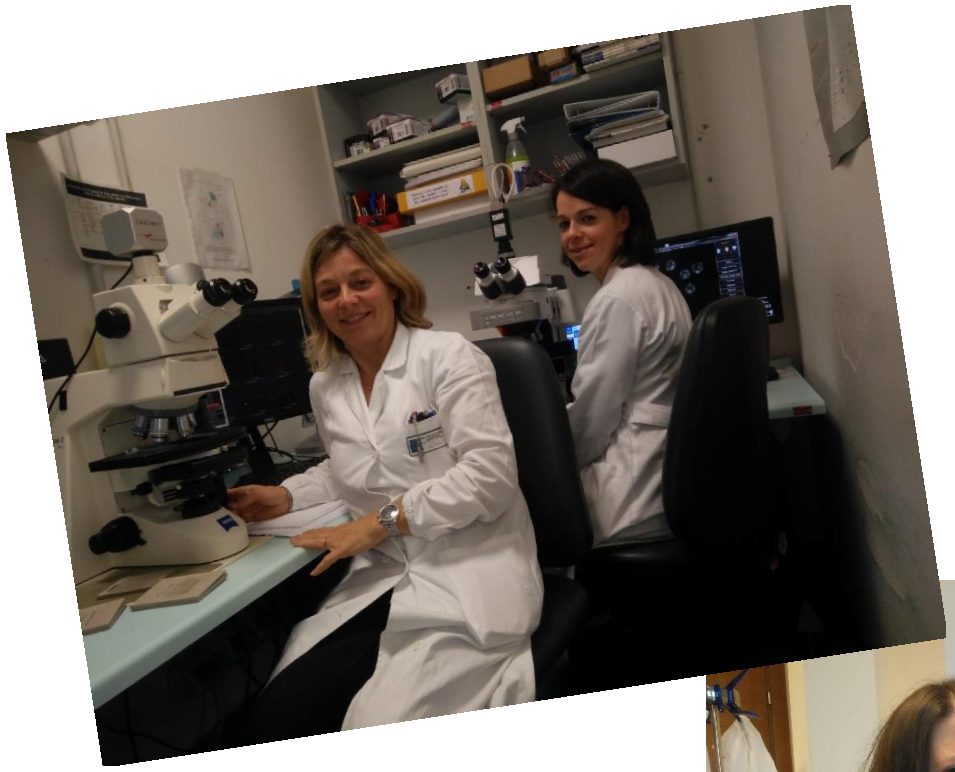


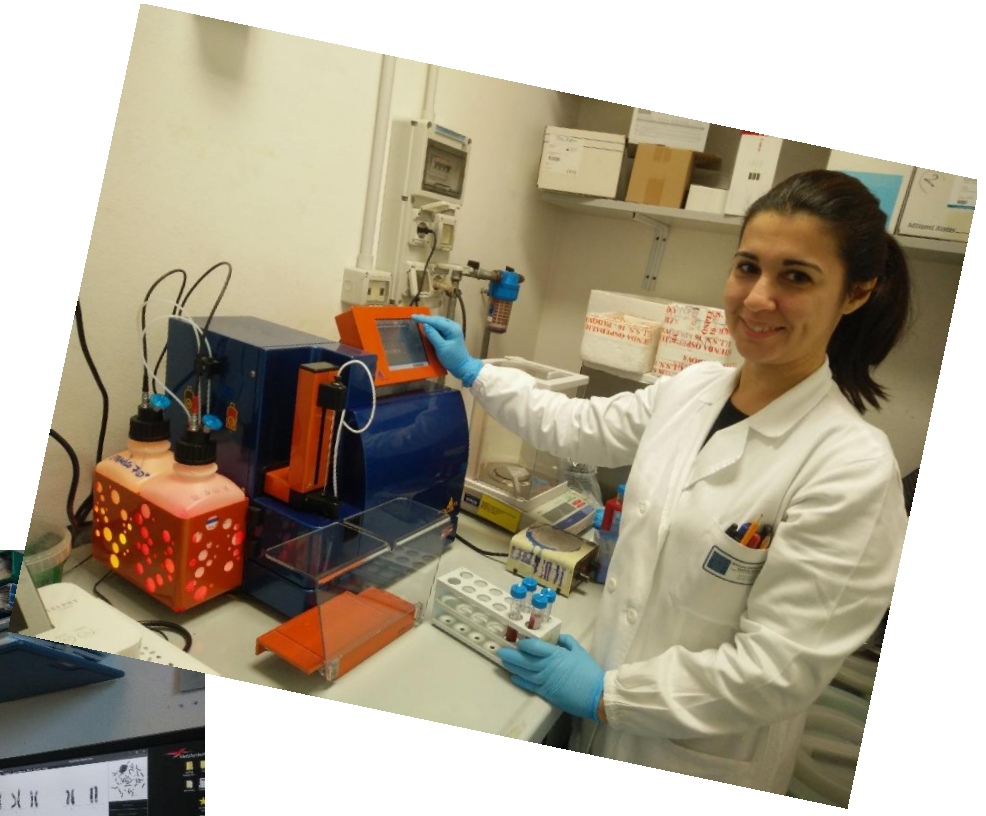
Ringraziamenti

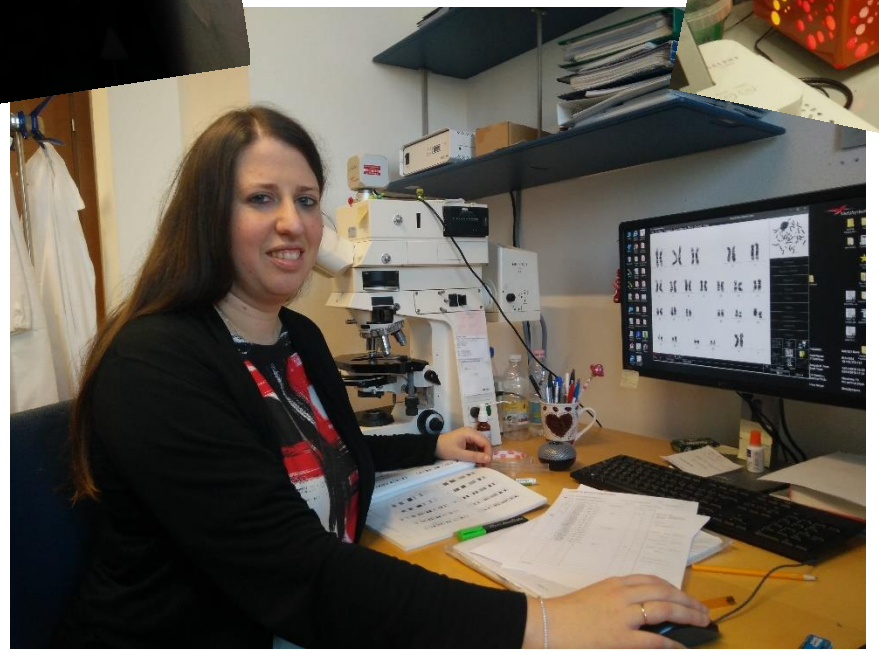
- Ematologia, Azienda Ospedaliera di Padova
  Prof. G ianpietroSemenzato
  Dott. Renato Zambello
  Dott. Gregorio Barilà
  Dott. Tamara Berno
  Laboratorio di Citofluorimetria

- Ematologia, Azienda Ospedaliera Universitaria Integrata di Verona
- Oncoematologia, Ospedale di Mirano ULSS3
- Oncologia – Medicina Interna, Ospedale di Vittorio Veneto ULSS2
- Oncoematologia, Ospedale di Rovigo ULSS 5
- Day Service Ematologico, Ospedale di Camposampiero ULSS 6
- Oncologia, Ospedale di Schiavonia ULSS6
- Oncologia, IOV
- Tutti i laboratori di citofluorimetria delle varie sedi

Il Laboratorio di Citogenetica dello IOV







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