Somatic mutations in the proofreading domain of POLE

in 8% of endometrial tumours

missense, heterozygous mutations

early events

Hotspots: P286R, S297F, V411L or S459F

other rarer mutations P286H/L, S297Y, F367S, L424V/I, P436R, M444K, A456P

mutations affect the proofreading of the protein

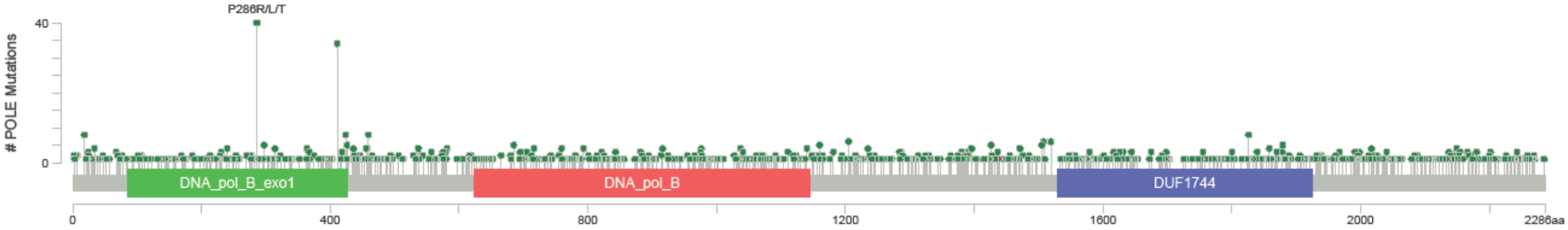
resulting in ultramutation with an overrepresentation of C>A.

mutational signature 10 (Alexandrov et al)

TCG>TTG and TCT>TAT substitutions and transcriptional strand bias.

Mutation spectrum

POLE gene is 63.6 kb long and composed of 49 coding exons,
where the first and last one also have a UTR region.



Which *POLE* variants do qualify as *POLE*mut EC?

PROTEIN CHANGE	NUCLEOTIDE SUBSTITUTION	EXON	n TCGA of all POLEmut EC	N PORTEC
P286R	**c.857C>G**	**9**	**21**	**54**
V411L	**c.1231G>T/C**	**13**	**13**	**34**
S297F	**c.890C>T**	**9**	**3**	**6**
S459F	**c.1376C>T**	**14**	**2**	**4**
A456P	**c.1366G>C**	**14**	**2**	**6**
F367S	c.1100T>C	11	2	0
L424I	c.1270C>A	13	2	0
M295R	c.884T>G	9	1	0
P436R	c.1307C>G	13	1	0
M444K	c.1331T>A	13	1	1
D368Y	c.1102G>T	11	1	0

11 variants "excepted" to qualify for POLEmut EC

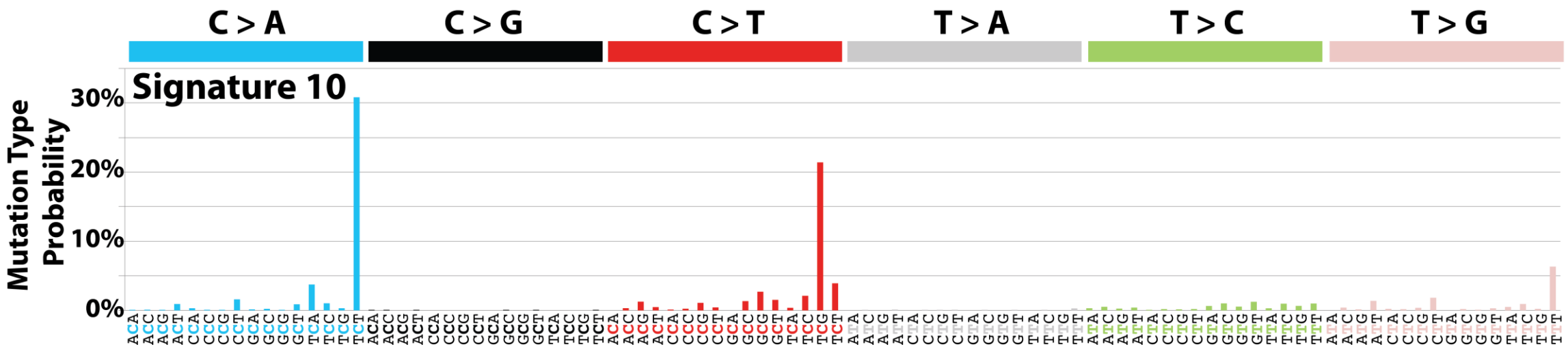
Top 5:

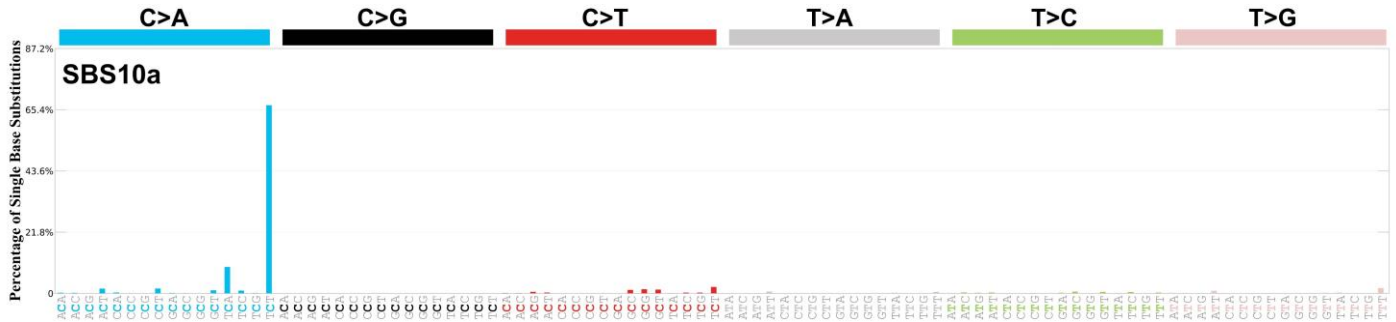
- 90% of all POLE EDM
- 98% of all POLEmut EC reported to date

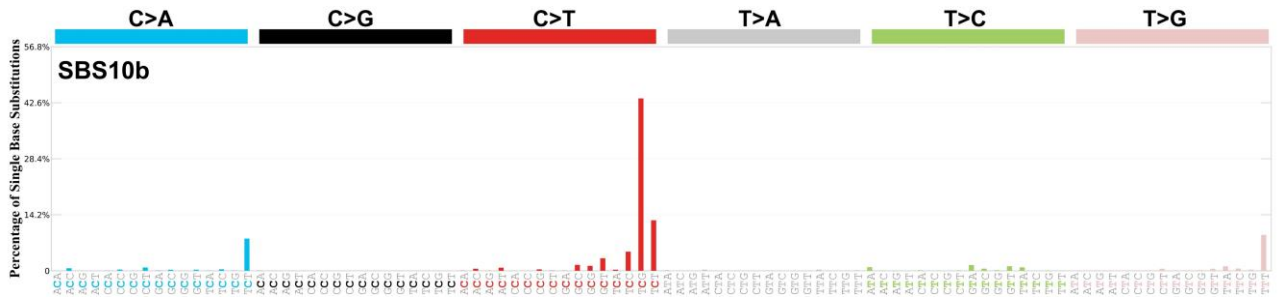
Rare pathogenic EDM found in <1% of all ECs tested to date

International consensus and standardized *POLE* interpretation is currently being developed

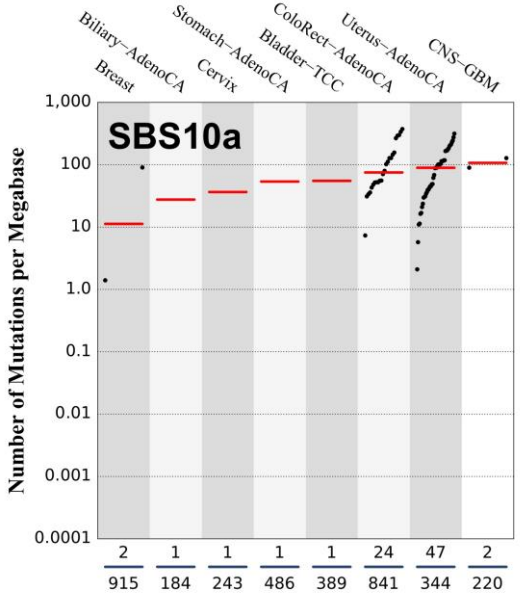
Leon-Castillo et al., Journal of Path 2019

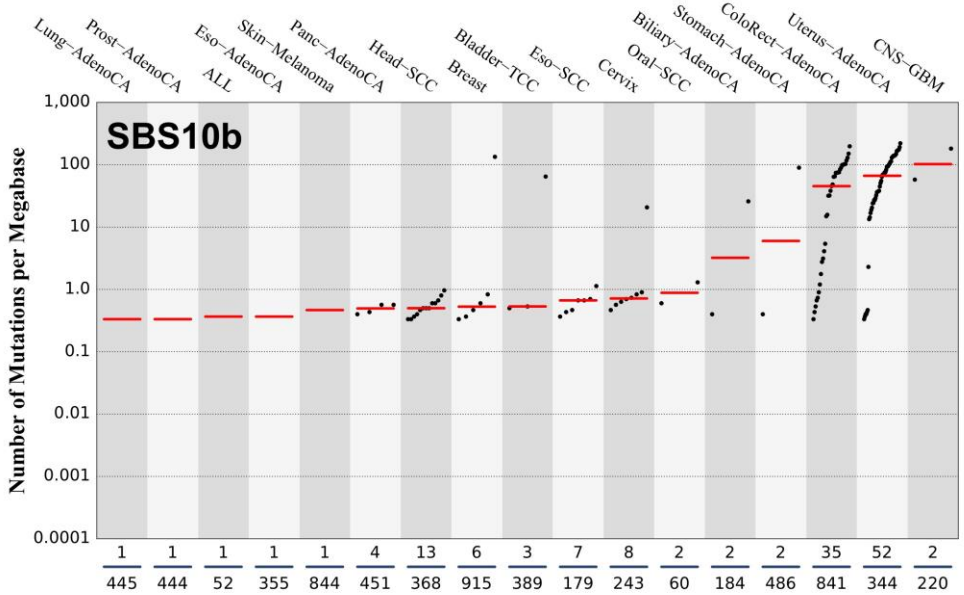

C > A
C > G
C > T
T > A
T > C
T > G
Signature 10
Mutation Type Probability
30%
20%
10%
0%

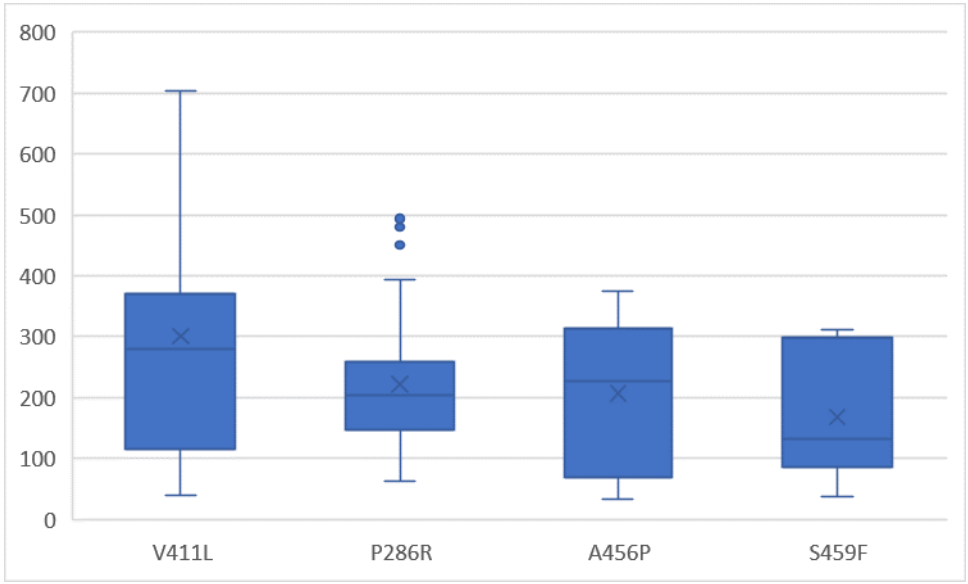

C>A
C>G
C>T
T>A
T>C
T>G
SBS10a
Percentage of Single Base Substitutions
87.2%
65.4%
43.6%
21.8%
0

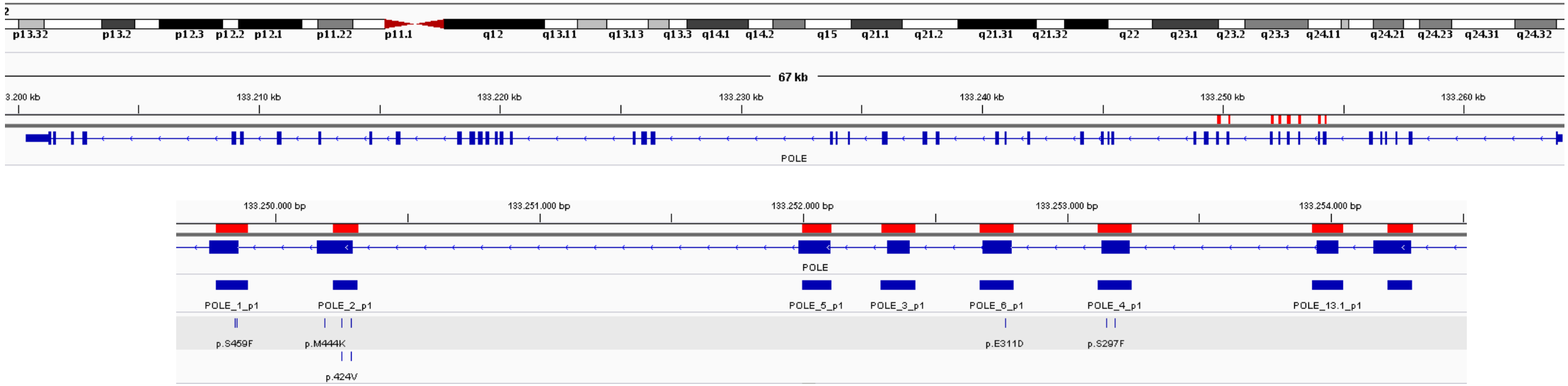

C>A
C>G
C>T
T>A
T>C
T>G
SBS10b
Percentage of Single Base Substitutions
56.8%
42.6%
28.4%
14.2%
0

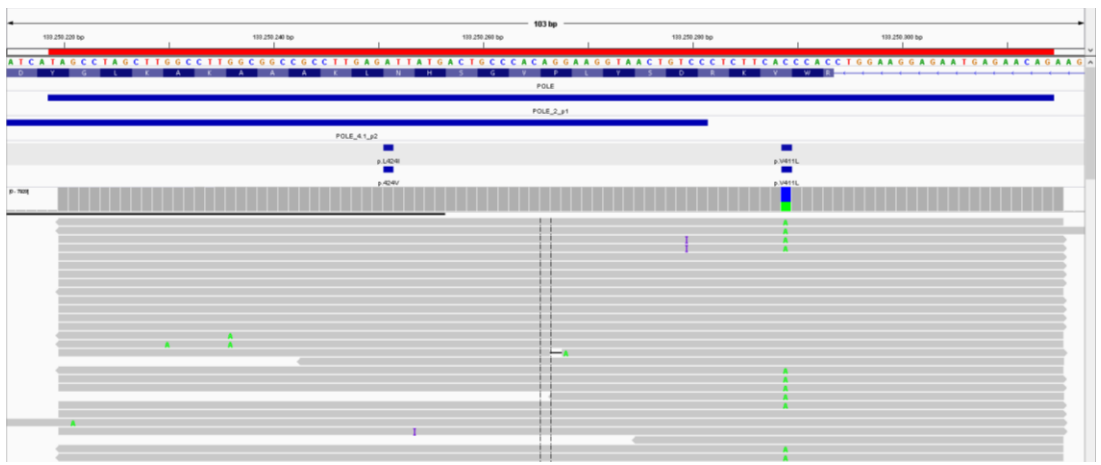
Signature 10

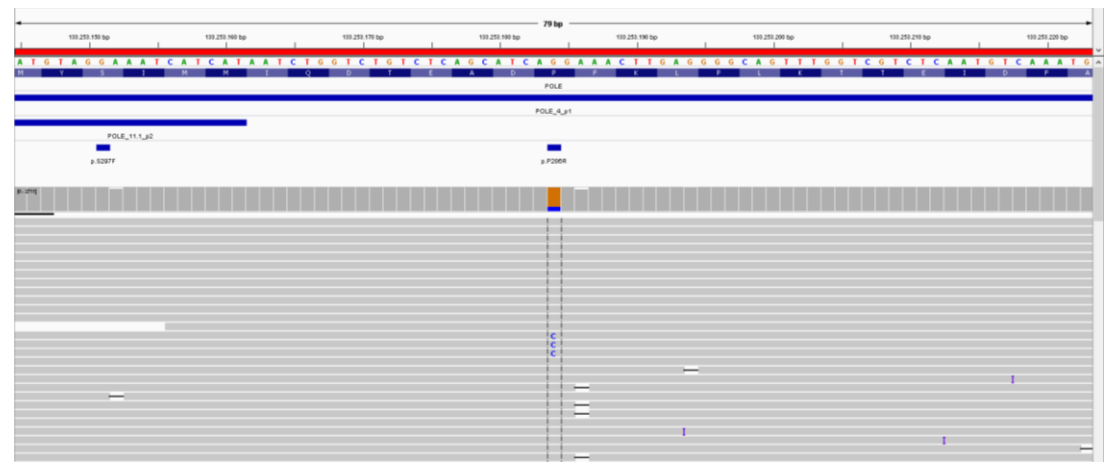












V411L	c.1231G>T

P286R	c.857C>G

POLE c.1231G>T p.Val411Leu

Endometrium carcinoom

TCP

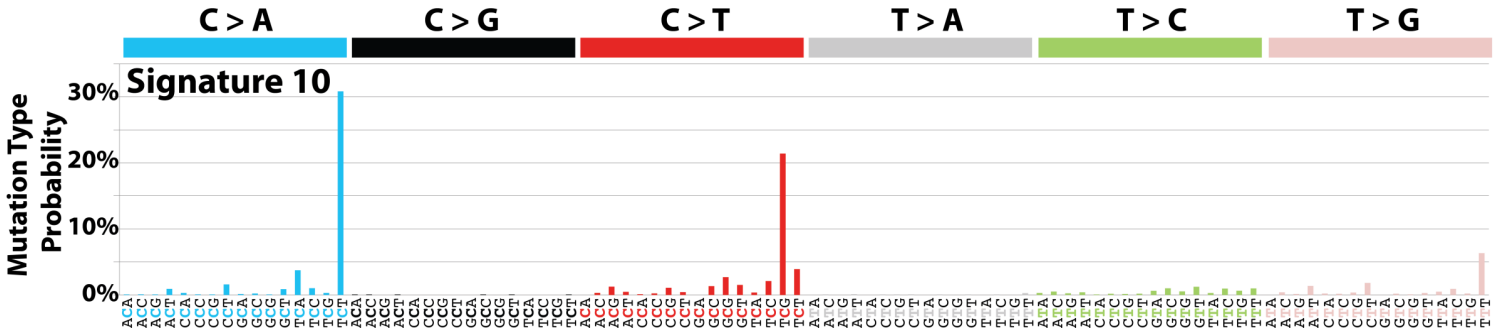
mutatie aan in POLE: V411L

VAF 25%

14 overige somatische mutaties met een VAF ~25%

In o.a. APC, ATM, ERBB4, KIT, MED12, PIK3CA en TP53

11x C>T/G>A



detectie methodes

Geintegreerd in standard Cancer Hotspot panel

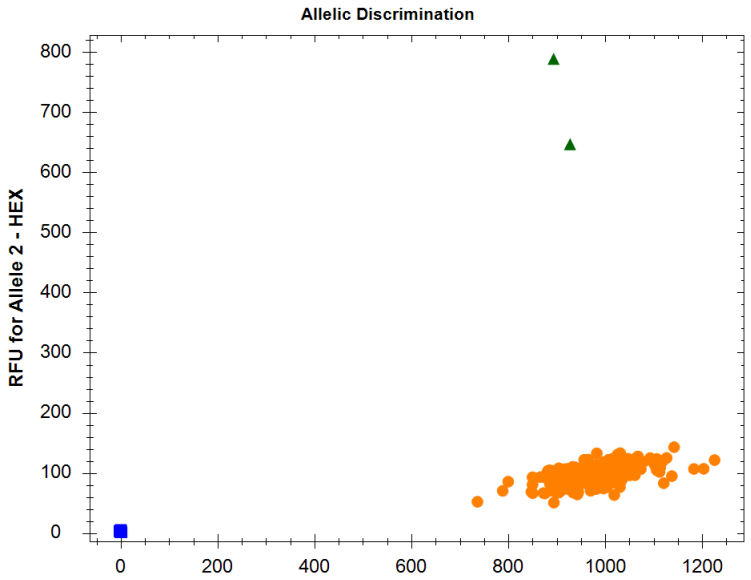
Onderdeel van een groot panel

TSO500, Oncomine OCA+, etc

- Voldoende informatie voor POLE signature

Prescreen met targeted hotspot test,

- (Multiplex) allel specifieke test voor 5 mutaties
- ~98% alle POLE varianten



strategie

Testen

NGS-approach, geintegreerd in de MD workflow

Standaard NGS panel, detectie alle EDM varianten

Groot TMB-panel, tevens signature

Targeted prescreen (taqman

- positief-> voorselectie voor NGS
- Negatief, grote zekerheid, geen POLE mutatie?

- Interpretatie
- POLE, pathogeen of VUS, overleg KMBP noodzakelijk