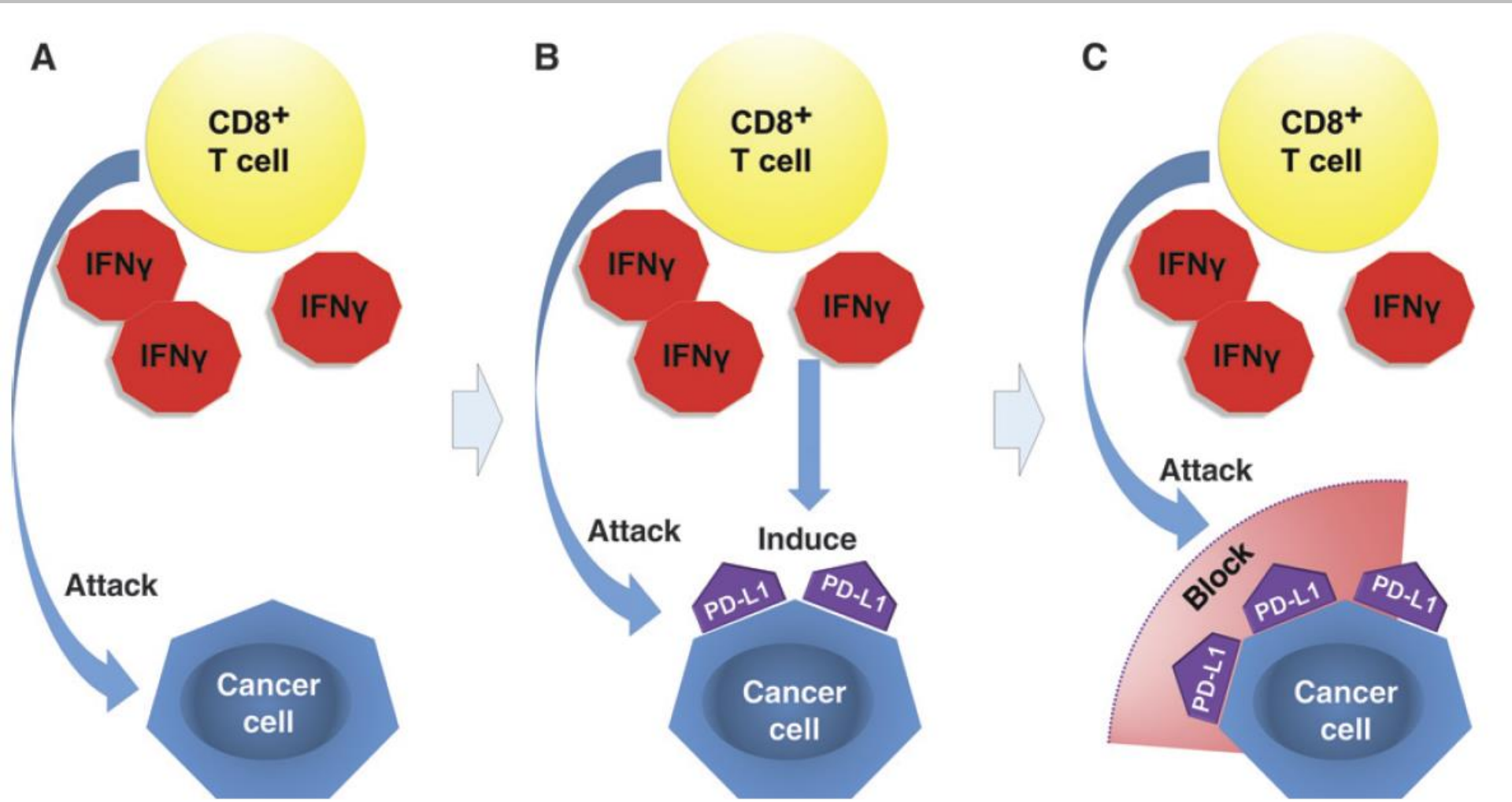
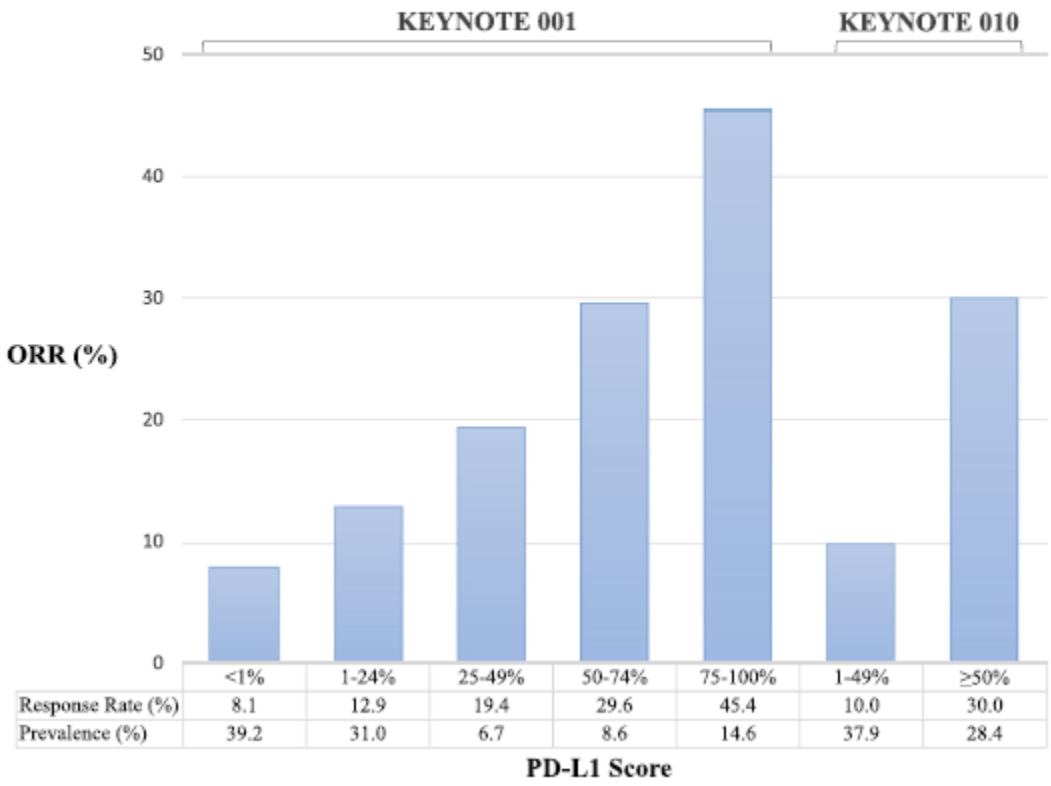
PD-L1, mutational burden and MSI.

P. Pauwels
(UZA, UA)

Kennis / Ervaring / Zorg



Clin Cancer Res; 22(10) May 15, 2016



	<1%	1-24%	25-49%	50-74%	75-100%	1-49%	≥50%
Response Rate (%)	8.1	12.9	19.4	29.6	45.4	10.0	30.0
Prevalence (%)	39.2	31.0	6.7	8.6	14.6	37.9	28.4

Fig. 1 PD-L1 proportion scores and their relationship to objective response rates to pembrolizumab in KEYNOTE 001 and KEYNOTE 010

PD-L1 IHC: an enrichment factor, but not fro oncogenic driver mutations?

EGFR

BRAF

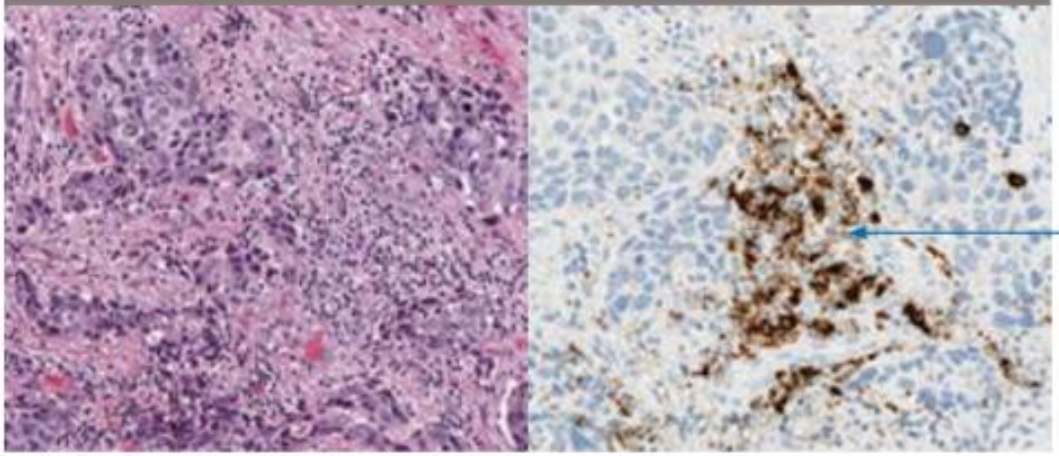
PD-L1 Testing in Bladder Cancer

- Bladder TCs do not express detectable levels of PD-L1 as often as other carcinomas
- PD-L1-positive ICs are more common in bladder cancer
- Need to score ICs through entire sample
- Antibodies can be used interchangeably on platforms
  - Perform rigorous validation studies first
- Results should be clearly communicated to oncologist
  - Disclose clone used for testing
  - Report percentage of positive TCs and positive ICs
  - Oncologist will determine how results will be used to select treatment strategy

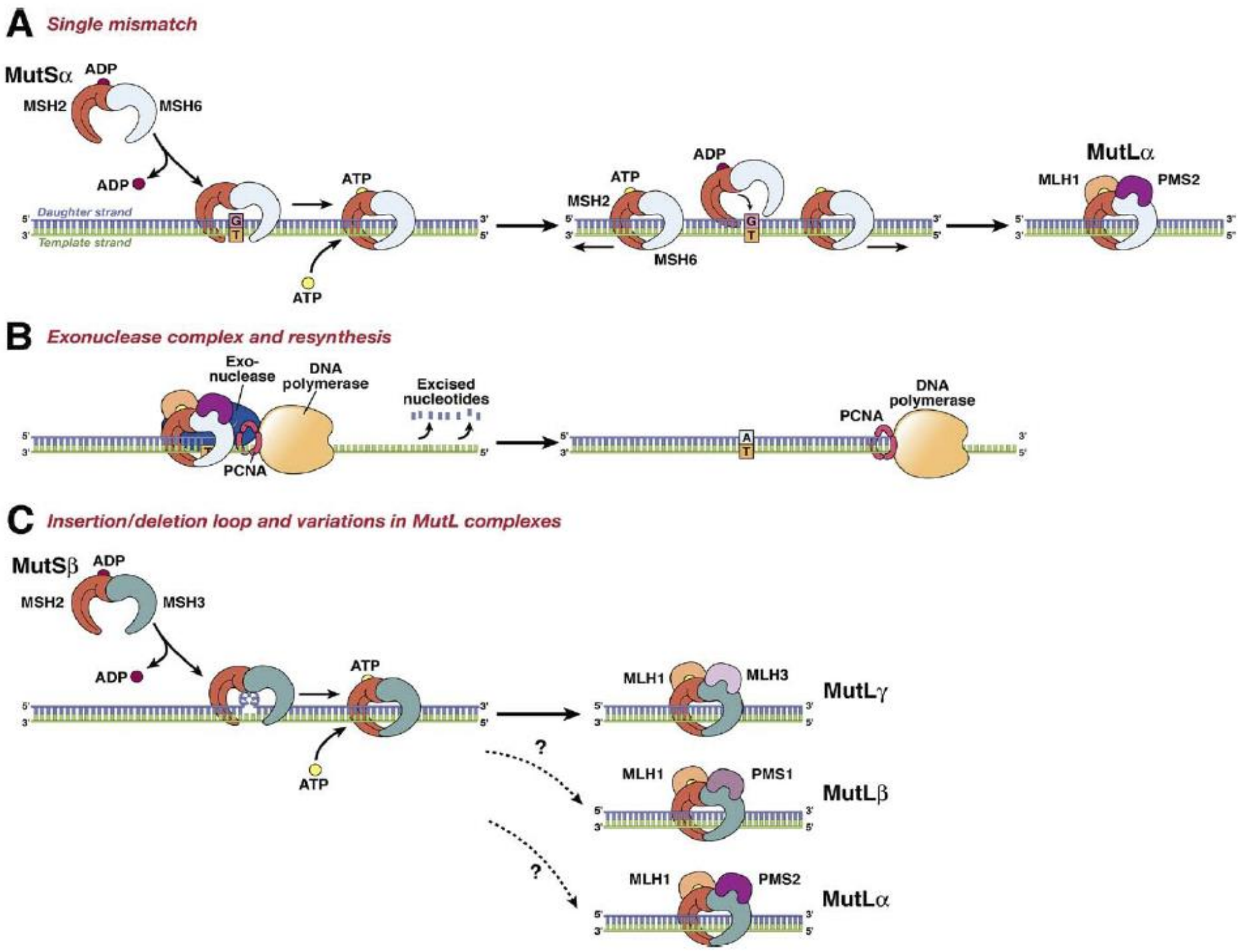
PD-L1 expression in the tumor microenvironment

The PD-L1 (SP142) IHC Assay stain highlights a heterogeneous population of immune cells. The majority of these cells are morphologically consistent with lymphocytes, macrophages, dendritic cells and granulocytes. Immune cell staining can be observed as aggregates in intratumoral or contiguous peritumoral stroma as single-cell spread among tumor cells, or in association with tumor cell staining.

Often observed as aggregates in the intra- or peritumoral stroma



Urothelial carcinoma tissue, 10x


A
Single mismatch
MutSα
ADP
MSH2
MSH6
ADP
Daughter strand
Template strand
5'
3'
G
T
ATP
ATP
ATP
ADP
MSH2
MSH6
MutLα
MLH1
PMS2
B
Exonuclease complex and resynthesis
Exo-nuclease
DNA polymerase
Excised nucleotides
PCNA
A
T
DNA polymerase
PCNA
C
Insertion/deletion loop and variations in MutL complexes
MutSβ
ADP
MSH2
MSH3
ADP
ATP
ATP
MLH1
MLH3
MutLγ
?
MLH1
PMS1
MutLβ
?
MLH1
PMS2
MutLα

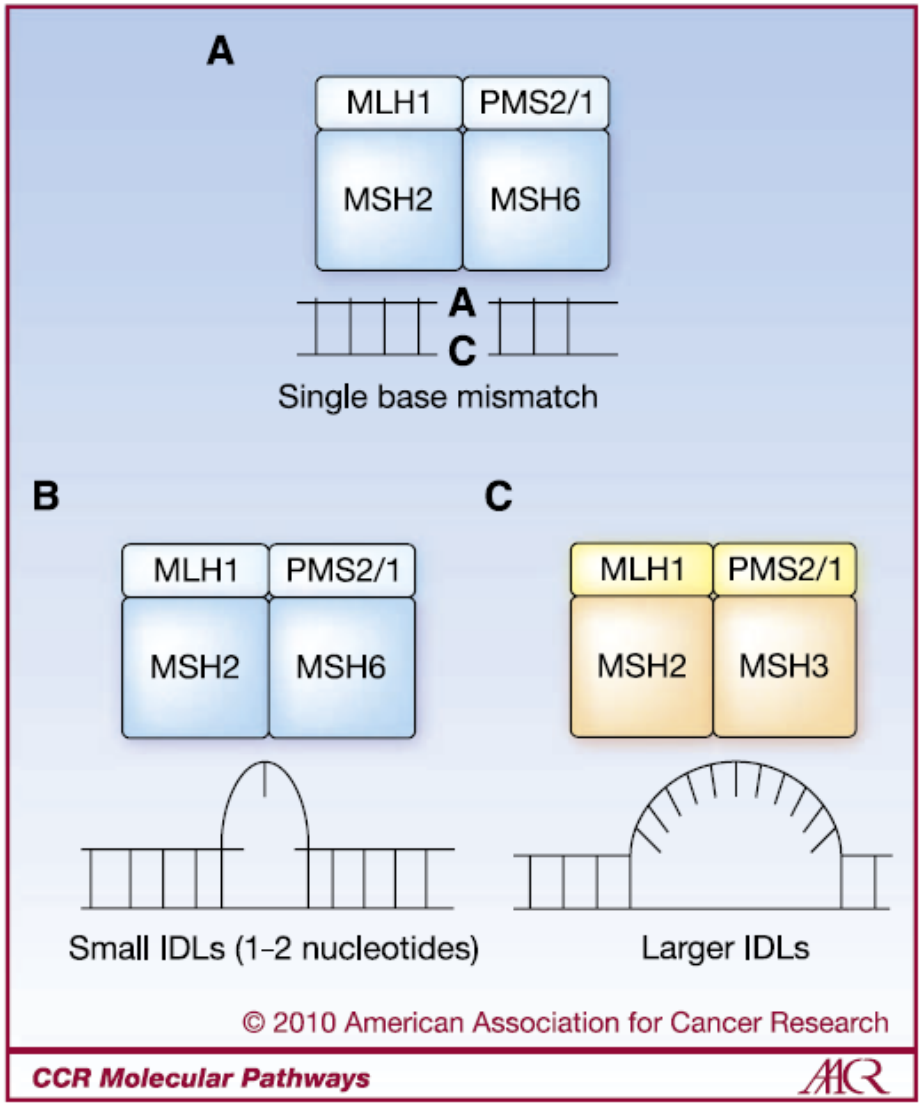
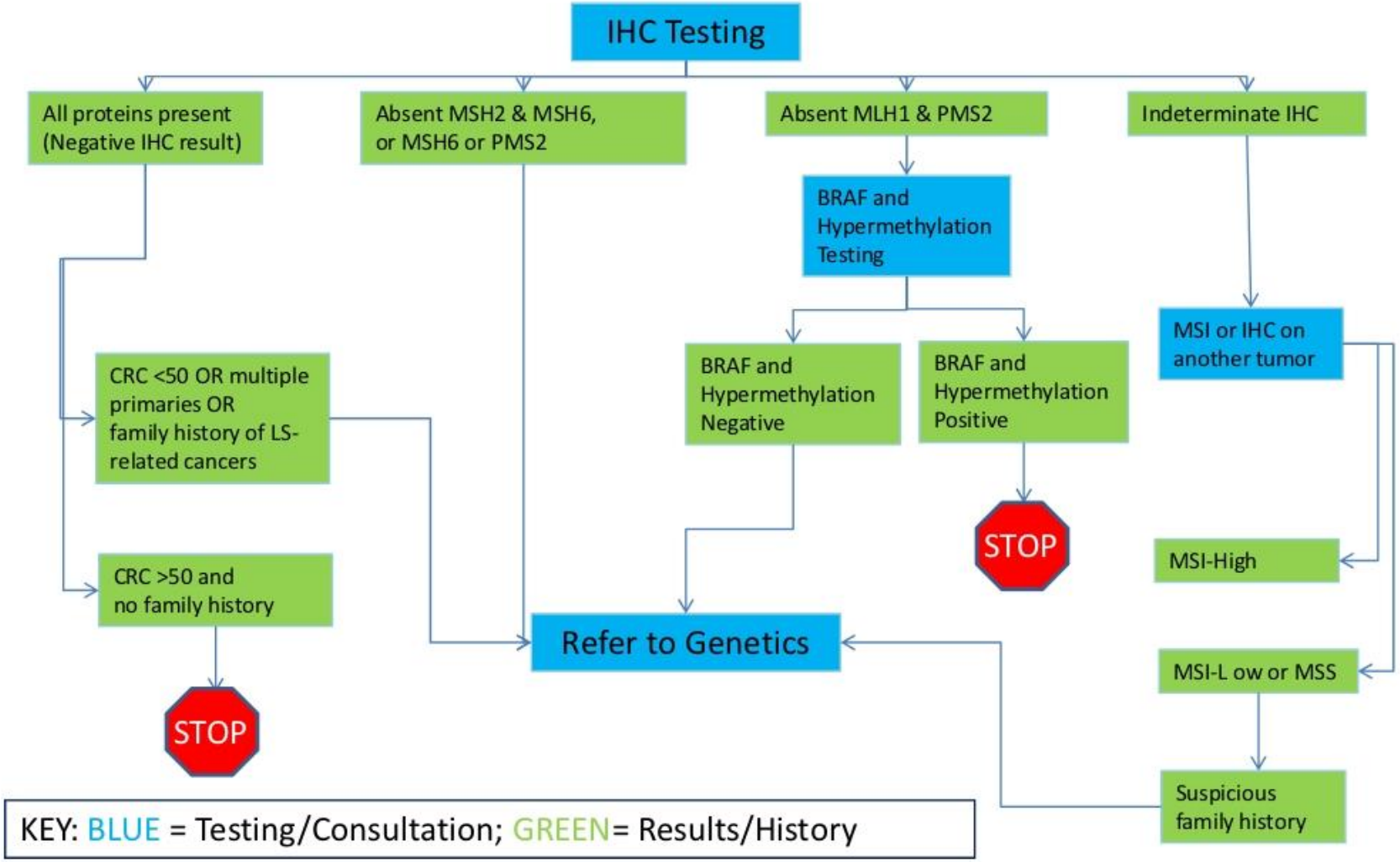


Fig. 1. Schematic of DNA damage recognized by the MMR pathway. A, the MutSα (MSH2/MSH6) heterodimer recognizes base-base mismatches and B, small insertion-deletion loops (IDL). The MutSβ (MSH2/MSH3) heterodimer recognizes single nucleotide IDLs and C, longer IDLs (10-nucleotide loops). In association with the MutL heterodimer and other associated proteins, these mismatches are excised and repaired.

IHC Testing Schematic

(With BRAF and Hypermethylation)



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Tumour Review

Tumor genotype and immune microenvironment in POLE-ultramutated and MSI-hypermutated Endometrial Cancers: New candidates for checkpoint blockade immunotherapy?

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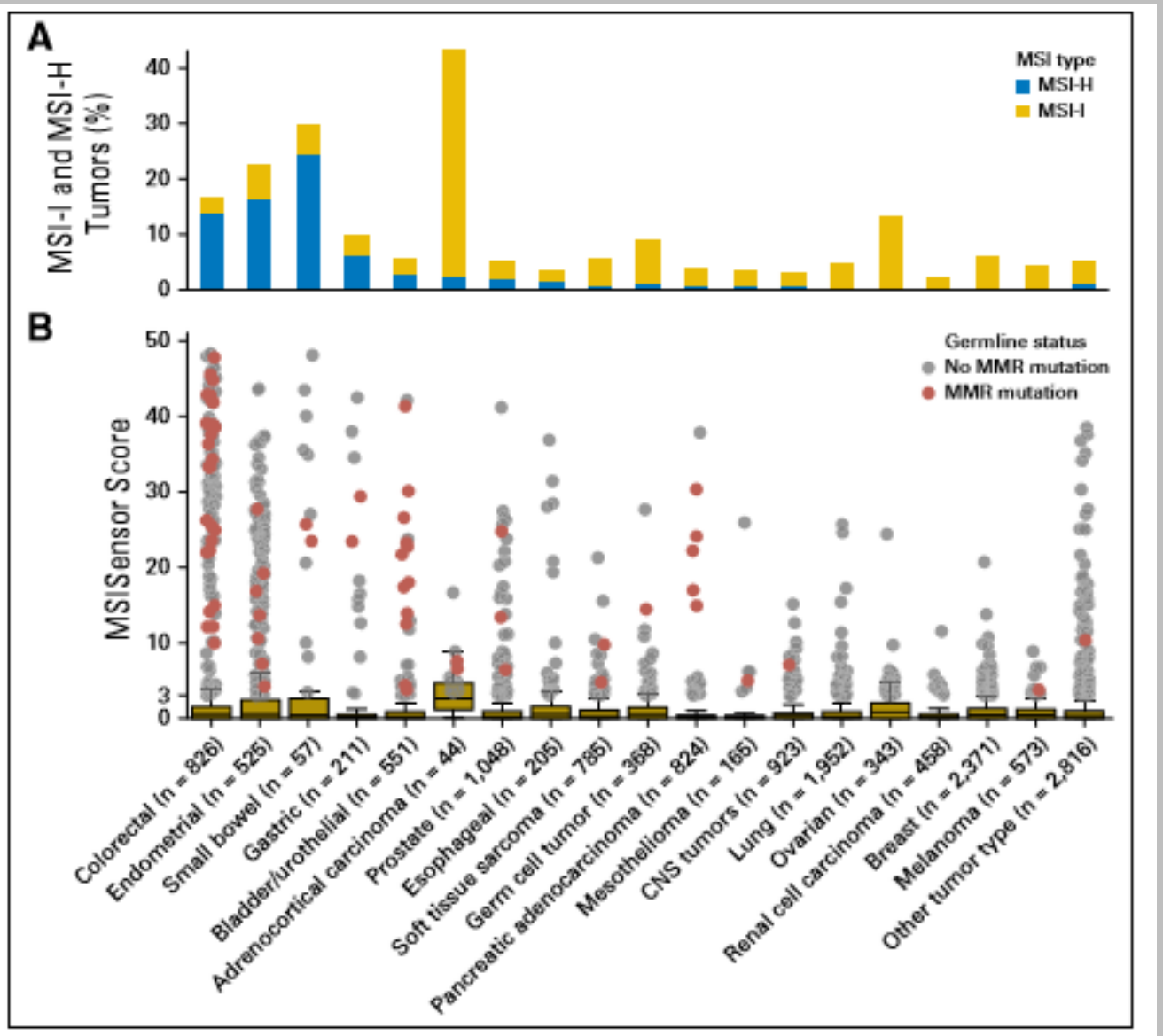
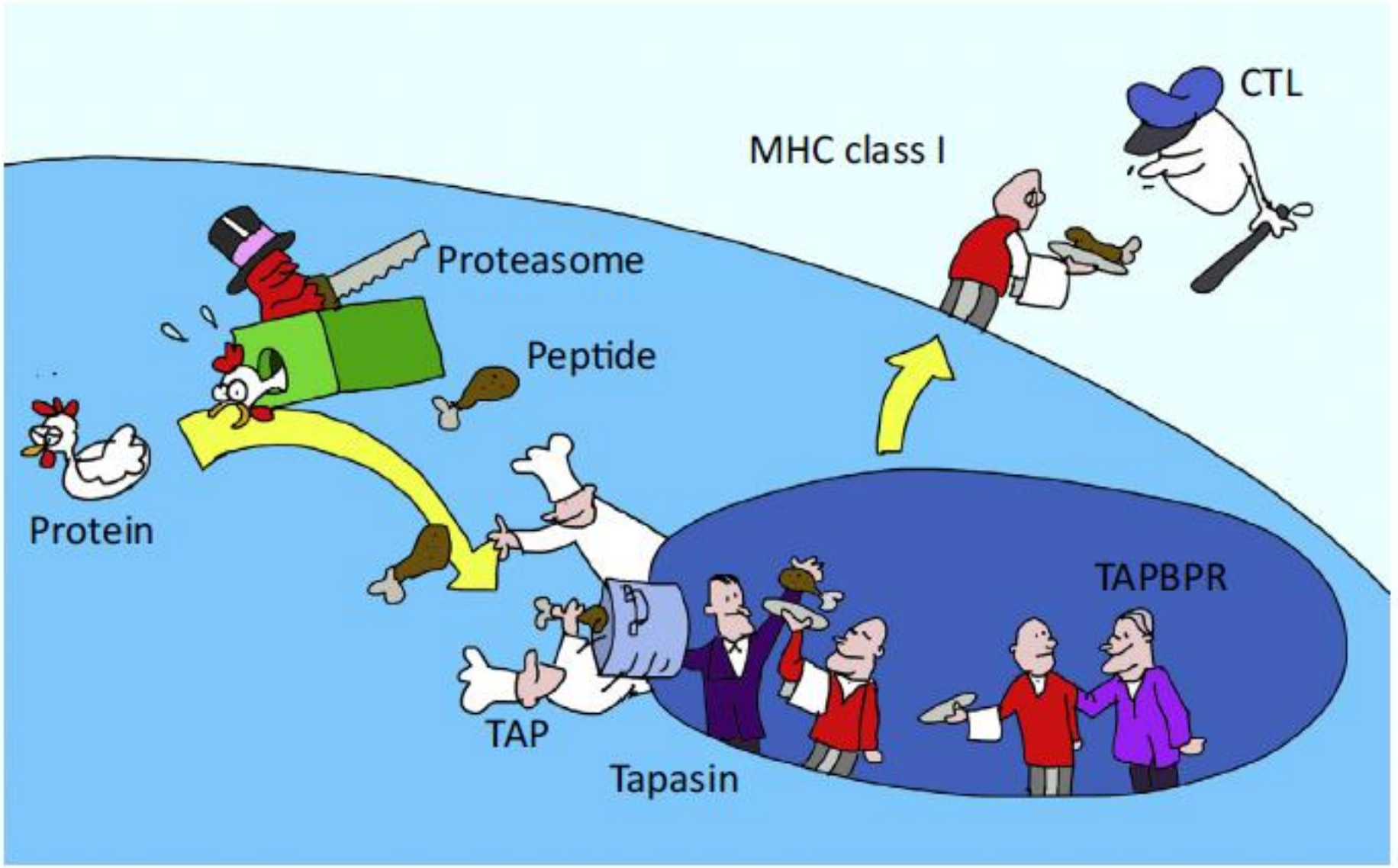
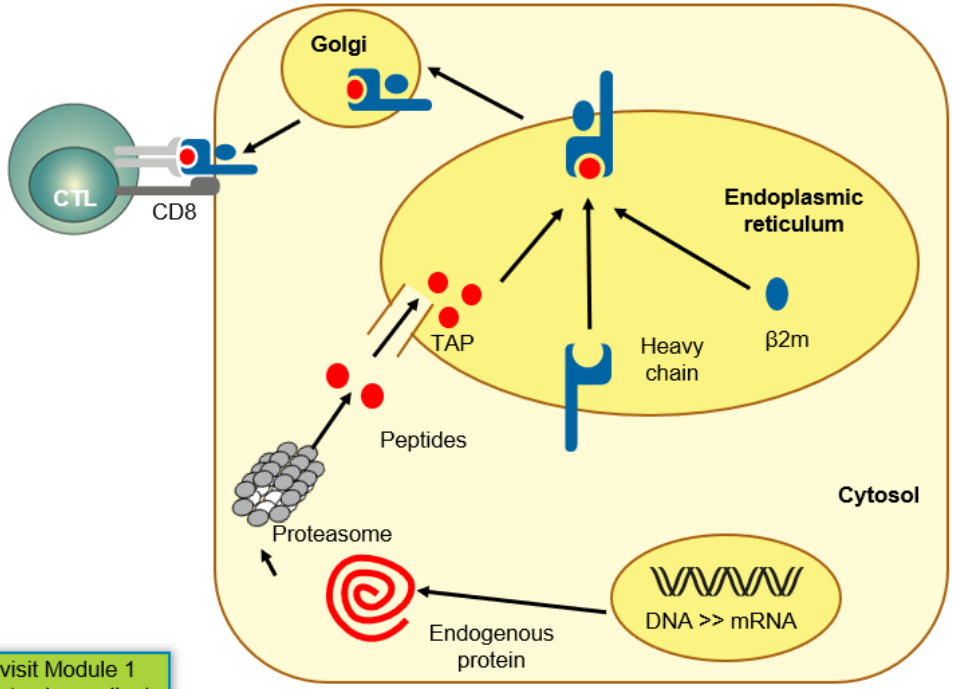




Trends in Immunology

Cytolytic T lymphocytes can recognize tumor-specific antigens on the surface of tumor cells

- Tumor antigens created by oncogenesis are released and captured by APCs such as dendritic cells for processing[1]
- Processing occurs via the HLC class I antigen pathway[2]
  - Proteins are degraded by the proteasome
  - Next, the resultant peptides are translocated by TAP into the ER lumen and loaded onto HLA class I molecules
  - The peptide–HLA class I complexes are then released from the ER and transported via the Golgi to the plasma membrane
- The antigenic tumor peptide is presented to CTLs (CD8+ T cells)[1]



Revisit Module 1
(Link to view online)

APCs, antigen presenting cells; ß2m, beta$_2$ microglobulin; CTLs, cytolytic T lymphocytes; ER, endoplasmic reticulum; HLA, human leukocyte antigen; TAP, transporter associated with antigen presentation.
1. Chen DS and Mellman I. Immunity. 2013;39(1):1–10. 2. Neefjes et al. Nat Rev Immunol 2011;11:823–36.

LETTER

doi:10.1038/nature13988

Checkpoint blockade cancer immunotherapy targets tumour-specific mutant antigens

Matthew M. Gubin[1], Xiuli Zhang[2], Heiko Schuster[3], Etienne Caron[4], Jeffrey P. Ward[1,5], Takuro Noguchi[1], Yulia Ivanova[1], Jasreet Hundal[6], Cora D. Arthur[1], Willem-Jan Krebber[7], Gwenn E. Mulder[7], Mireille Toebes[8], Matthew D. Vesely[1], Samuel S. K. Lam[1], Alan J. Korman[9], James P. Allison[10], Gordon J. Freeman[11], Arlene H. Sharpe[12], Erika L. Pearce[1], Ton N. Schumacher[8], Ruedi Aebersold[4,13], Hans-Georg Rammensee[3], Cornelis J. M. Melief[7,14], Elaine R. Mardis[6,15], William E. Gillanders[2], Maxim N. Artyomov[1] & Robert D. Schreiber[1]

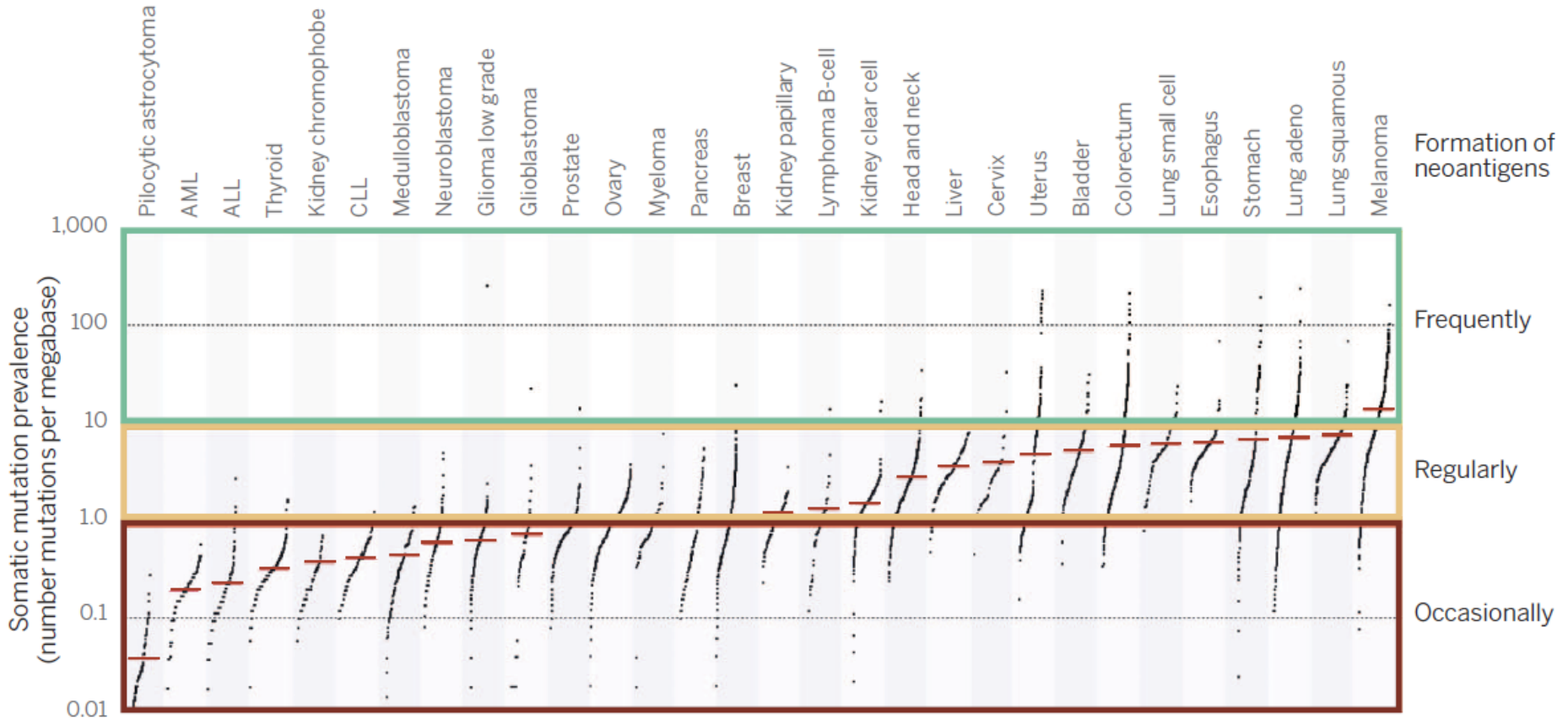


Fig. 2. Estimate of the neoantigen repertoire in human cancer. Data depict the number of somatic mutations in individual tumors. Categories on the right indicate current estimates of the likelihood of neoantigen formation in different tumor types. Adapted from (*50*). It is possible that the immune system in melanoma patients picks up on only a fraction of the available neoantigen repertoire, in which case the current analysis will be an underestimate. A value of 10 somatic mutations per Mb of coding DNA corresponds to ~150 nonsynonymous mutations within expressed genes.

Size Matters: Dissecting Key Parameters for Panel-Based Tumor Mutational Burden (TMB) Analysis

Short title: Panel-based TMB detection

Ivo Buchhalter[1,2], Eugen Rempel[1], Volker Endris[1], Michael Allgäuer[1], Olaf Neumann[1], Anna-Lena Volckmar[1], Martina Kirchner[1], Jonas Leichsenring[1], Amelie Lier[1], Moritz von Winterfeld[1], Roland Penzel[1], Petros Christopoulos[3, 4], Michael Thomas[3, 4], Stefan Fröhling[5, 6], Peter Schirmacher[1,6], Jan Budczies[1, 6,*], Albrecht Stenzinger[1, 6, *]

doi: 10.1002/ijc.31878

Other platform problems:

- Tumor purity.
- Depth of sequencing.
- Cut off.
- Bioinformatics challenge.
- Blueprint.
- TAT.
- Drop out.

TUMOR IMMUNOLOGY

Clonal neoantigens elicit T cell immunoreactivity and sensitivity to immune checkpoint blockade

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Mutations and TMB

- Resistance: Jak, STK11, B2 microglobulin.
- Mutations vs TMB (renal cell carcinoma, MCC, melanoma...)

Conclusions:

- PDL1.
- MSI.
- TMB.