Biomarkers in Head & Neck Cancer

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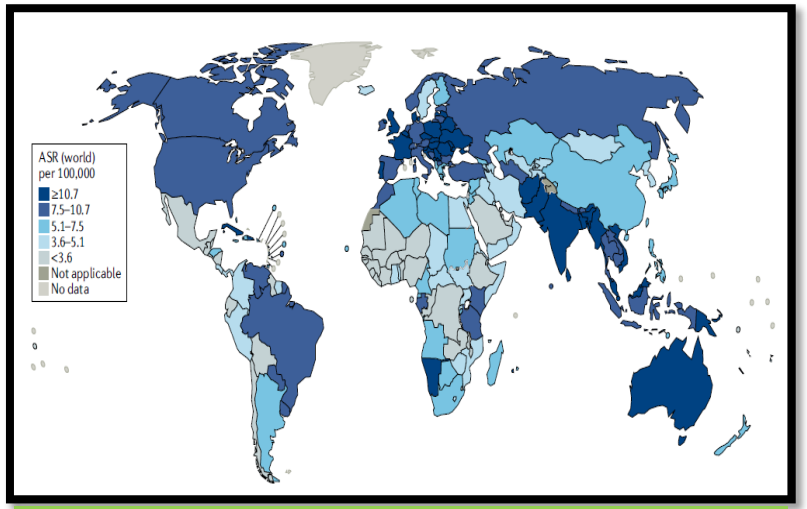
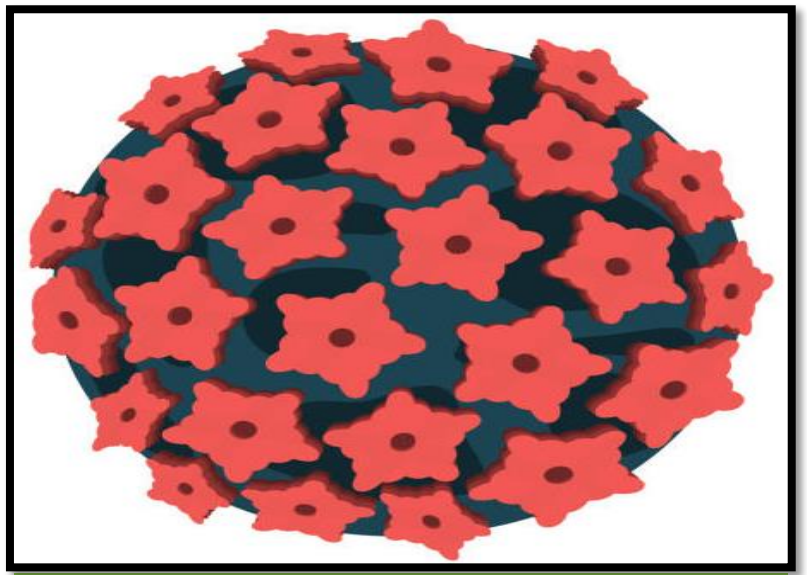
What do we know about Head & Neck Cancers?

Head & Neck Cancers are….

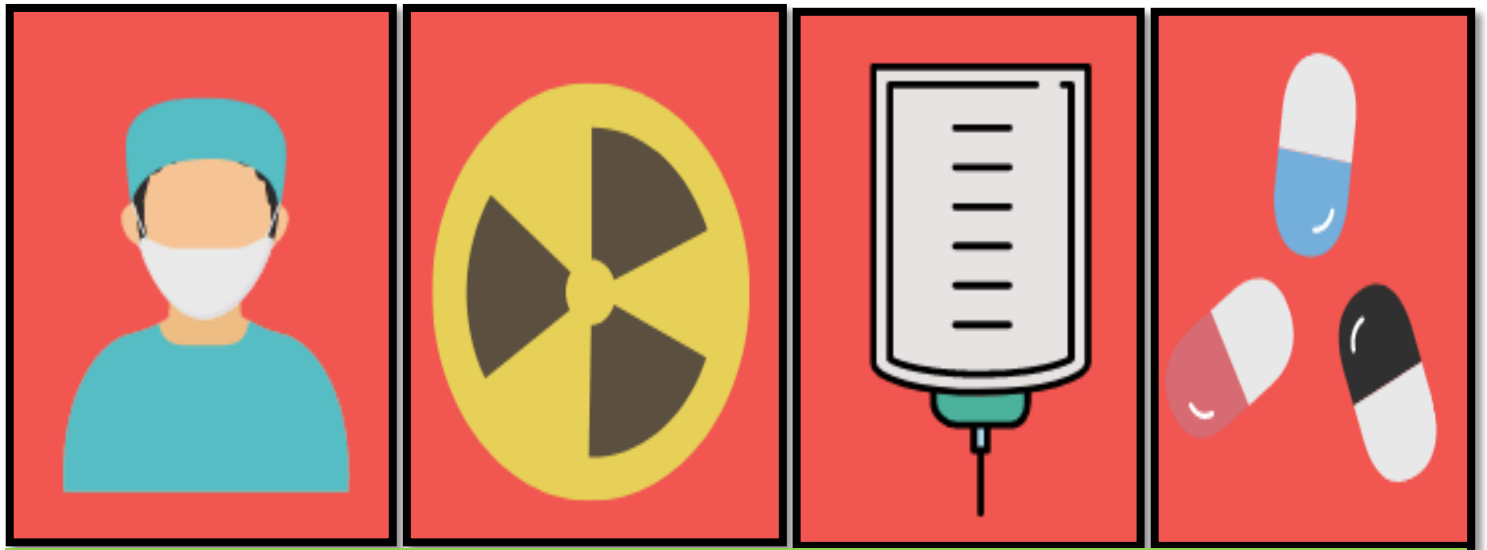


Global burden of HNSCC

Causes



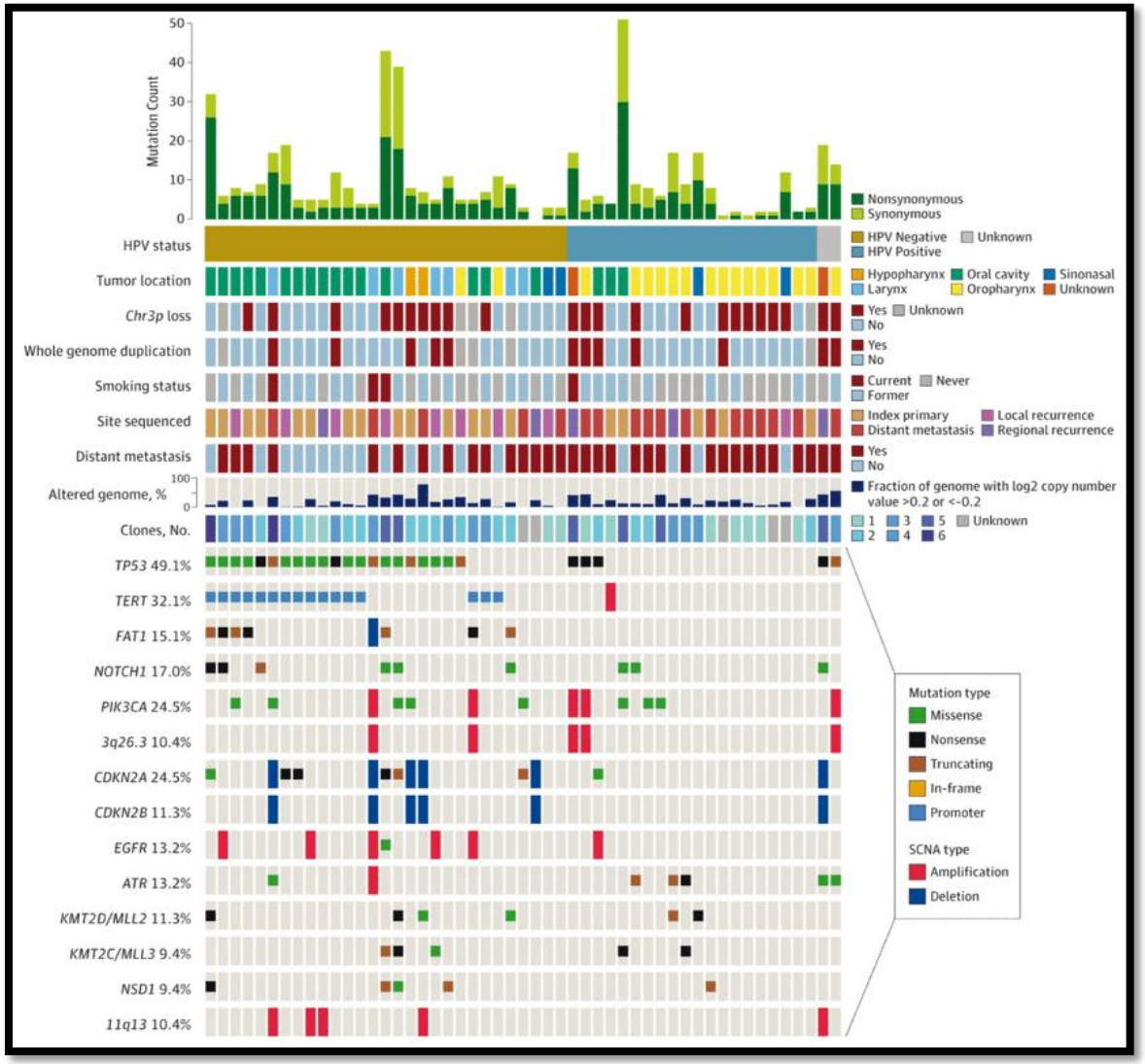
Human Papillomavirus (HPV)



Treatment Options

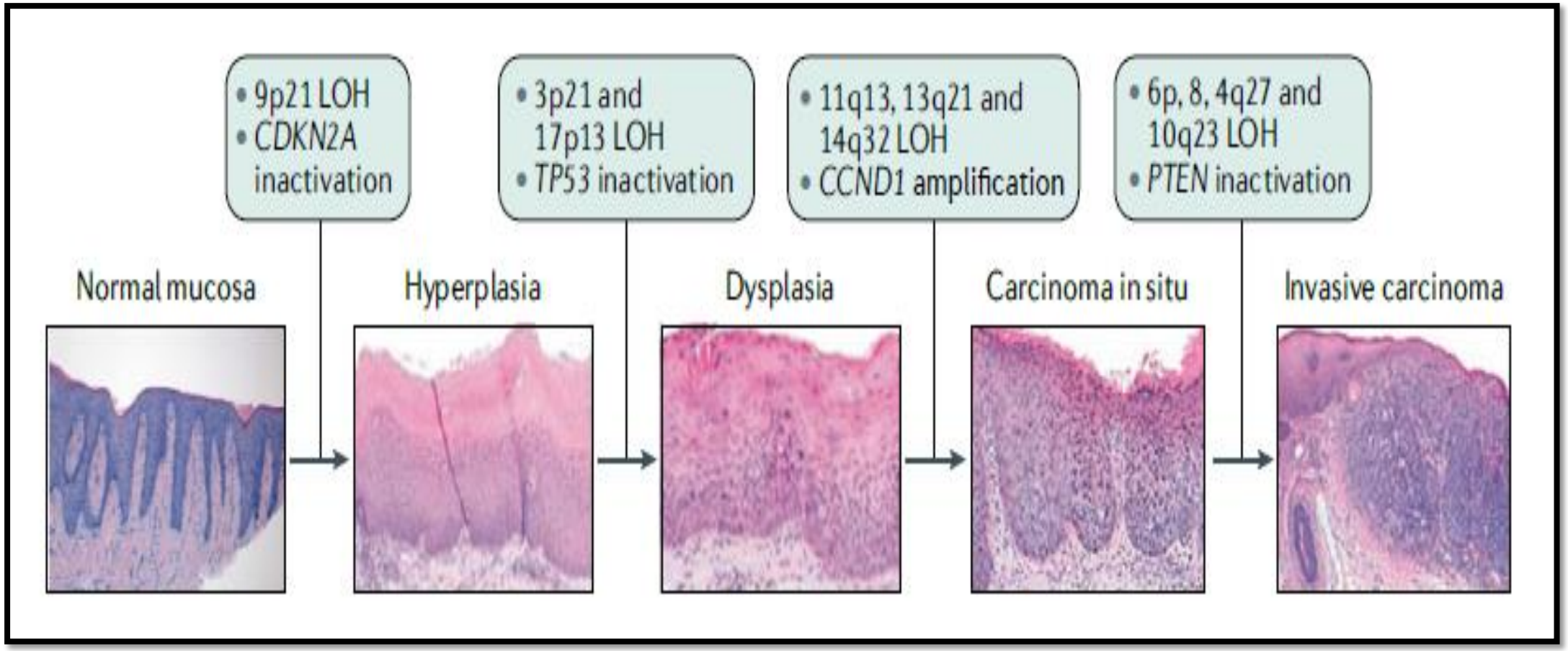
Alsahafi. Cell Death Dis. 2019;10:540. Cramer. Oral Oncol. 2019;9:104460; Nature Review: (2020) 6:92

What is the Molecular landscape of Head & Neck Cancers?



Morris et al, JAMA Oncology (2018)

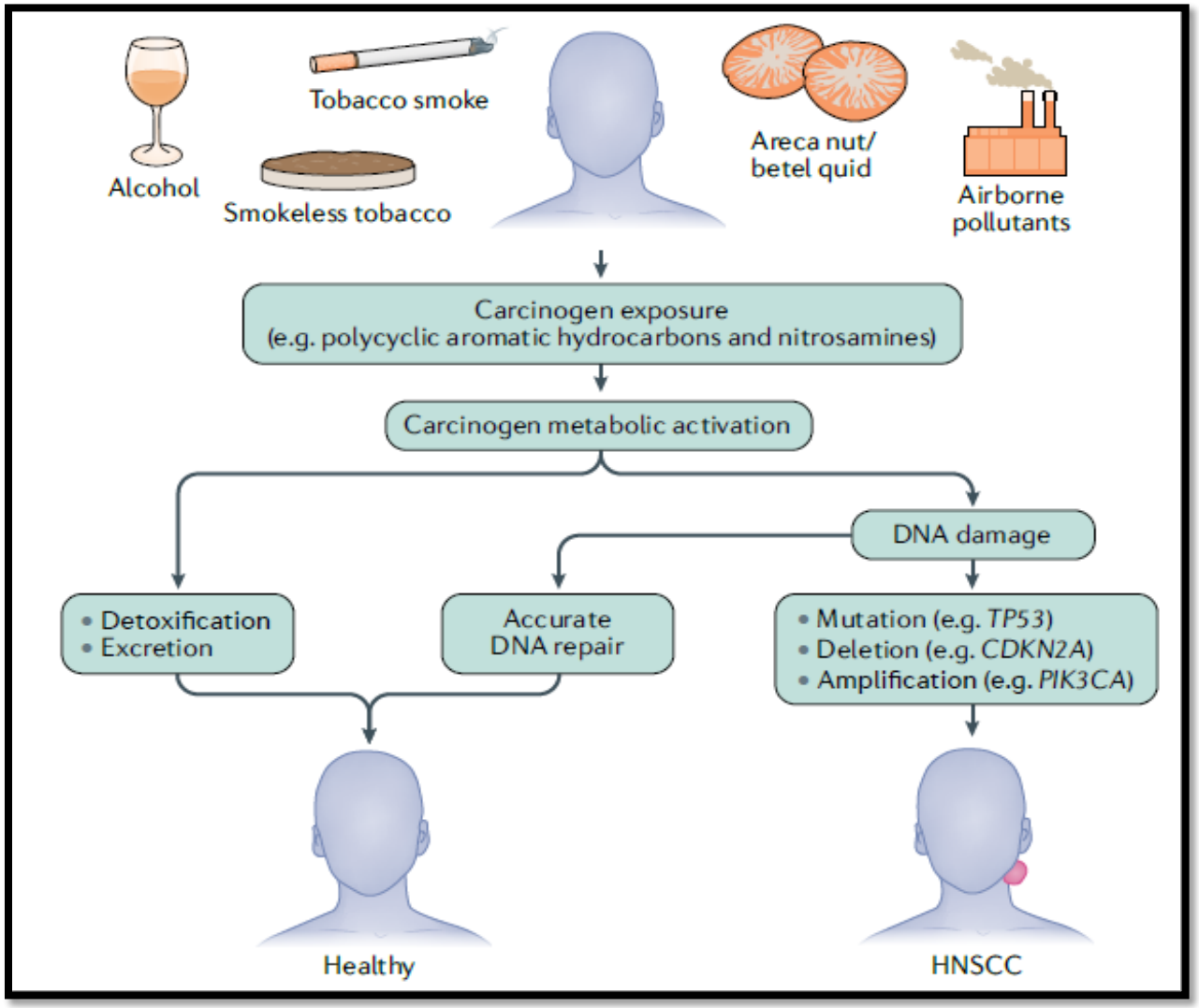
Quick glimpse: Genomic alterations

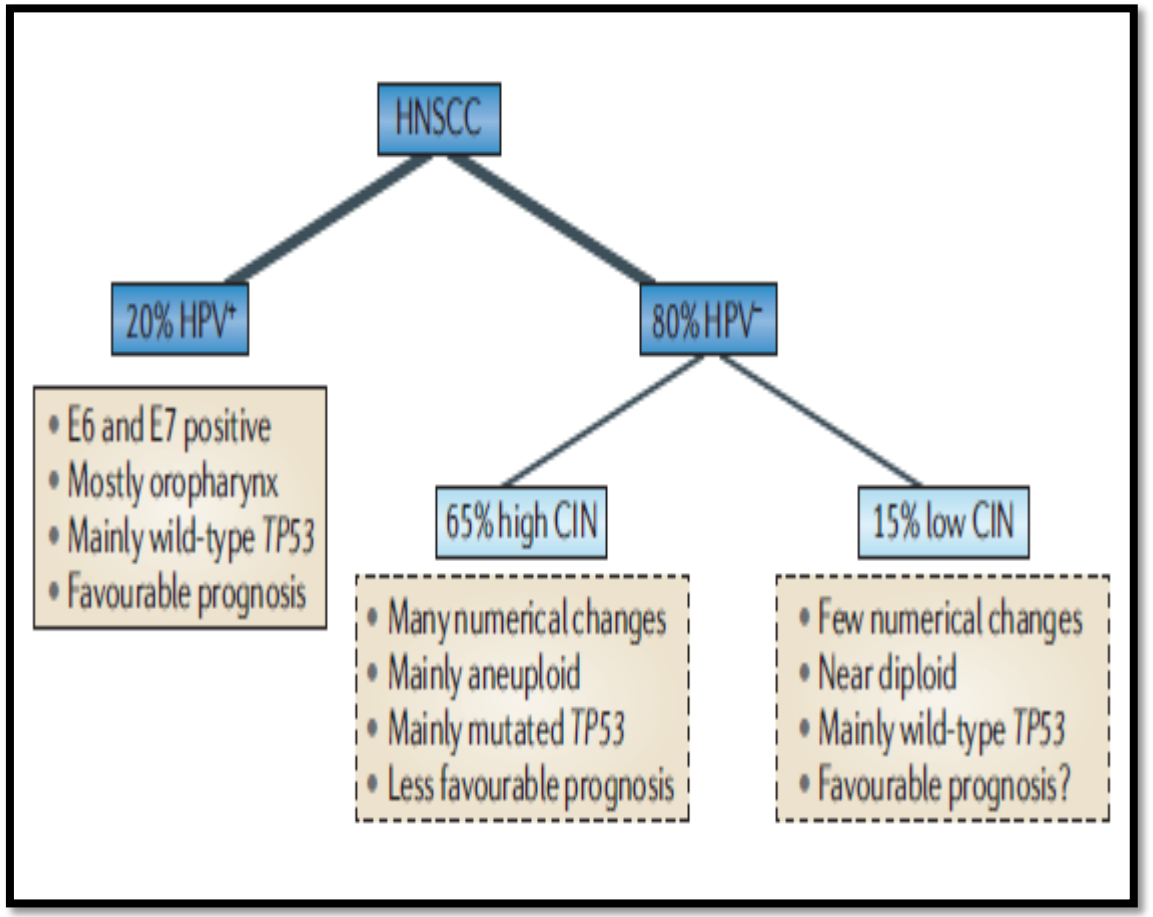


The availability of a model of ordered histological progression of HNSCC has enabled assignment of some chromosomal abnormalities to specific stages of progression

Leemans et al Nature Reviews Cancer volume 18, pages269–282 (2018); Grandis et al; Nature Reviews- Disease primers; 2020;6:92.

Quick glimpse: Key pathways

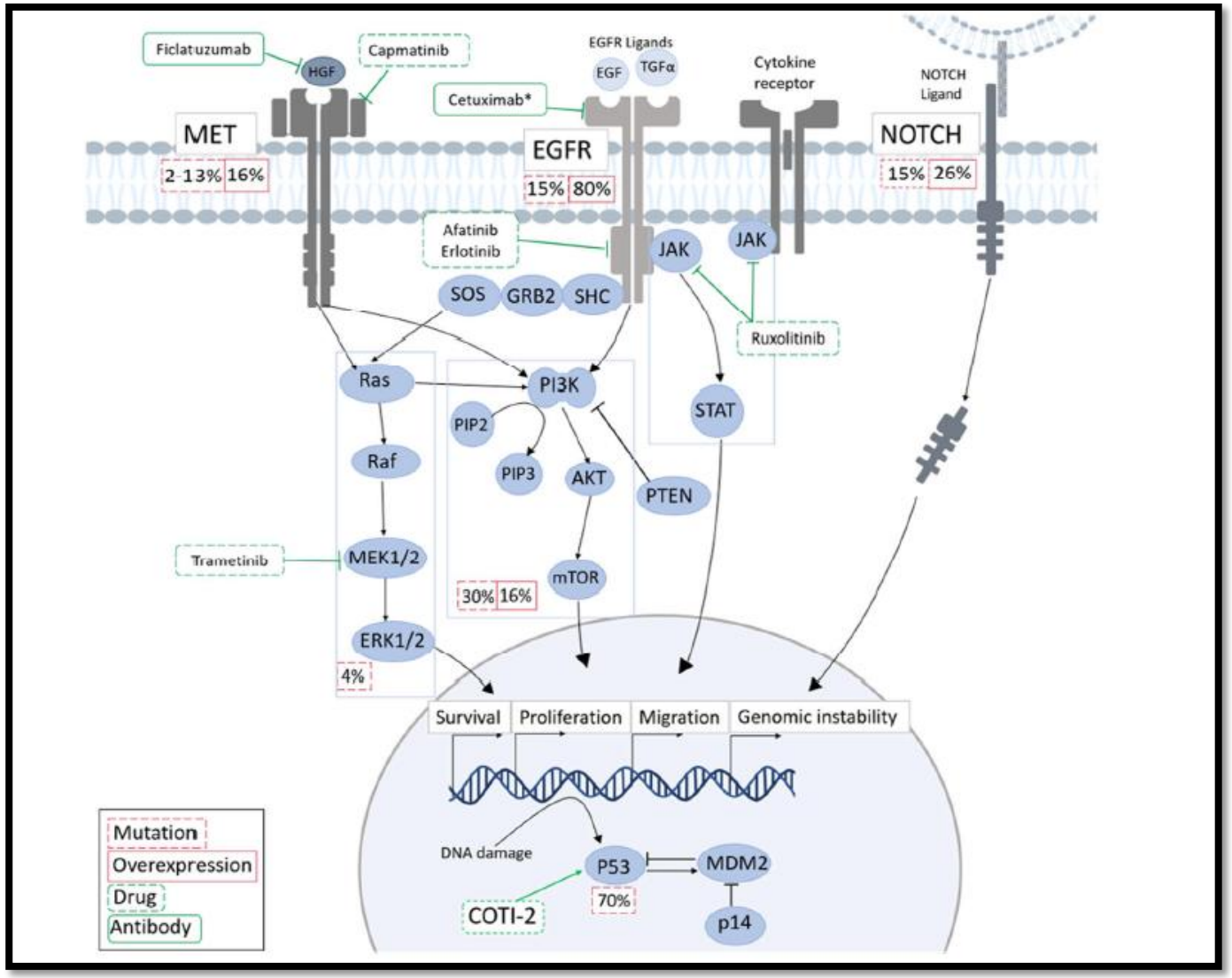




Schematic overview of the genetic classification of head & neck squamous cell carcinoma

Leemans et al Nature Reviews Cancer volume 18, pages269–282 (2018); Grandis et al; Nature Reviews- Disease primers; 2020;6:92.

Quick glimpse: Molecular Pathway



Alsahafi et al. Cell Death and Disease (2019) 10:540.

Quick glimpse: Mutational Profiling

Biomarker	Tumor Suppressor Gene (TSP)/Oncogene
TP53, CDKN2A, FAT1, NOTCH1, KMT2D, NSD1, TGFBR2	Tumor suppressor Gene
RAS (KRAS, NRAS, HRAS)	Proto-oncogene
EGFR	Proto-oncogene
PIK3CA	Oncogene
PTEN	Oncogene

Leemans et al Nature Reviews Cancer volume 18, pages269–282 (2018)

Biomarkers and Targeted Drugs in Head and Neck Cancer

Biomarker	Drug	Head and Neck Cancer	Testing method
PD-L1	Pembrolizumab	First line in R/M HNSCC as monotherapy (CPS ≥ 1) and in combination with chemotherapy	IHC
PD-L1	Nivolumab, pembrolizumab	Monotherapy in R/M HNSCC with progression on/after platinum-based chemotherapy	IHC
MSI-H	Pembrolizumab	Monotherapy in R/M HNSCC with progression on/after prior treatment	PCR, NGS
TMB-H	Pembrolizumab	Monotherapy in head and neck cancers with progression on/after prior treatment	NGS
AR +	Leuprolide*, bicalutamide*	Salivary gland tumors	IHC
NTRK gene fusion	Larotrectinib, entrectinib	Salivary gland tumors	IHC, FISH, NGS
HER2+	Trastuzumab ± pertuzumab or docetaxel*, TDM-1*	Salivary gland tumors	IHC, FISH, NGS
EGFR	Cetuximab	HNSCC as monotherapy or in combination	RT PCR, NGS

*Guideline-recommended off-label use under certain circumstances.

Pembrolizumab PI. Nivolumab PI. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®): Head and Neck Cancers. Version 1.2021. 11/08/2020

Tumor Agnostic Markers: Wave of the Future

Agent	Targeted Molecular Alteration	Status
Pembrolizumab	MSI-H/dMMR	Approved across tumor types
Larotrectinib	TRK fusions	Approved across tumor types
Entrectinib	TRK/ALK/ROS1 fusions	Approved across tumor types
Selpercatinib (LOXO-292)	RET fusions and activating point mutations	Approved for NSCLC, medullary thyroid cancer, other thyroid cancers
Pralsetinib (BLU-667)	RET alterations	Phase III
Repotrectinib (TPX-0005)	TRK, ALK, ROS1 fusions	Phase I/II
Selitrectinib (LOXO-195)	TRK fusions	Phase I/II
TAS-120	FGFR aberrations	Phase I/II
Debio 1347	FGFR aberrations	Phase I/II
Agerafenib (RXDX-105)	RET alterations	Phase I

One target: One Drug: All tumors

Hierro. Clin Cancer Res. 2019;25:3210.

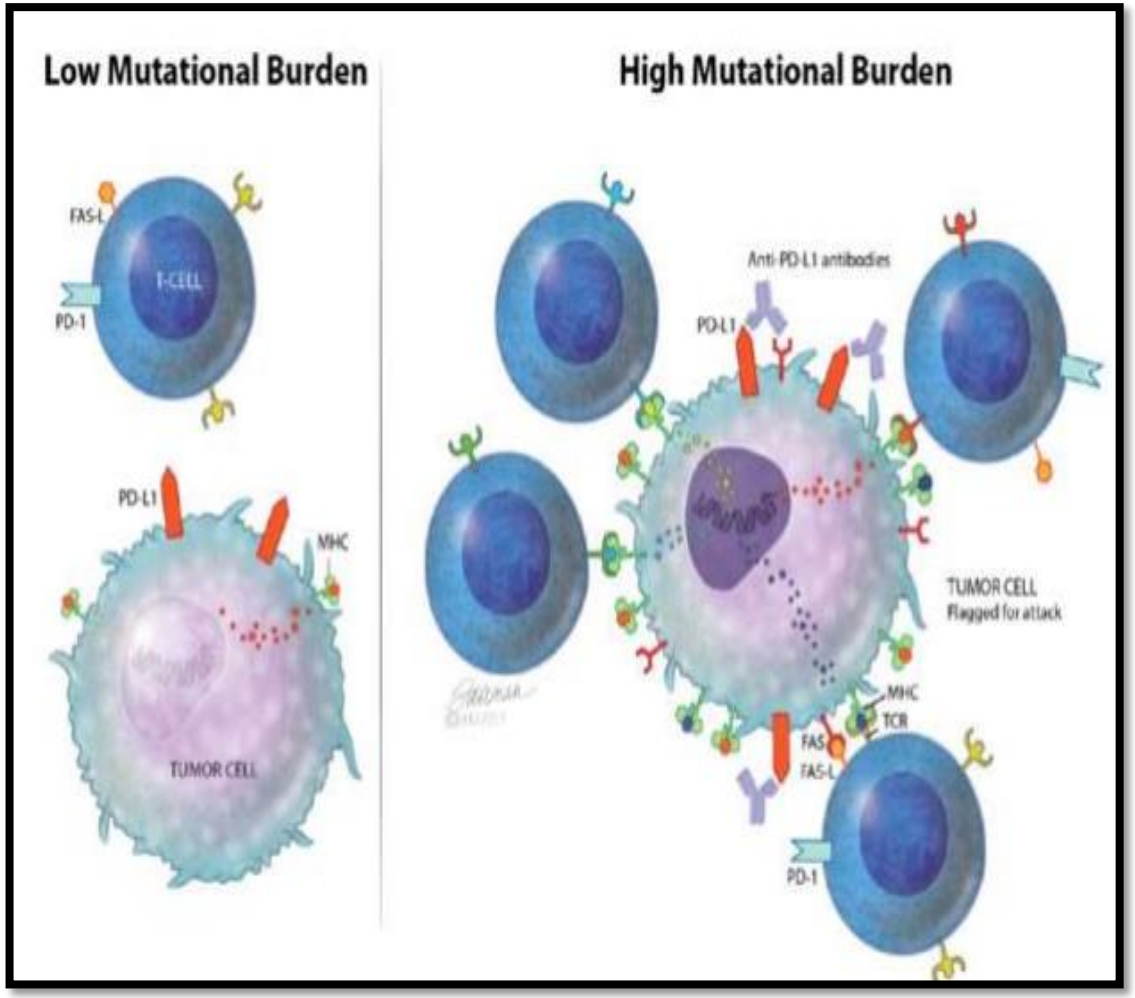
PDL1: Biomarkers in Immunotherapy

Trials	PD-L1 Staining Cells	Eligibility PD-L1 Required	Antibody Used	Population Defined	Response in Total Population	Response by PD-L1 Subgroups
KEYNOTE-012, cohort B[21,22]	Tumor cells (TPS)	Yes, ≥1%	22C3	NA	18%	ORR, 21% in CPS ≥1 vs 6% in CPS <1
KEYNOTE-012, cohort B2[21,22]	Tumor cells (TPS)	No				
KEYNOTE-055[23]	CPS	No	22C3	82% CPS ≥1	16%	ORR, 18% in CPS ≥1 vs 12% in CPS <1; ORR, 27% in CPS ≥50 group
KEYNOTE-040[27]	CPS and TPS	No	22C3	79% CPS ≥1 26% TPS ≥50	14.6% with immunotherapy	HR, 0.74 (95% CI, 0.58–0.93) for survival in CPS ≥1; HR, 0.53 (95% CI, 0.35–0.81) for survival in TPS ≥50
CheckMate 141[24–26]	Tumor cells	No	28-8	57% PD-L1 ≥1	13.3% with immunotherapy	HR, 0.55 (95% CI, 0.36–0.83) for survival in PD-L1 ≥1
KEYNOTE-048[28]	CPS	No	22C3	85% CPS ≥1 43% CPS ≥20	16.9% with immunotherapy	12-month survival CPS ≥20: 23% (pembrolizumab) 24% (pembrolizumab + chemotherapy) 11%–12% (EXTREME) 12-month survival CPS ≥1: 20% (pembrolizumab) 19% (pembrolizumab + chemotherapy) 11%–12% (EXTREME) 12-month survival total: 17% (pembrolizumab) 17% (pembrolizumab + chemotherapy) 12%–14% (EXTREME)

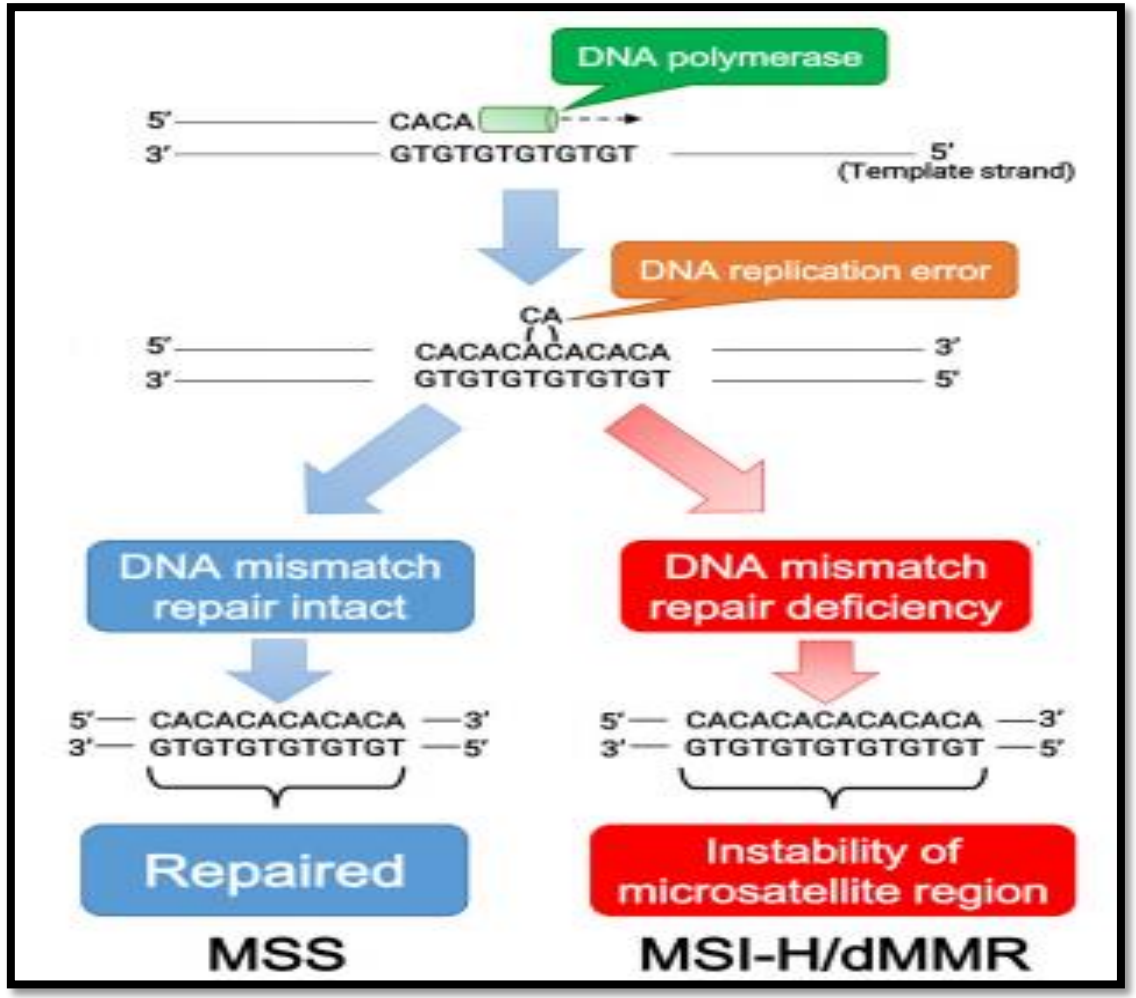
Le et al, JNCCN Vol 18: 7 2020

TMB & MSI : Biomarkers in Immunotherapy

TMB: Tumor Mutation Burden



MSI: Microsatellite Instability



Marusawa et al; J Gastroenterol (2020) 55:15–26

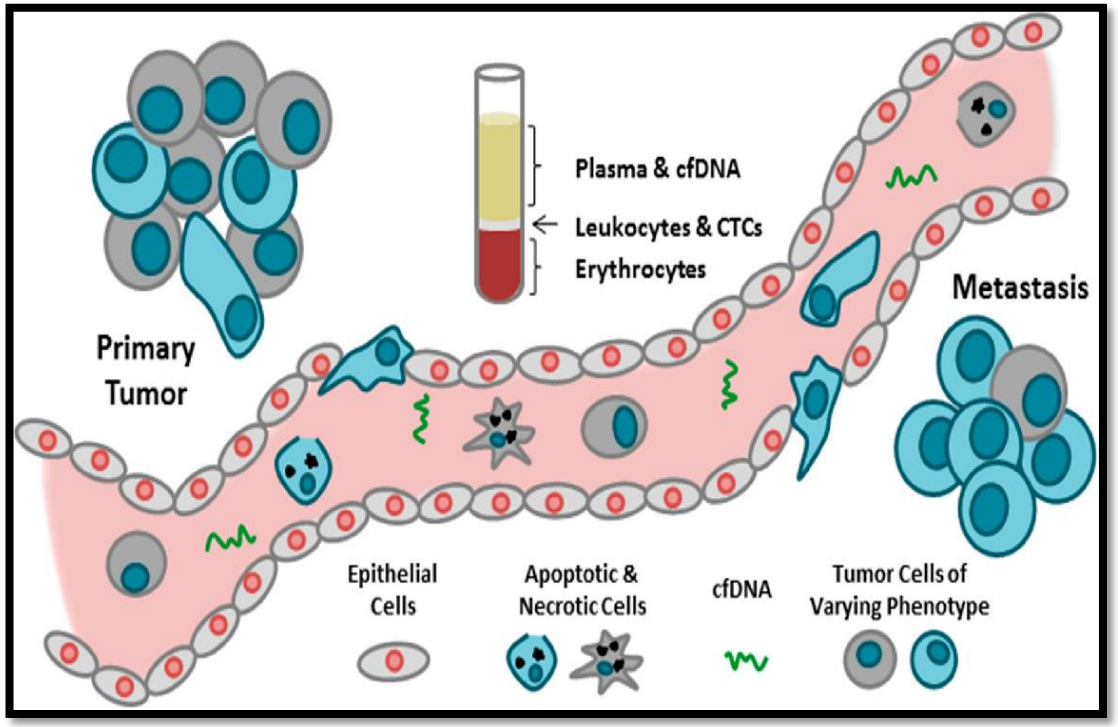
Sample type

Option 1: Tissue biopsy
Formalin Fixed Paraffin Embedded (FFPE) block

Ideal sample size

In reality

Option 2: Liquid biopsy
(circulating tumor DNA in blood – somatic)



Bauml. Clin Cancer Res. 2018;24:4352. Lowes. Int J Mol Sci. 2016:17:E1505.

All molecular testing methods have limitations

	Single Gene Testing	Multigene Testing (eg, by NGS)
Advantages	▪ Potentially routine in practice ▪ Potential for local implementation, rapid turnaround ▪ Higher sensitivity with PCR platforms	▪ Minimizes use of tumor tissue ▪ Facilitates testing of multiple biomarkers, including emerging biomarkers for clinical trial enrollment ▪ Just need to know to test vs which biomarkers to test for ▪ Generally less costly than sequential testing
Limitations	▪ Tumor tissue samples often inadequate for multiple necessary tests ▪ May lead to repeat biopsy	▪ Multiple platforms available using different methodology that affect types of alterations detected ▪ Analysis of complex biomarker reports ▪ Preauthorization requirements ▪ May not be easily accessible in community practice

Be on the look out for…..Ongoing Clinical Trials

Current National Clinical Trials Network head and neck cancer trials

Protocol number	Phase	Protocol
EA3132	II	Randomized trial of radiotherapy with or without cisplatin for surgically resected HNSCC with *TP53* sequencing
EA3161	II/III	Randomized trial of maintenance nivolumab versus observation in patients with locally advanced, intermediate risk HPV-positive OPCA
EA3163	II	Randomized trial of neoadjuvant chemotherapy followed by surgery and postoperative radiation versus surgery and postoperative radiation for organ preservation of T3 and T4a NPNSCC
NRG-HN001	II/III	Randomized studies of individualized treatment for nasopharyngeal carcinoma based on biomarker EBV DNA
NRG-HN004	II/III	Randomized trial of radiotherapy with concurrent MEDI4736 (durvalumab) versus radiotherapy with concurrent cetuximab in patients with stage III–IVb head and neck cancer with a contraindication to cisplatin
NRG-HN005	II/III	Randomized trial of de-intensified radiation therapy for patients with early-stage, $p16^+$, non-smoking-associated oropharyngeal cancer
RTOG-1008	II	Randomized study of adjuvant concurrent radiation and chemotherapy versus radiation alone in resected high-risk malignant salivary gland tumours
RTOG-1216	II/III	Randomized trial of surgery and postoperative radiation delivered with concurrent cisplatin versus docetaxel versus docetaxel and cetuximab for high-risk HNSCC
EAY131	II	Molecular analysis for therapy choice (MATCH)
S1609	II	Dual anti-CTLA4 and anti-PD1 blockade in rare tumours (DART)

The table includes trials that were open for patient enrolment as of 15 April 2020. CTLA4, cytotoxic T lymphocyte antigen 4; EBV, Epstein–Barr virus; HNSCC, head and neck squamous cell carcinoma; HPV, human papillomavirus; NPNSCC, nasal and paranasal sinus squamous cell carcinoma; OPCA, oral and pharyngeal cancer.

Grandis et al; Nature Reviews- Disease primers; 2020;6:92.

Key take home message(s)

- Understanding tumor biology can help guide better treatment options for patients with Head and Neck cancers.
- NGS is critical to drug therapy decision making for patients with Head & Neck cancers.
- NGS trends are towards increasing the breadth of analysis for each patient.
- NTRK if negative by NGS (DNA), it is recommended to follow up with NGS (RNA).

Thank you

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