

What is the clinical impact of analyzing the cancer genome?

Felix Haglund de Flon

Associate Professor / Clinical Pathologist

Head of the Molecular Cancer Diagnostics Unit

Karolinska University Hospital Solna

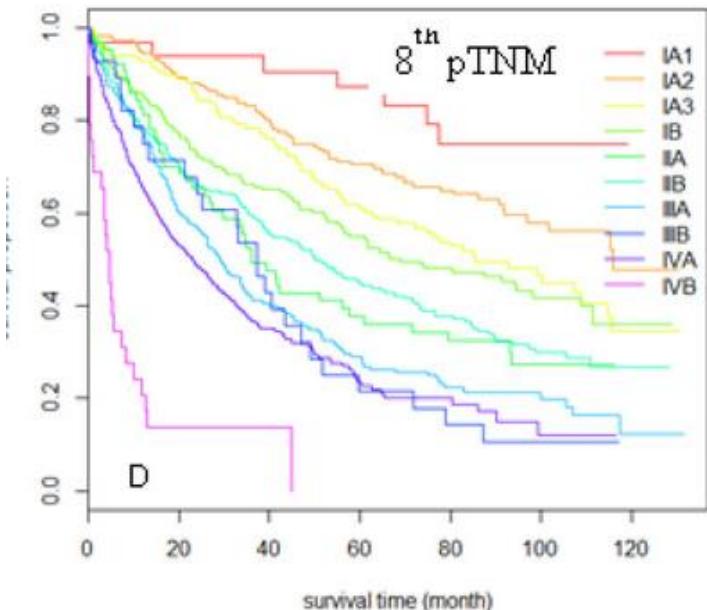
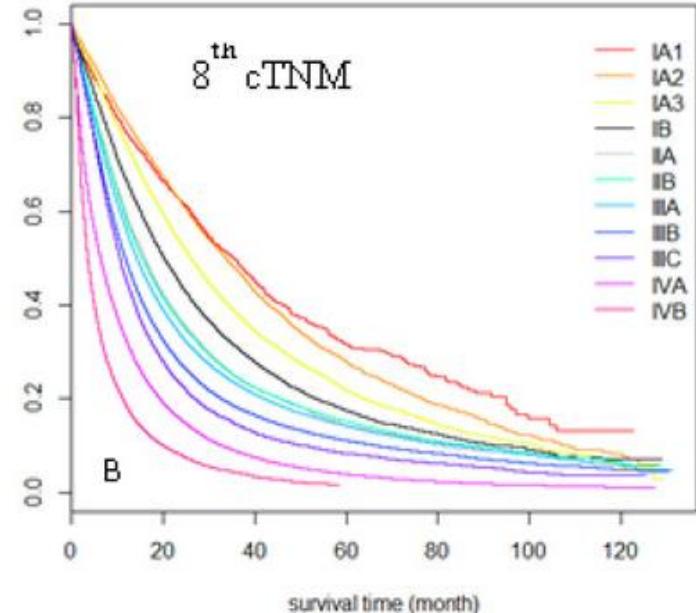
Molecular Pathology today



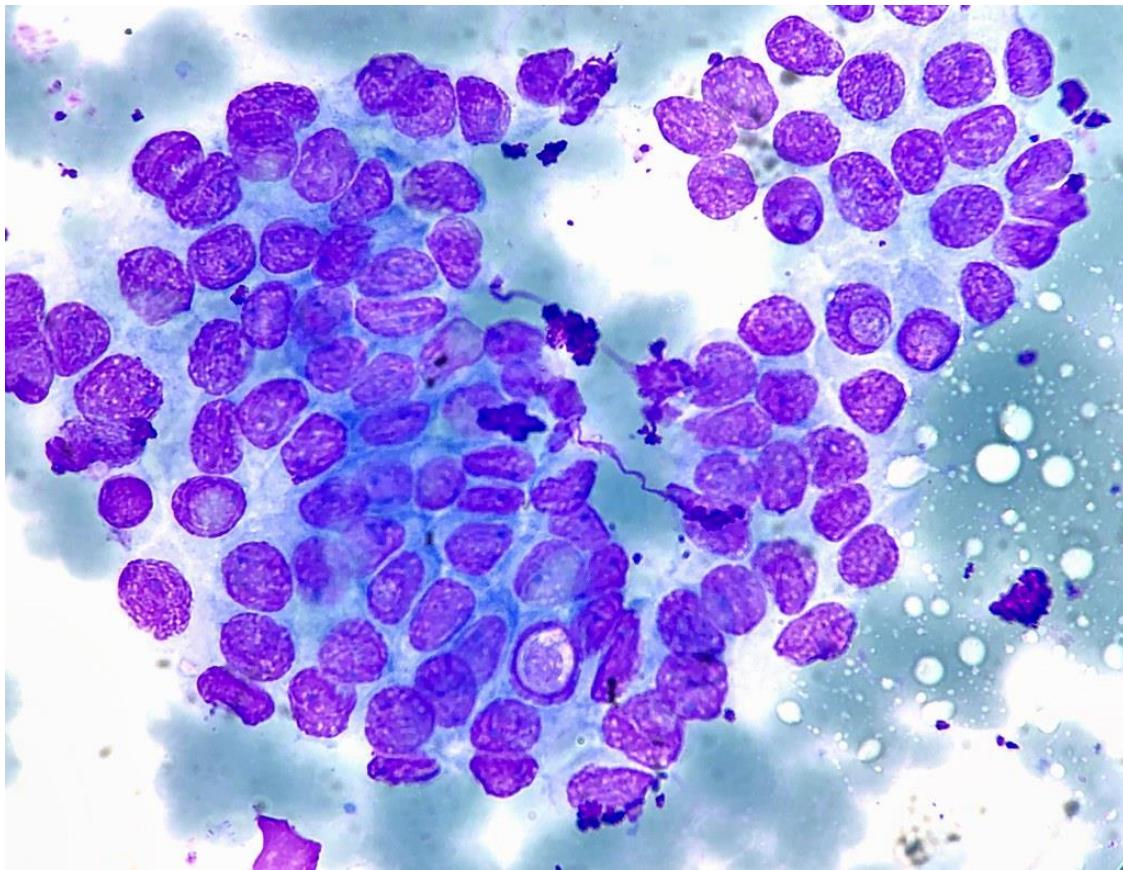
Histopathology

- Morphology (diagnosis)
- TNM (AJCC-system)
- Extremely good prognostic value
- No information about treatment

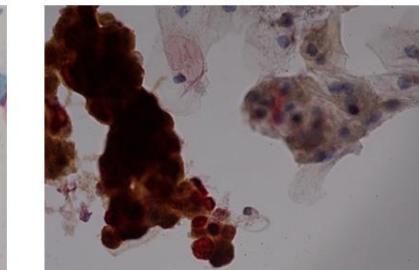
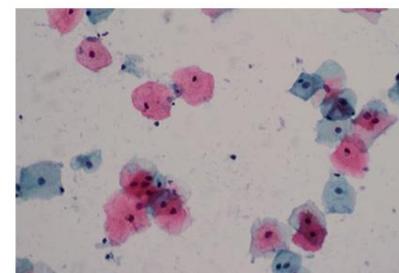
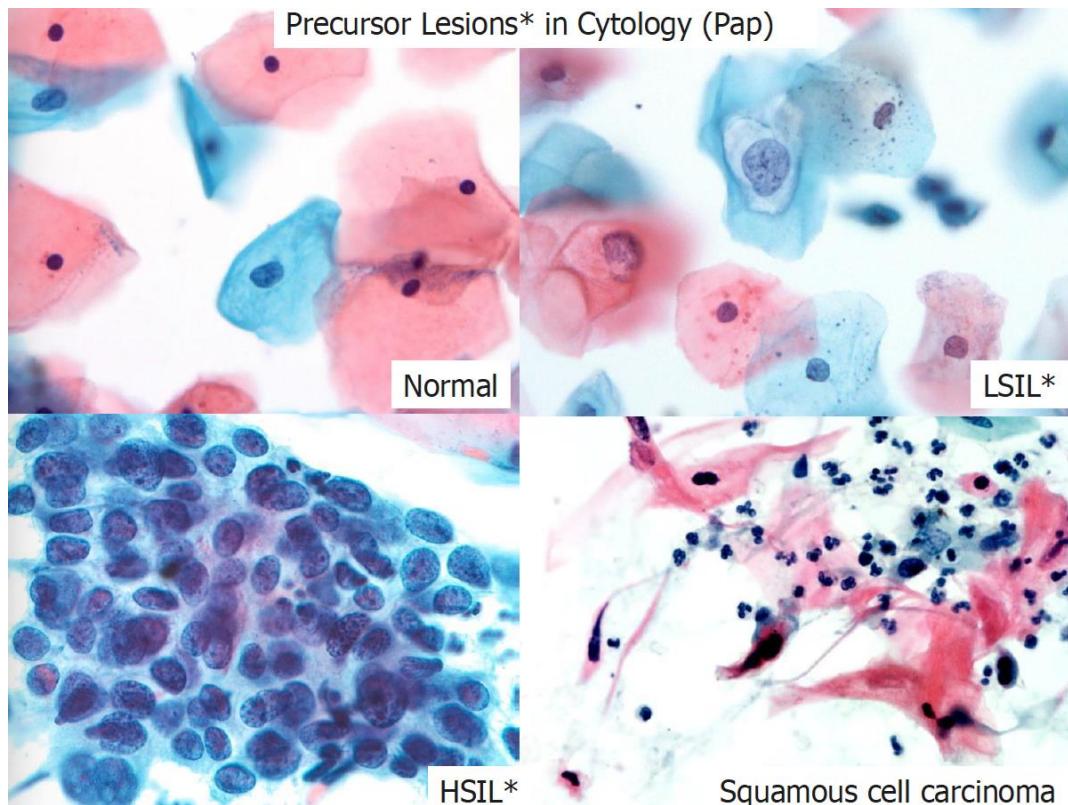
Primary tumor	
TX	Tumor cannot be assessed
T0	No evidence of primary tumor
Ta	Papillary noninvasive tumor
Tis	Carcinoma <i>in situ</i>
T1	Invasion of subepithelial connective tissue/lamina propria
T2	Invasion of muscularis propria
T3	Invasion of renal parenchyma or peripelvic/periureteral fat
T4	Invasion of adjacent organs or through parenchyma into perinephric fat
Regional lymph nodes*	
NX	Regional nodes cannot be assessed
N0	Negative nodes
N1	Single node < 2 cm
N2	Single node 2 - 5 cm; multiple nodes < 5 cm
N3	Multiple nodes > 5 cm
Metastasis	
M0	No distant metastasis
M1	Distant metastasis
TX	Tumor cannot be assessed
T0	No evidence of primary tumor



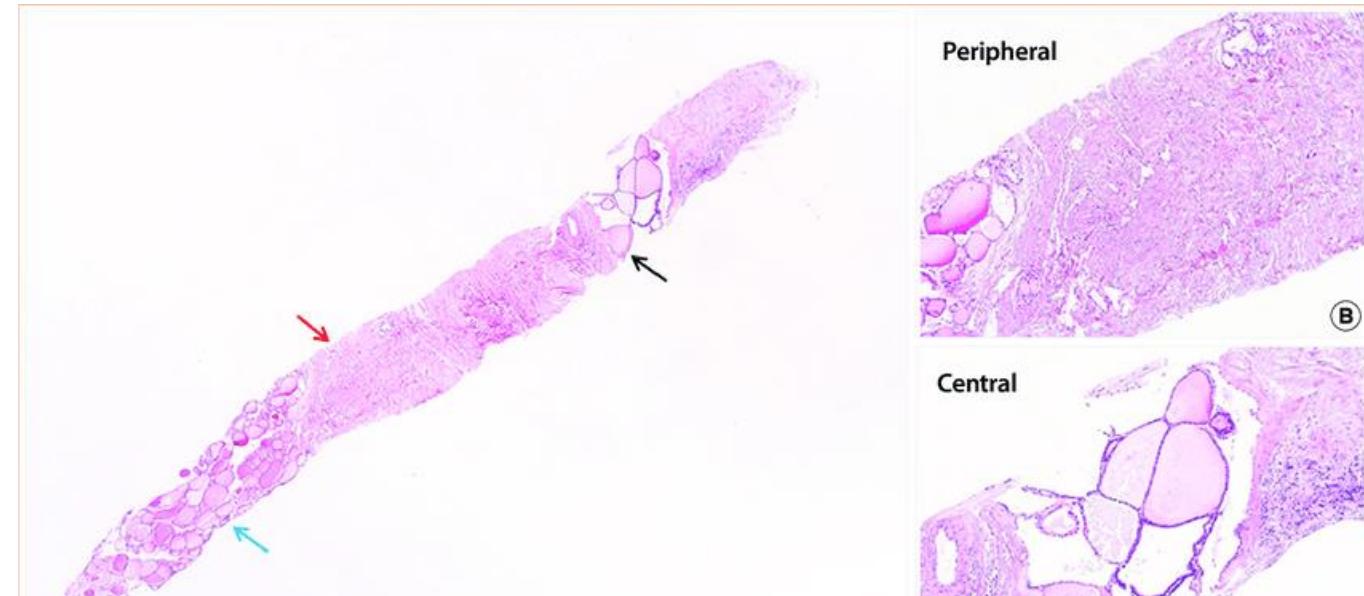
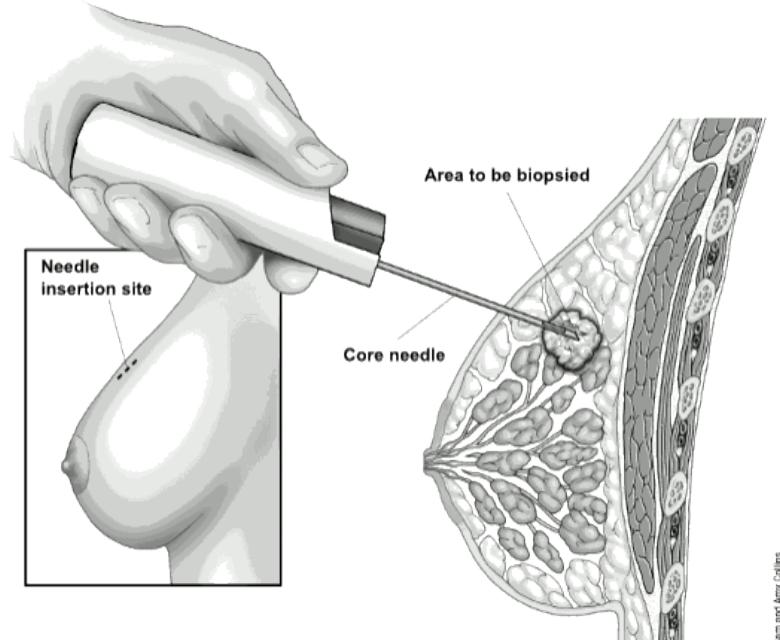
Aspiration Cytology



Liquid based cytology



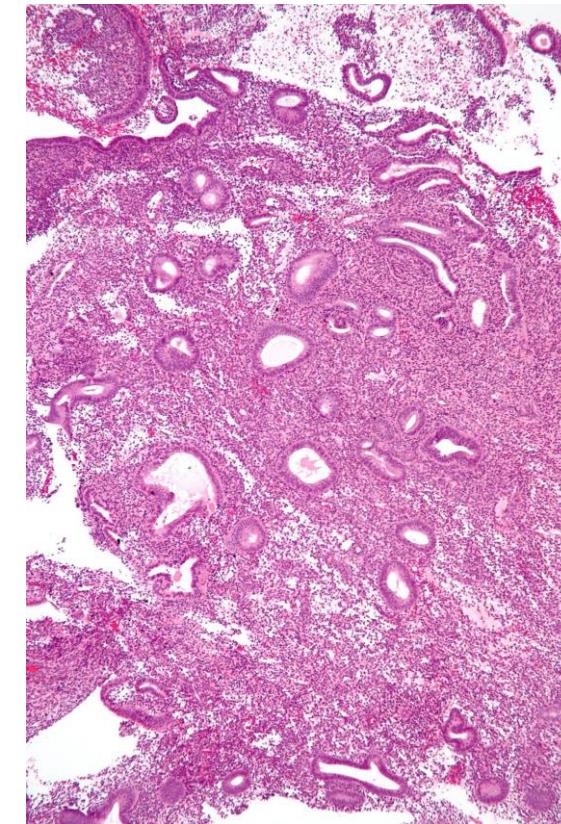
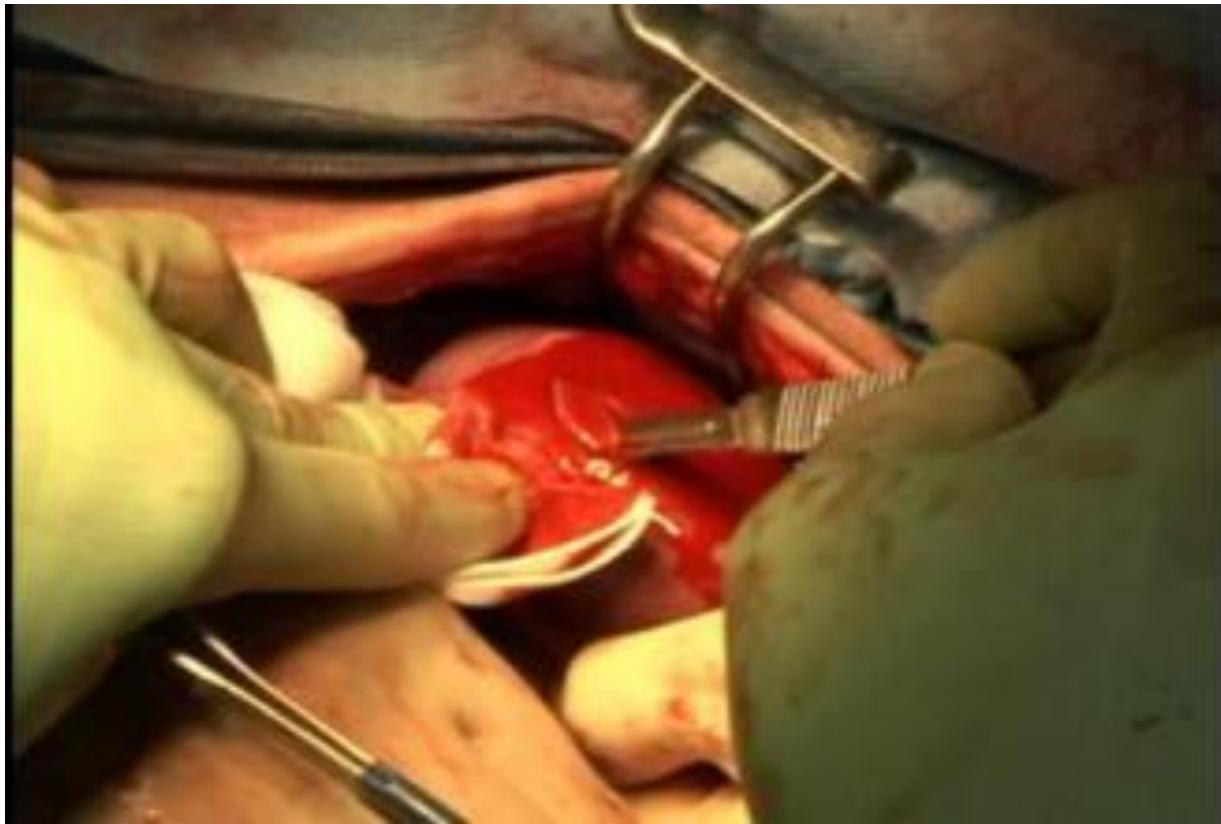
Core needle biopsies



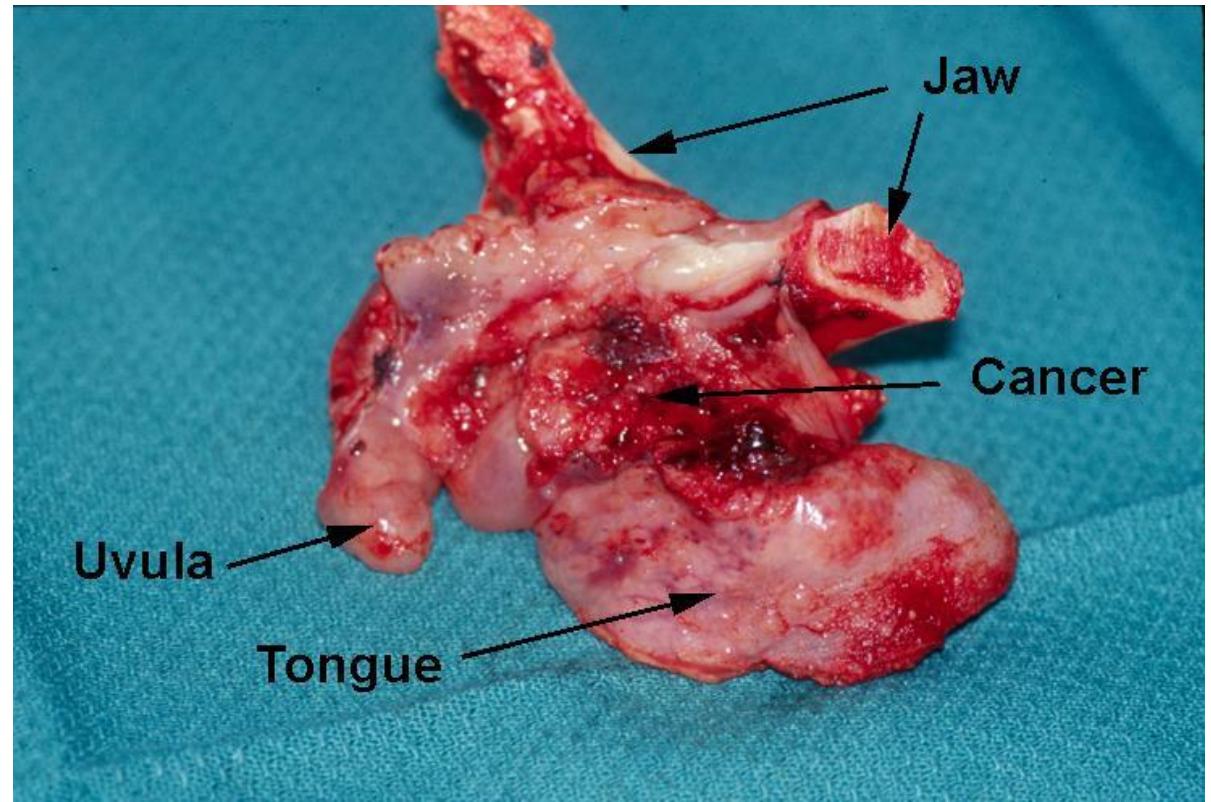
A

B

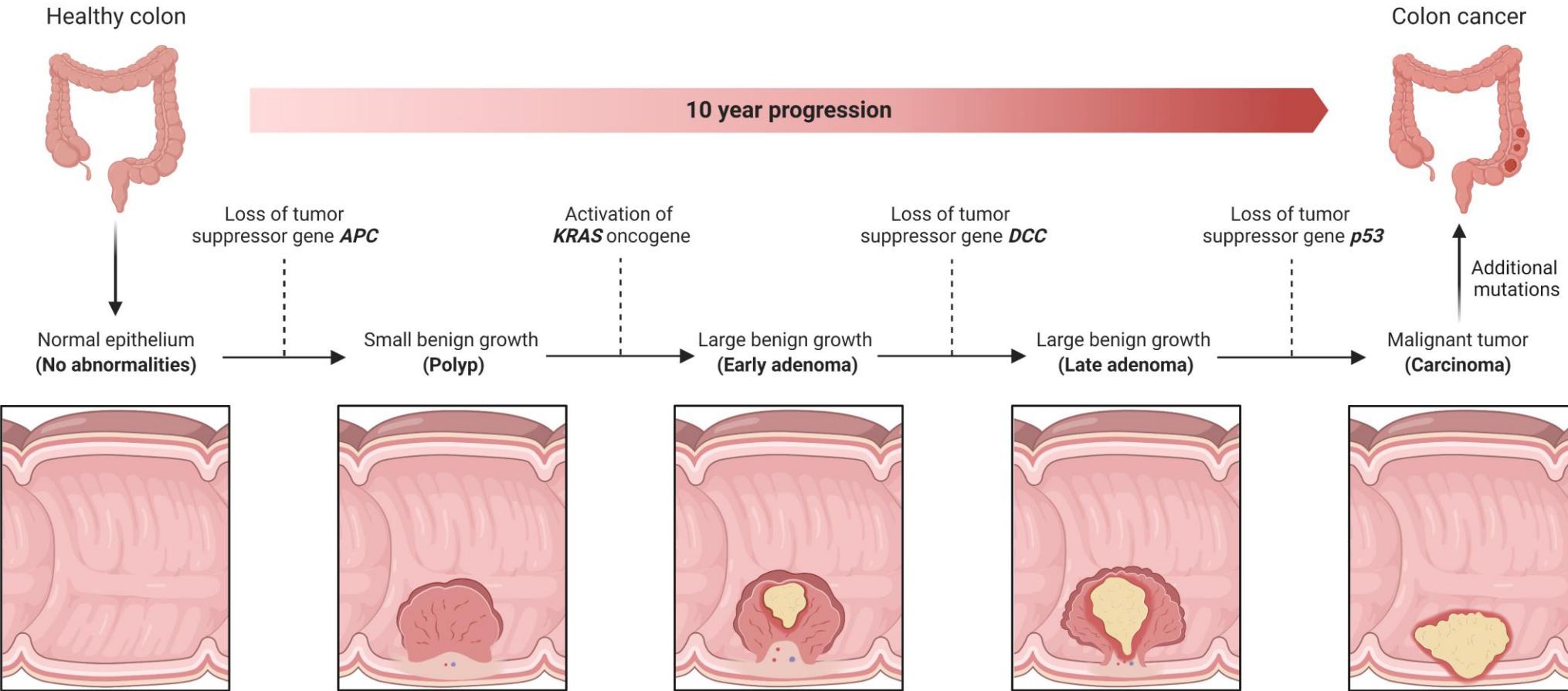
Surgical biopsies

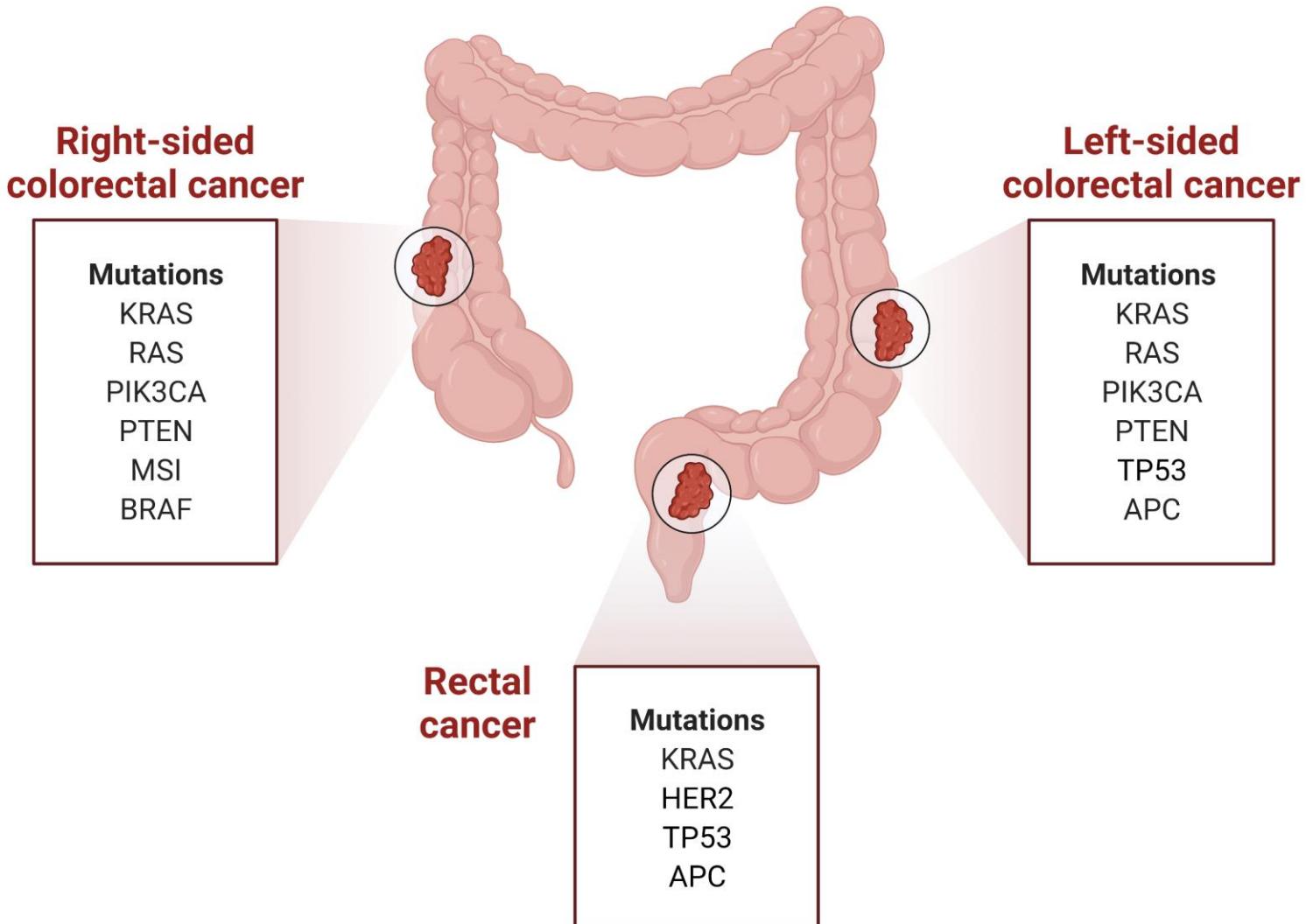


Resection specimens



The Multi-Hit Model of Colorectal Cancer

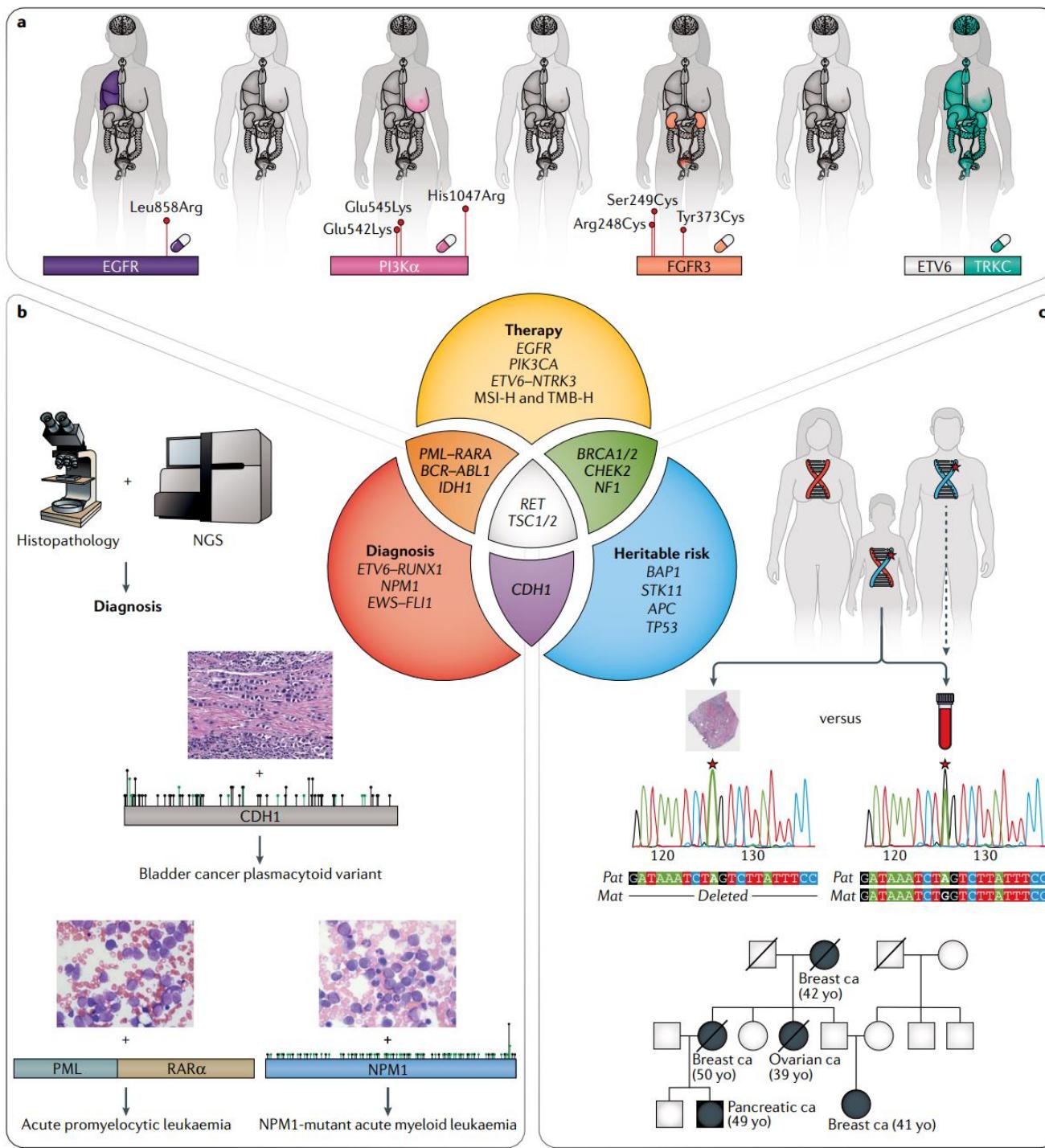


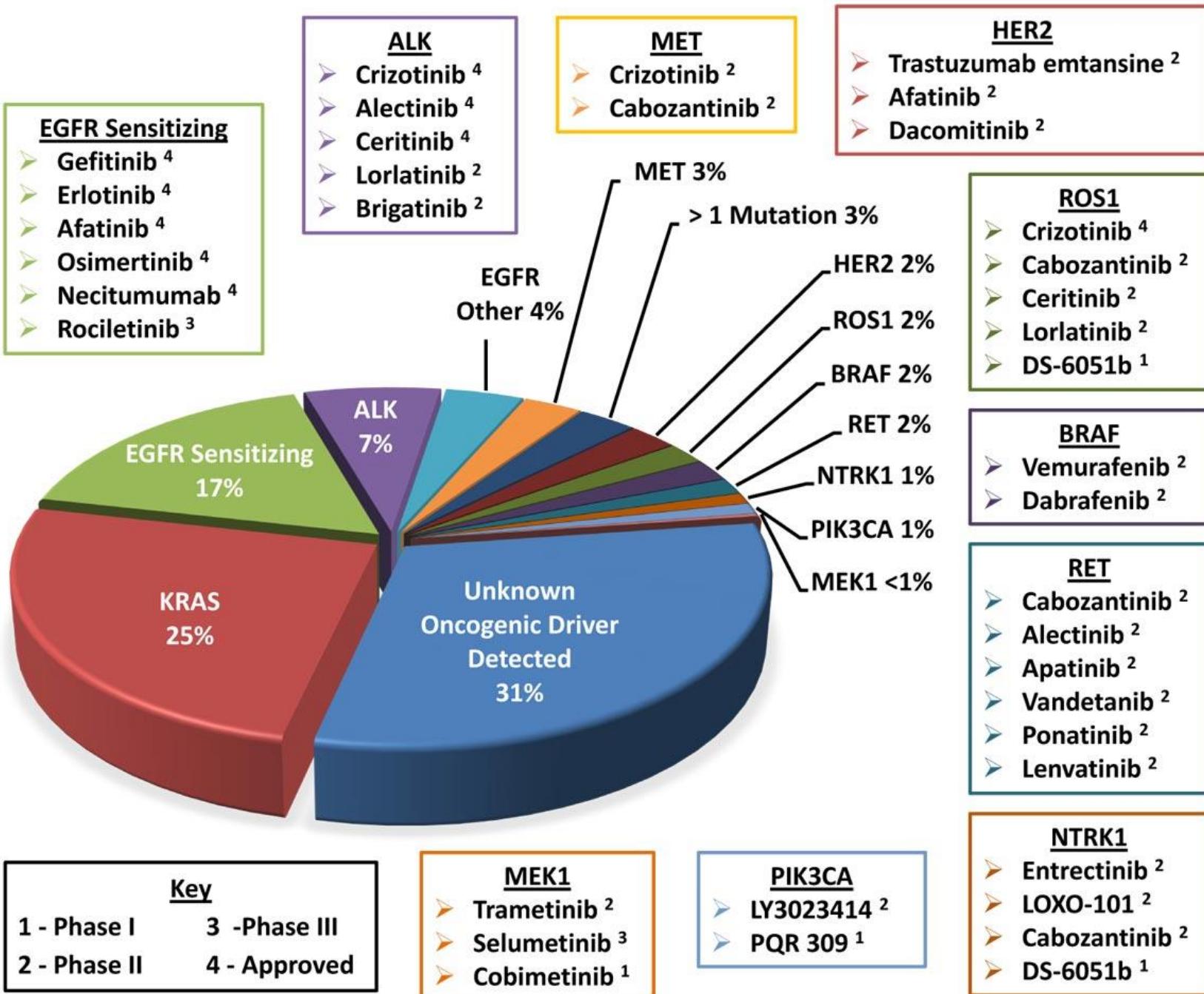


Molecular Pathology

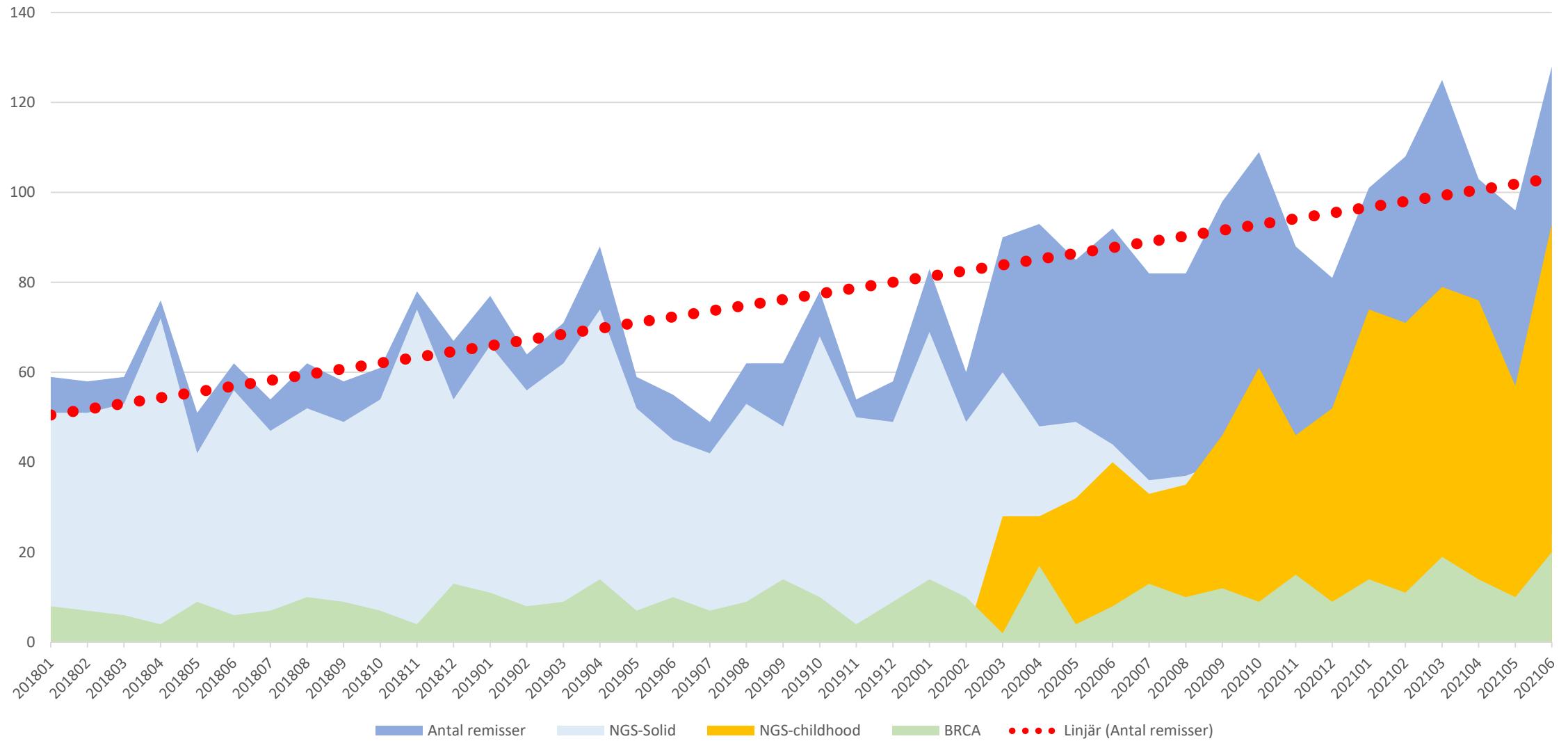
>4000 samples / year

- Diagnostic markers
- Therapy markers
- cfDNA
- Non-oncology tests
- NGS (panel 8 – 200 genes)
- Sanger sequencing
- Pyro sequencing
- Nanostring sequencing
- ddPCR
- qRT-PCR
- Fragment analysis



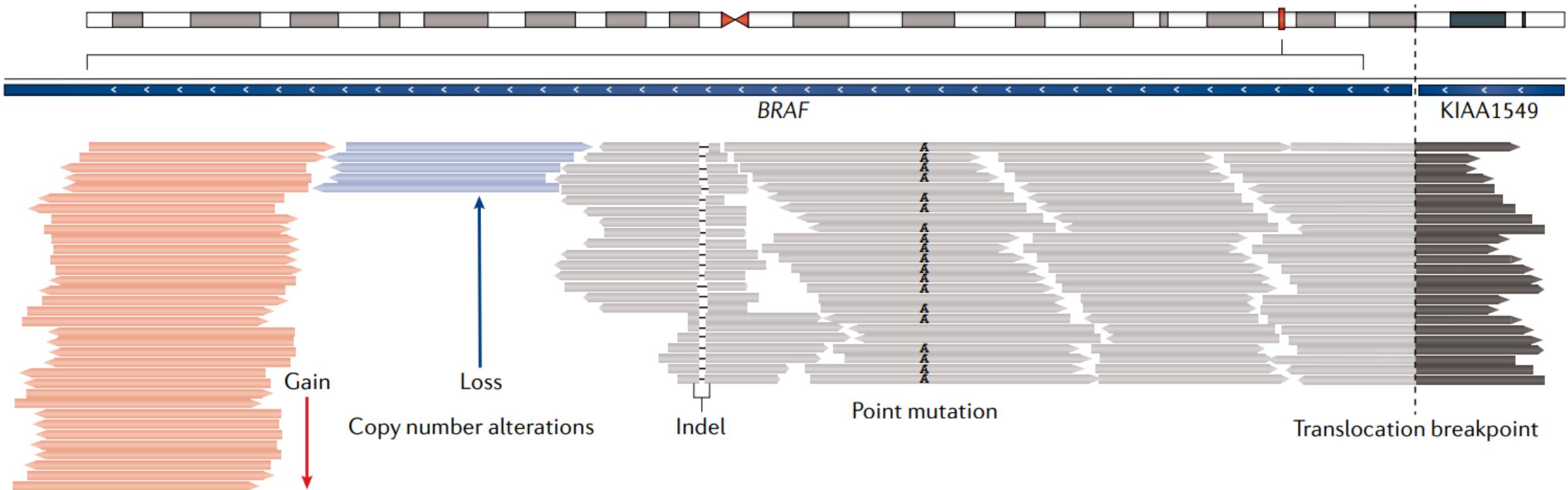


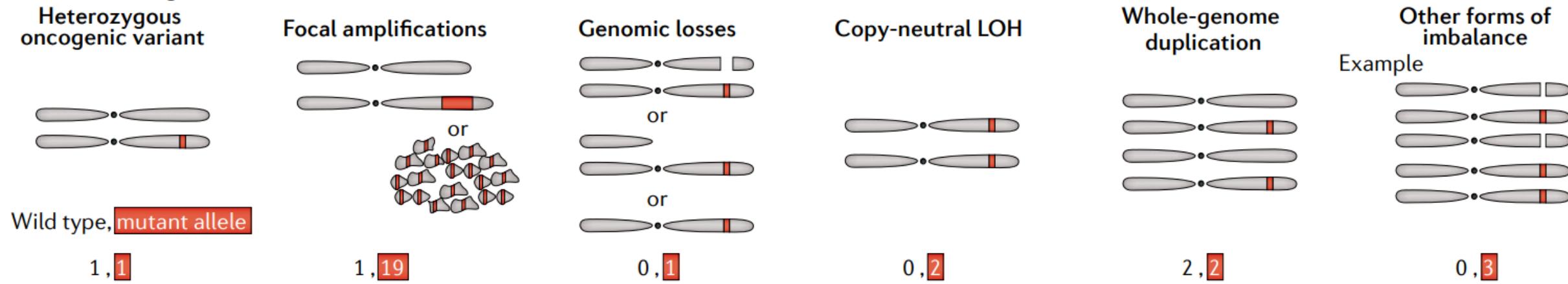
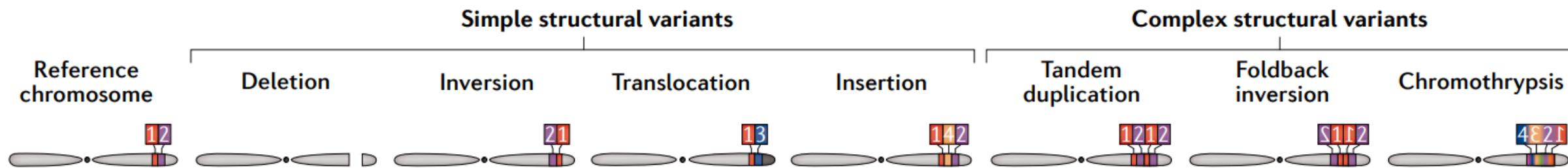
NGS/Månad MCD Solna



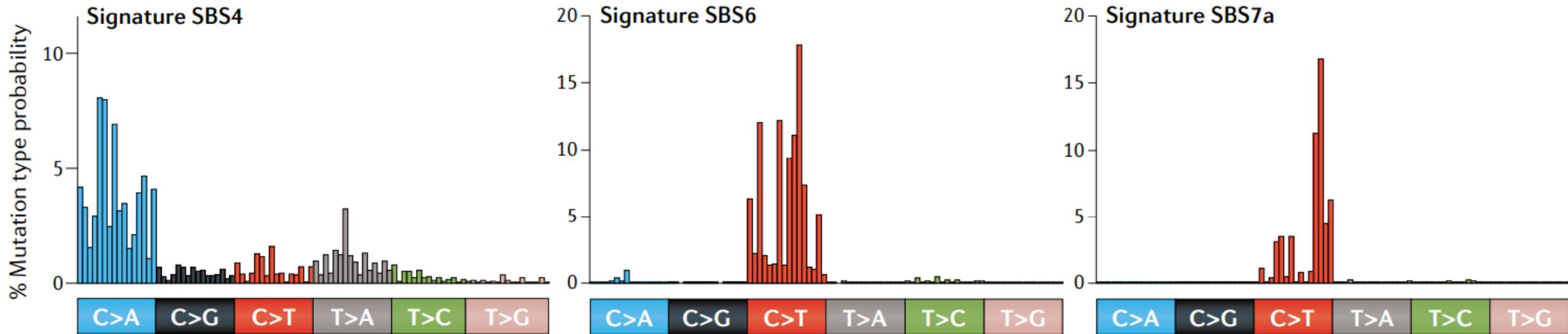
a Allele level

Reference sequence

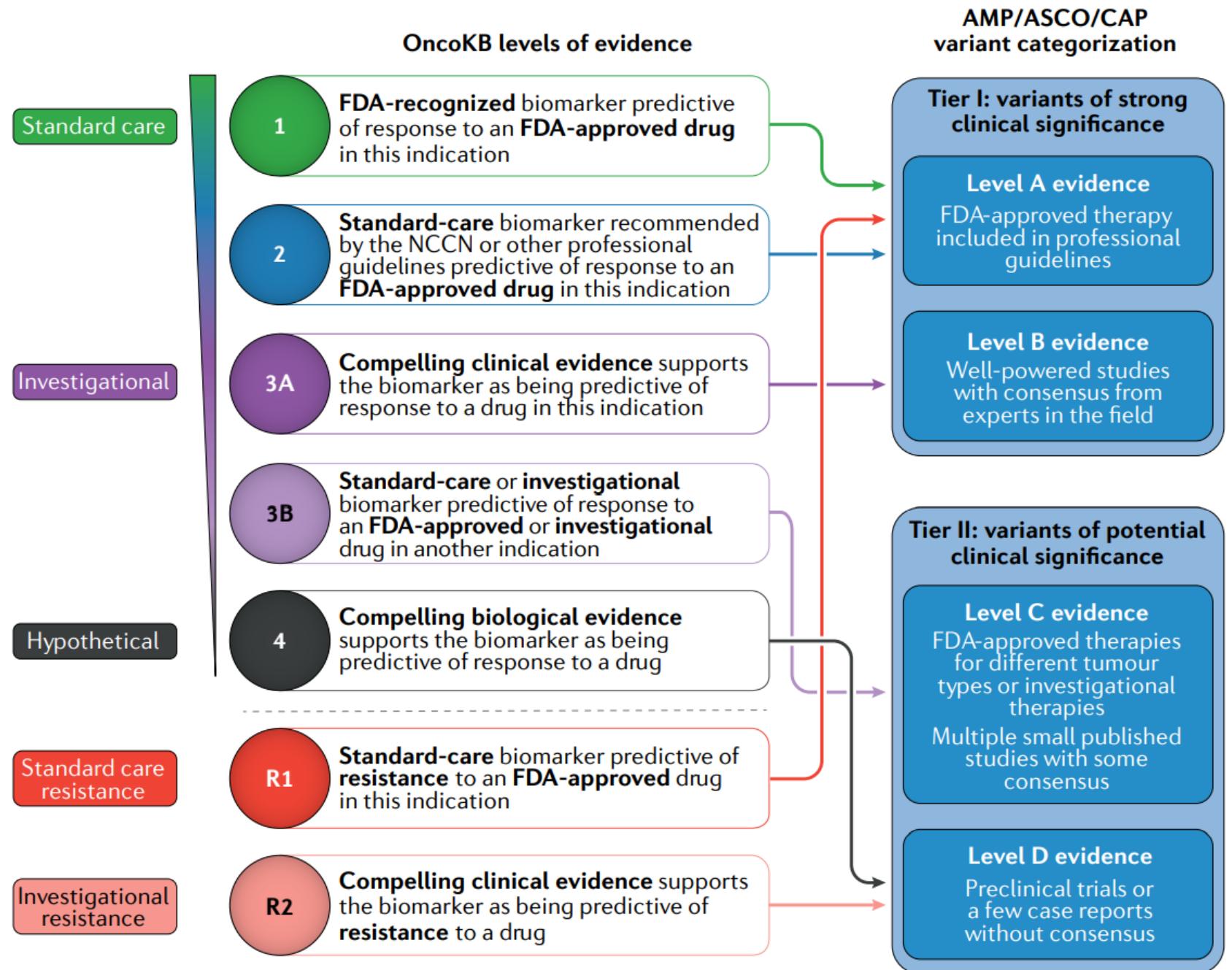


b Allelic configuration**c Structural variants**

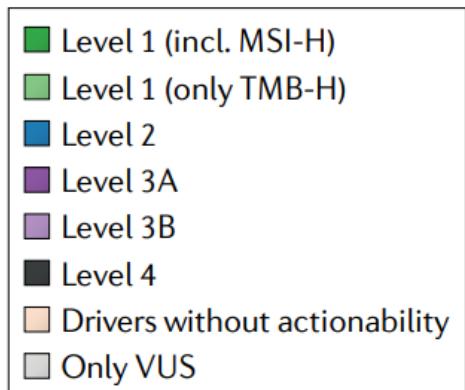
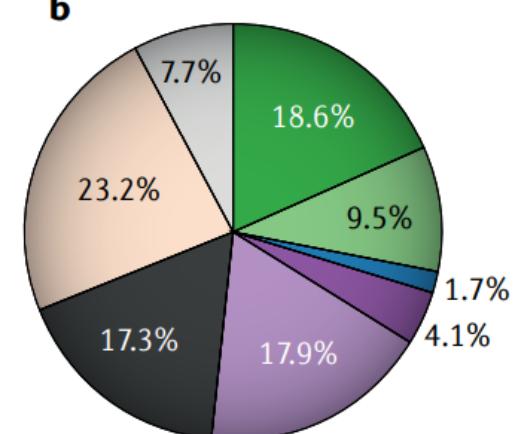
d Mutation signatures



a Mapping between the OncoKB levels of evidence and the AMP/ASCO/CAP consensus recommendation

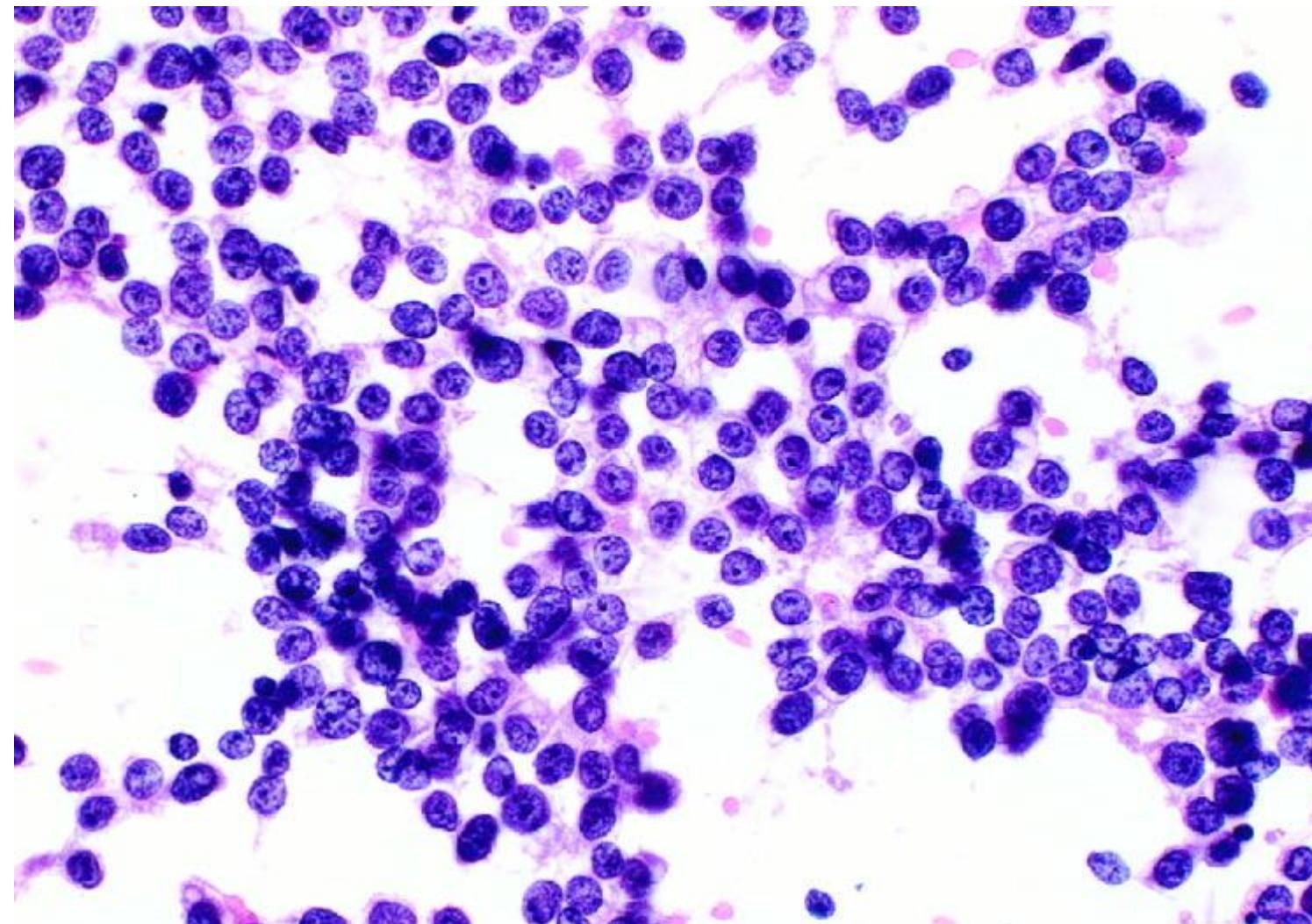


b



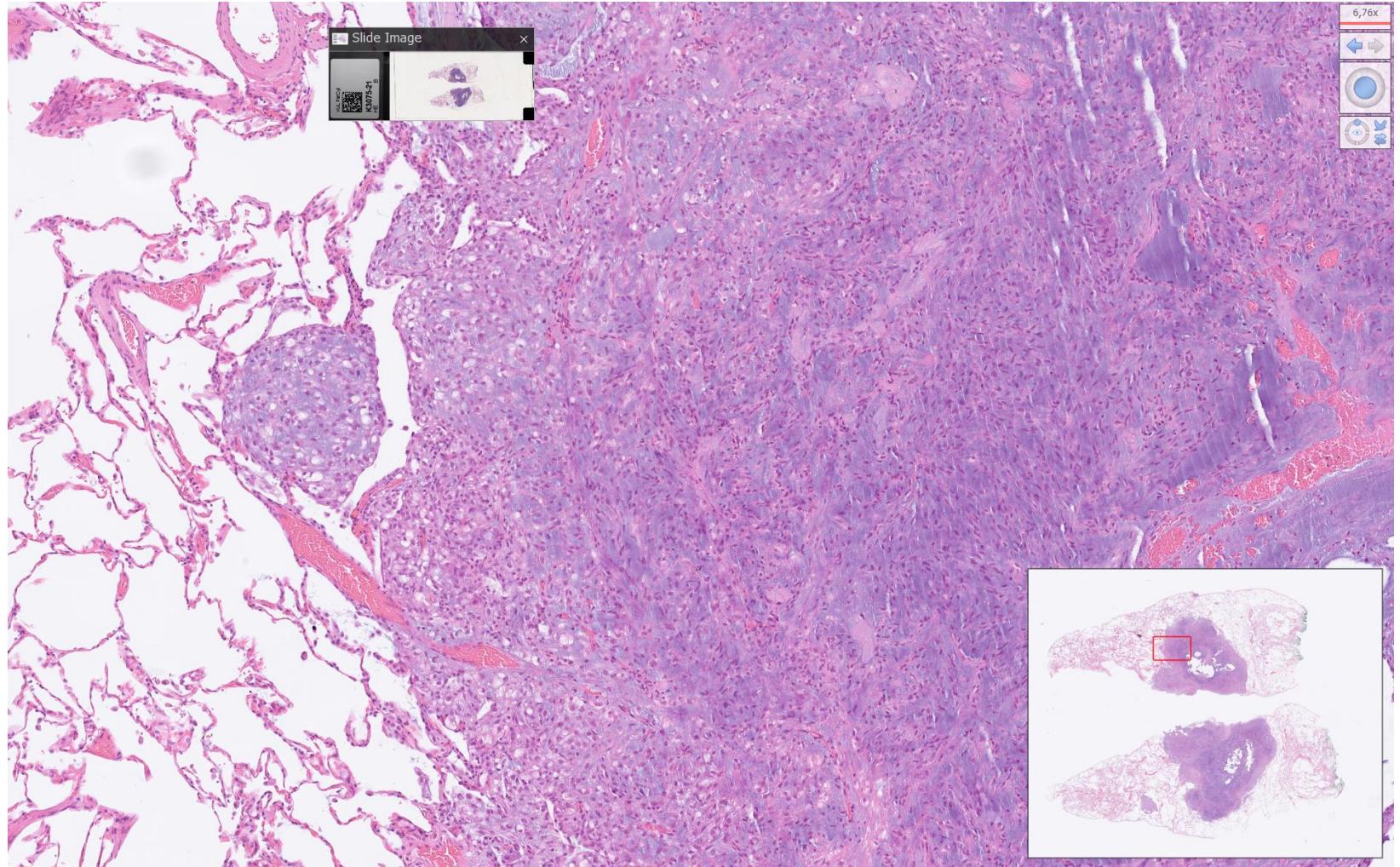
12 y.o. boy. Currently pain from the right femur, CT indicate a lytic lesion. Fine needle aspiration cytology

qRT-PCR: EWSR1 – FLI1



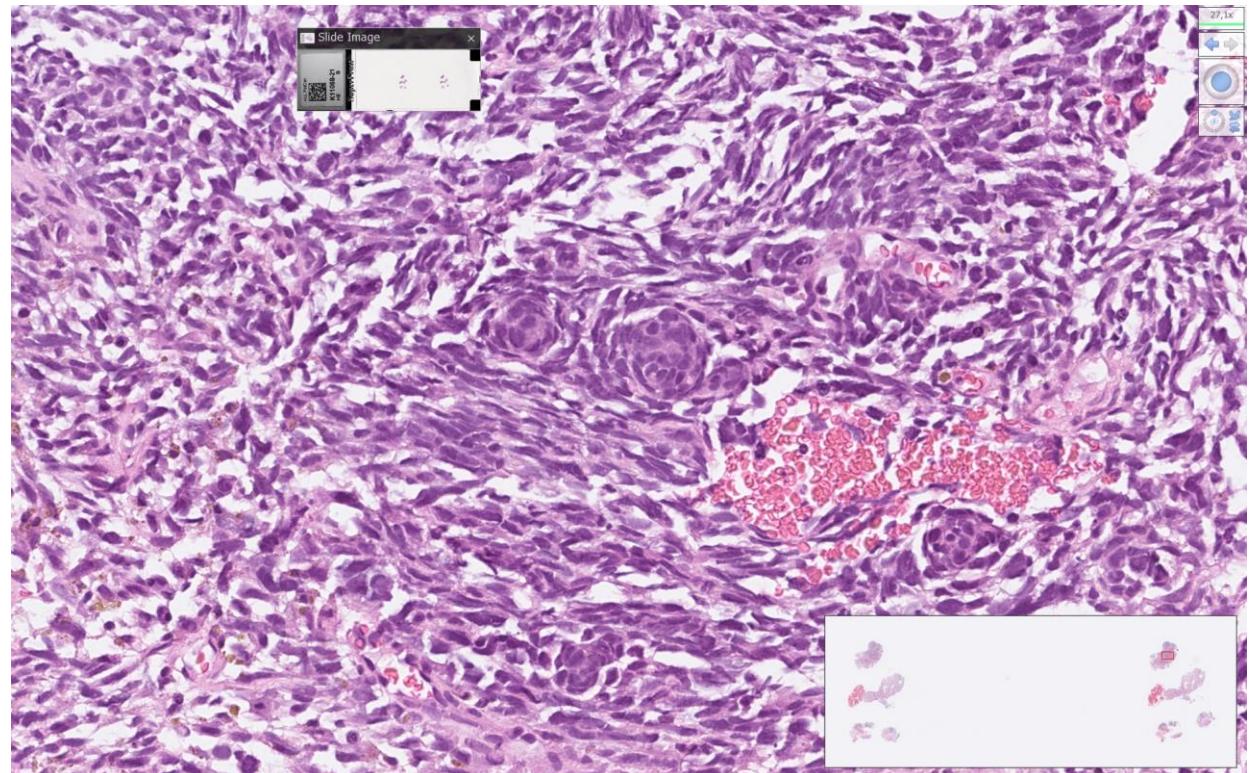
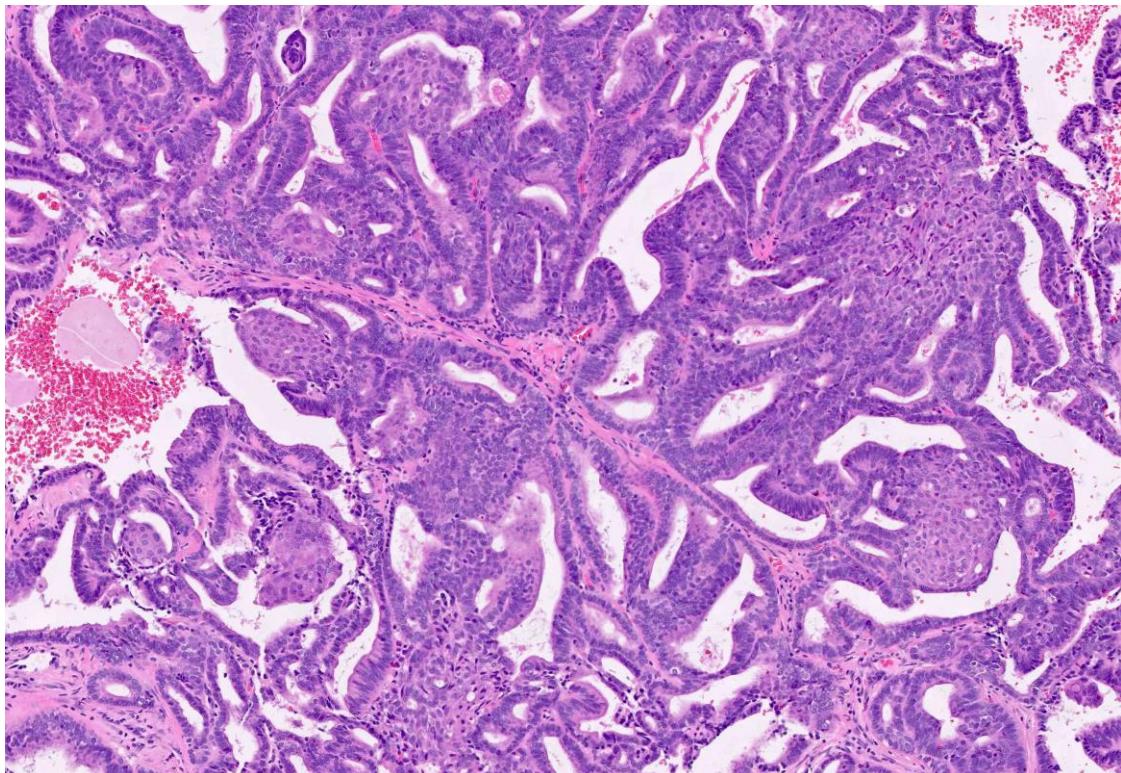
55 y.o. Male. B-cell lymphoma 2 years ago
in the ribs, treated with surgery and
chemo. Now multiple pulmonary nodules -
diagnostic operation.

NGS: EWSR1 - NR4A3



Woman with endometroid ovarian carcinoma,
low stage 1 year ago - tumor in complete
remission after chemotherapy. Now
presenting with a 6 cm abdominal tumor.

NGS: KRAS exon 2 (p.Gly12Val)



Molecular Pathology tomorrow



'The most perfidious way of **harming a cause** consists of defending it deliberately with faulty **arguments**.'

— Friedrich Nietzsche

Clinical cancer genomic profiling

Chakravarty et al.

- 92% of tumours harboured at least one oncogenic mutation
- 34% harboured at least one mutation classified as a predictive biomarker of response to an FDA-approved or investigational drug based on compelling clinical data (OncokB, levels 1–3A)
- Since 2017, there has been an approximately threefold increase from 9% to 30% in the fraction of tumours for which a disease-matched, standard-care predictive biomarker of response to an FDA-approved therapy would have been identified by tumour NGS, defined as OncokB levels 1 and 2

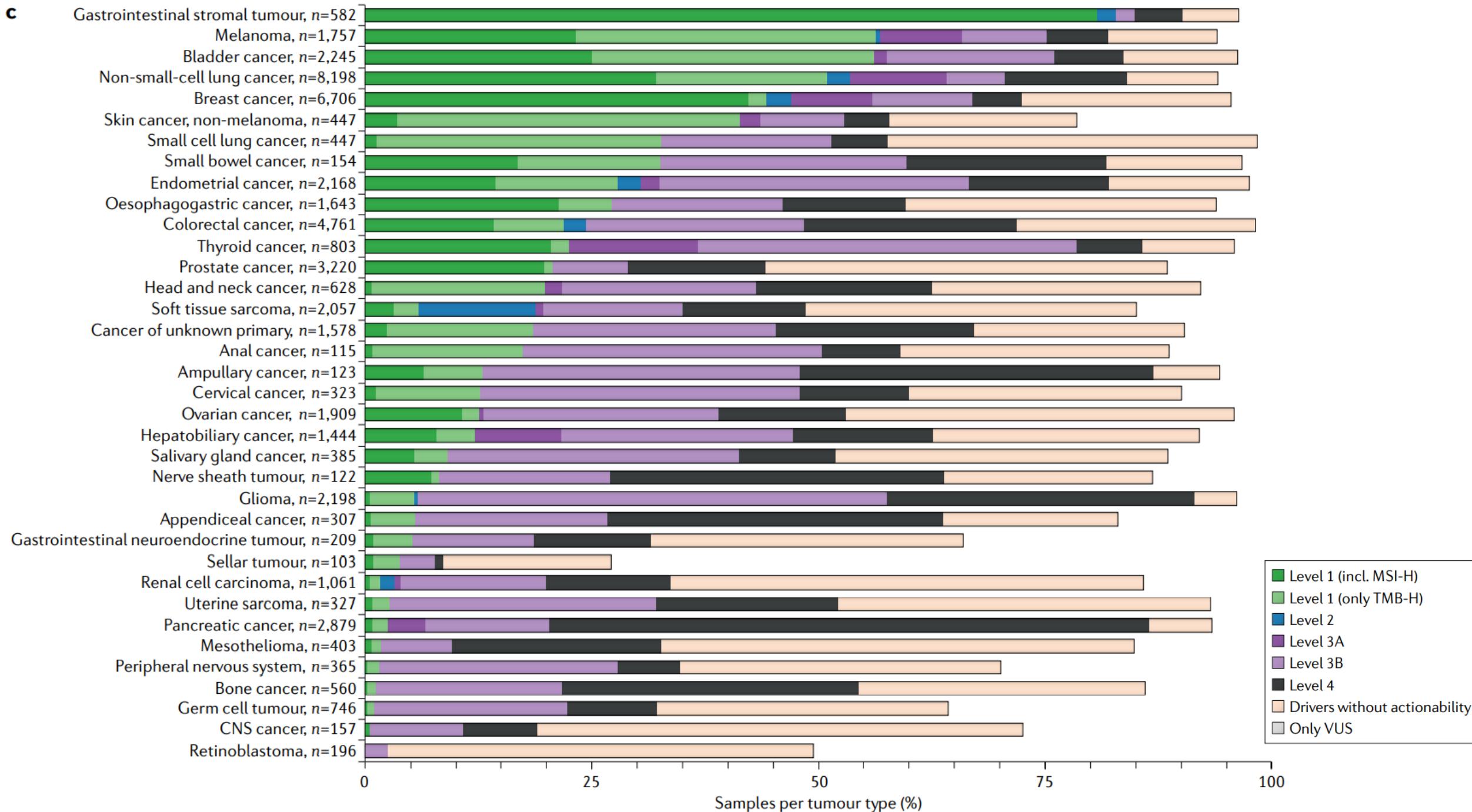
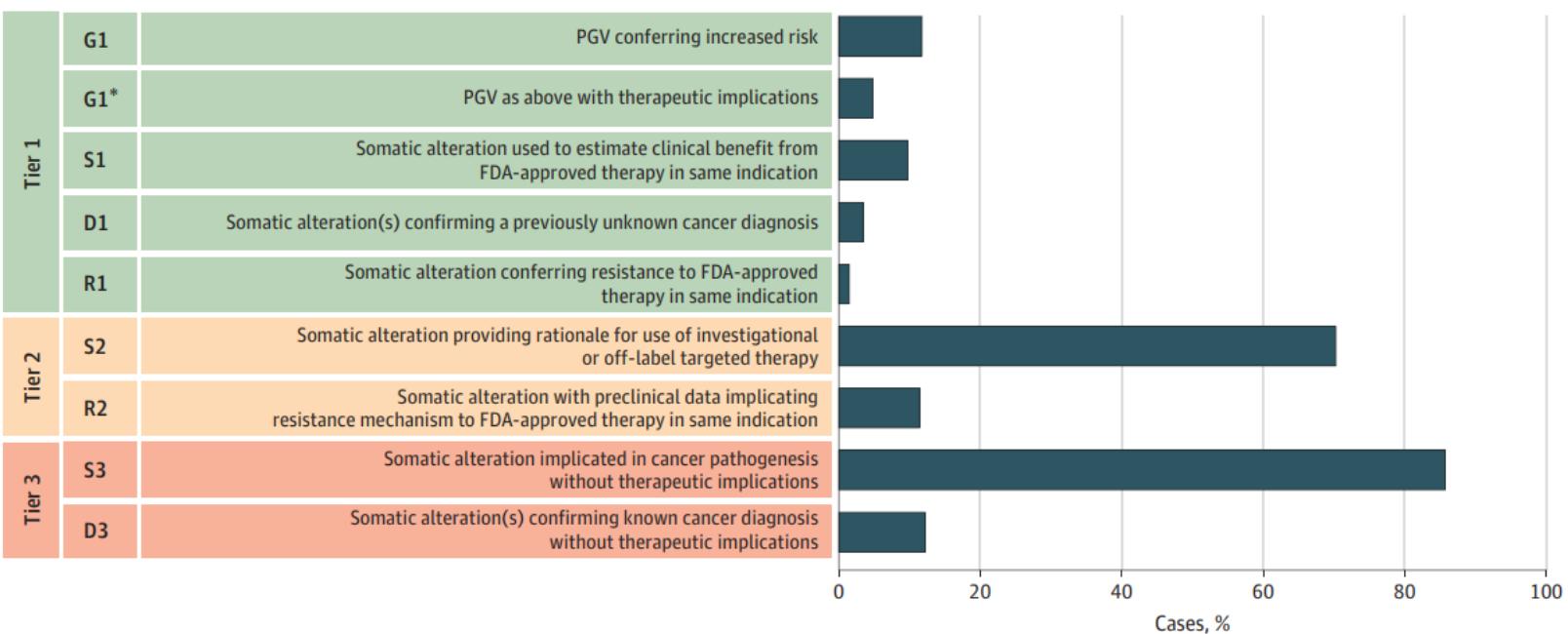
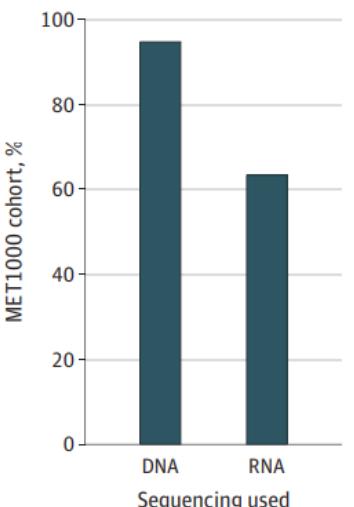
C

Figure 2. Clinical Tiering of Molecular Alterations Identified in Metastatic Cancer

A Clinical tiers



B Sequencing



C Mutations and events identified

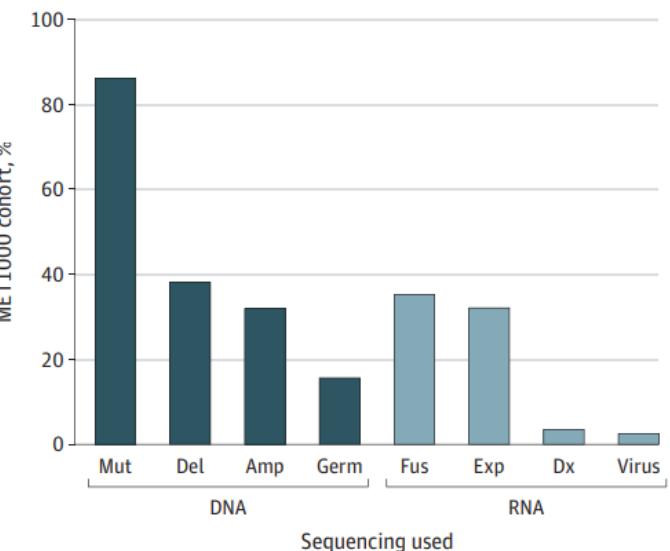
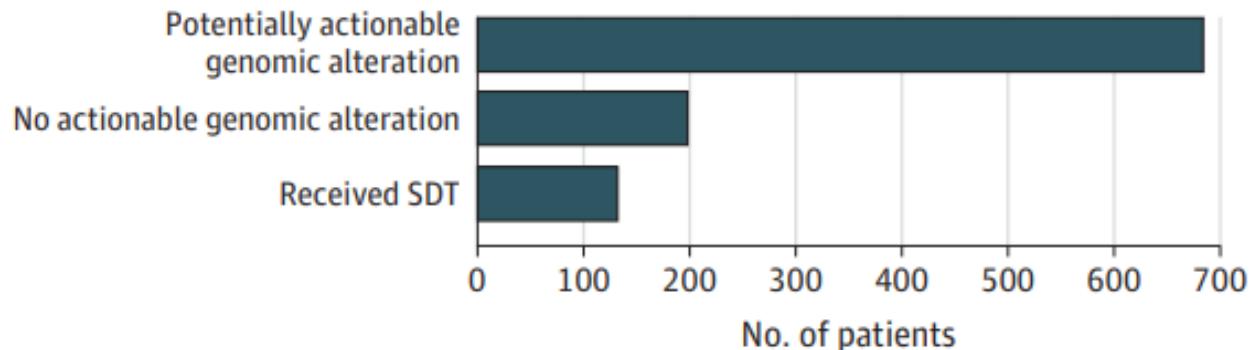
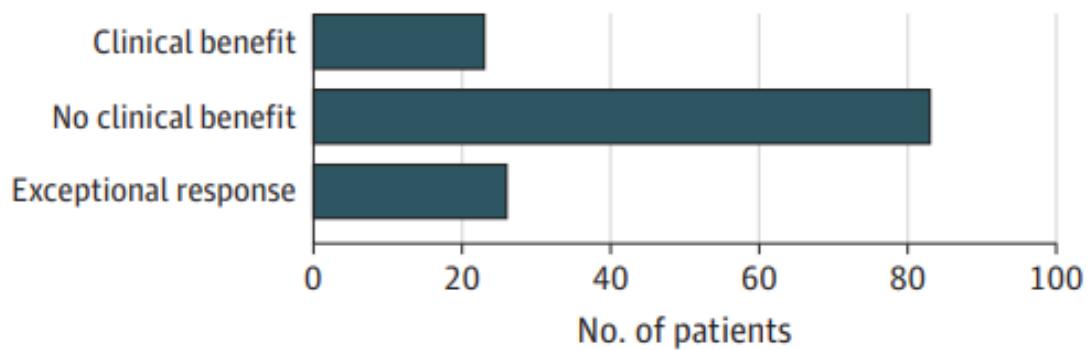


Figure 3. Patients Receiving Sequencing-Directed Therapy (SDT) in MET1000 Cohort and Exceptional Responses

A All patients



B Received SDT



Bar graphs depict proportion of patients in the MET1000 cohort ($n = 1015$) who received SDT and ultimately had clinical benefit or exceptional response to treatment.

Figure 4. Pathogenic Germline Variants (PGVs) Observed in the MET1000 Cohort

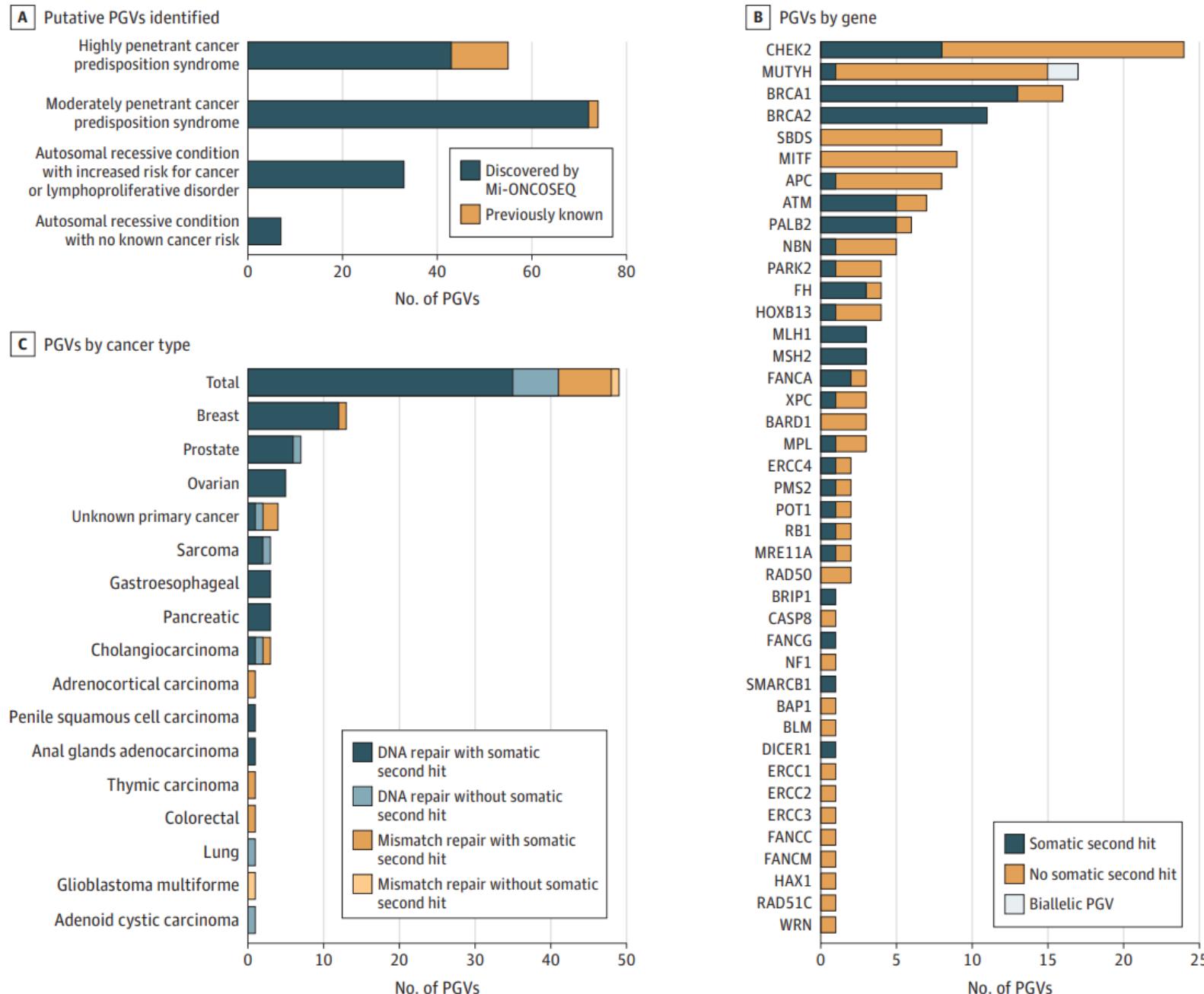
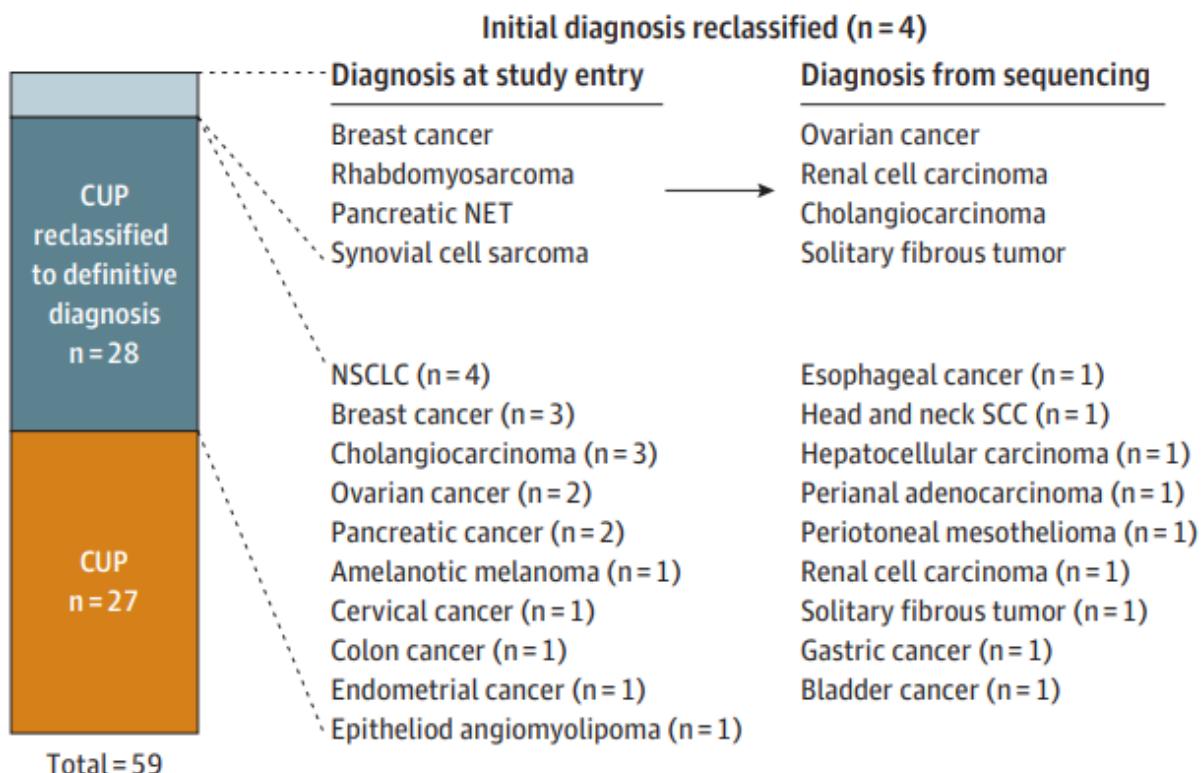
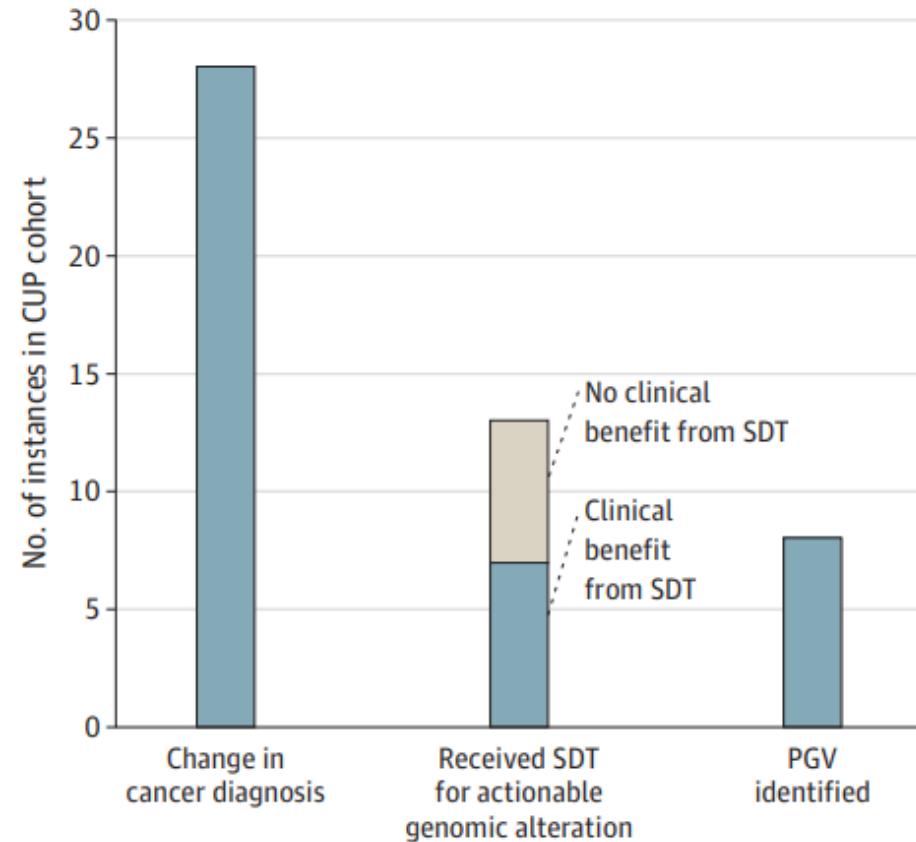


Figure 5. Cancers of Unknown Primary Origin in MET1000 Cohort

A Classification of diagnoses

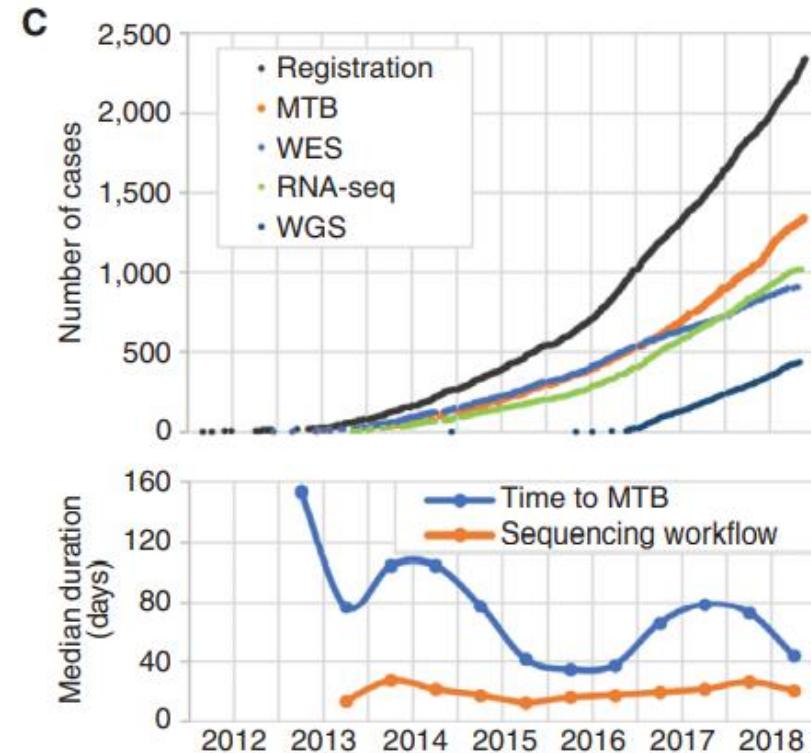
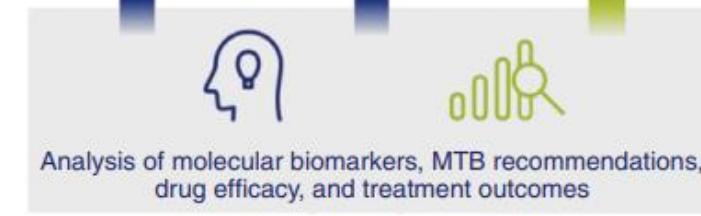
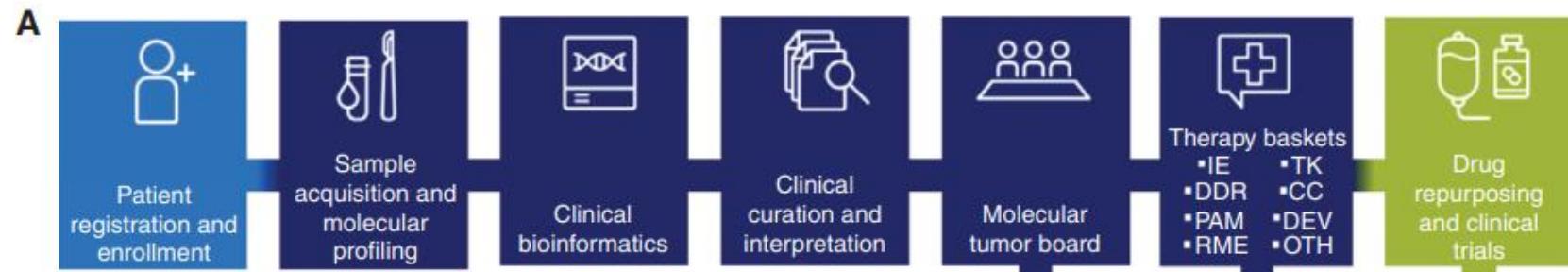


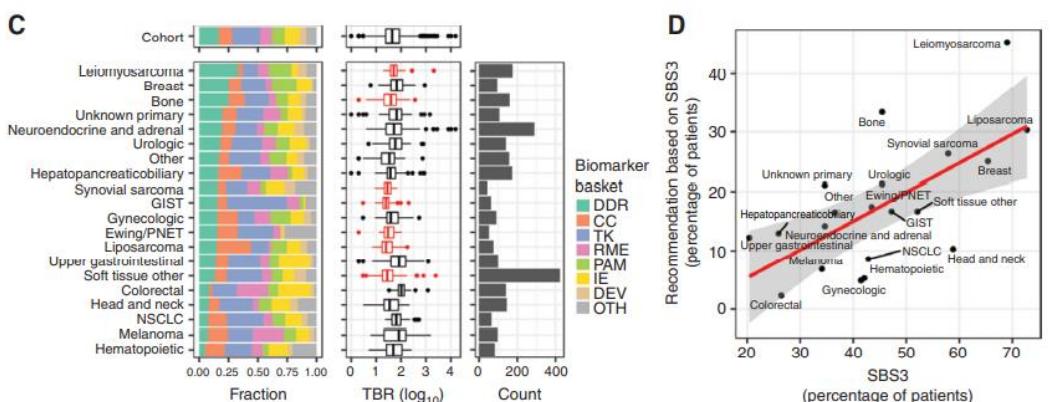
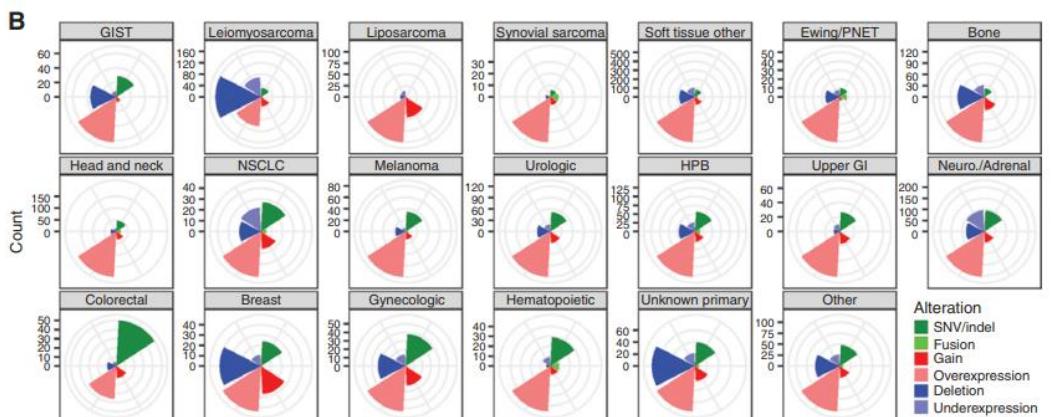
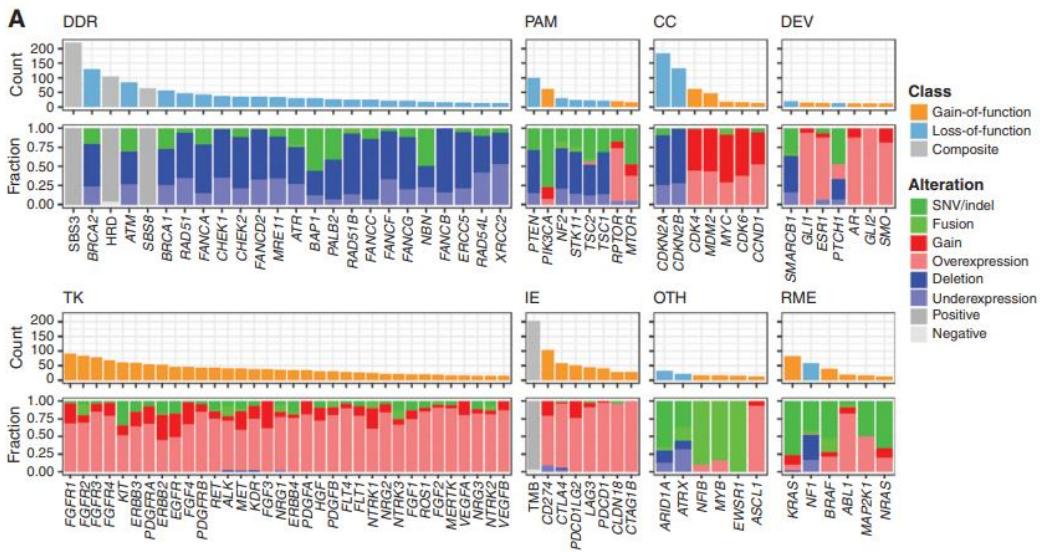
B Sequencing results

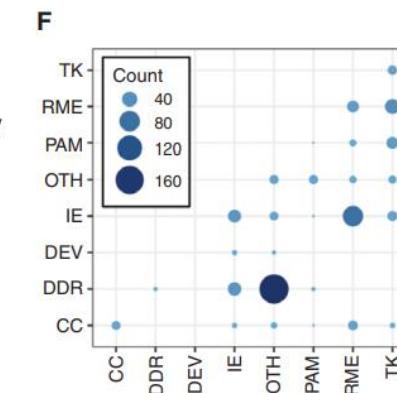
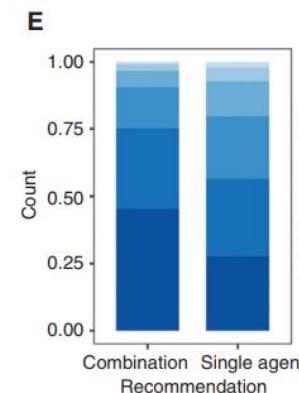
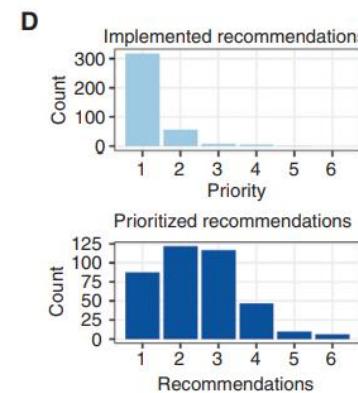
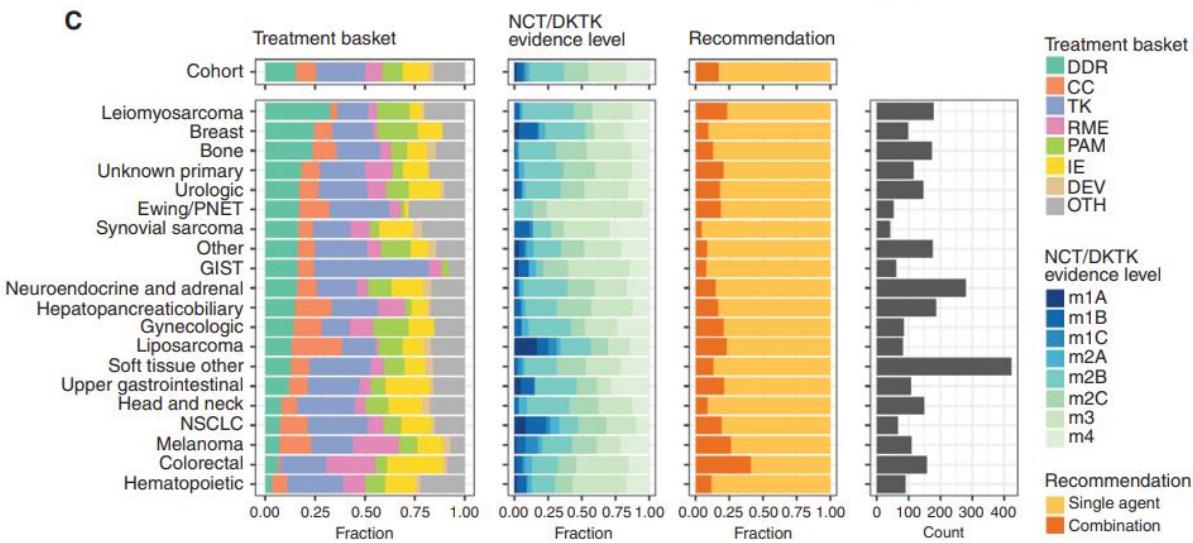
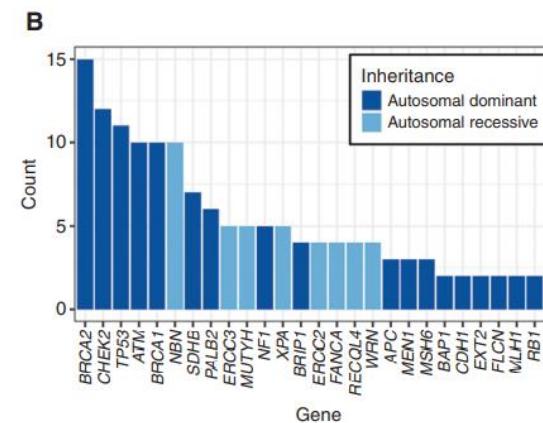
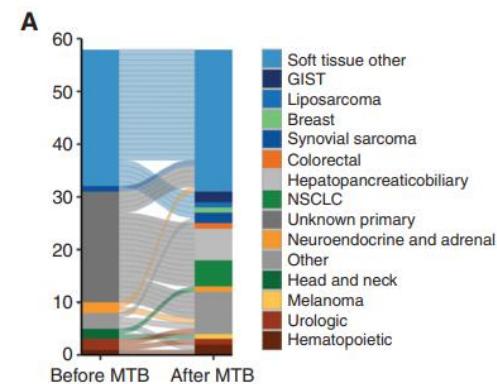


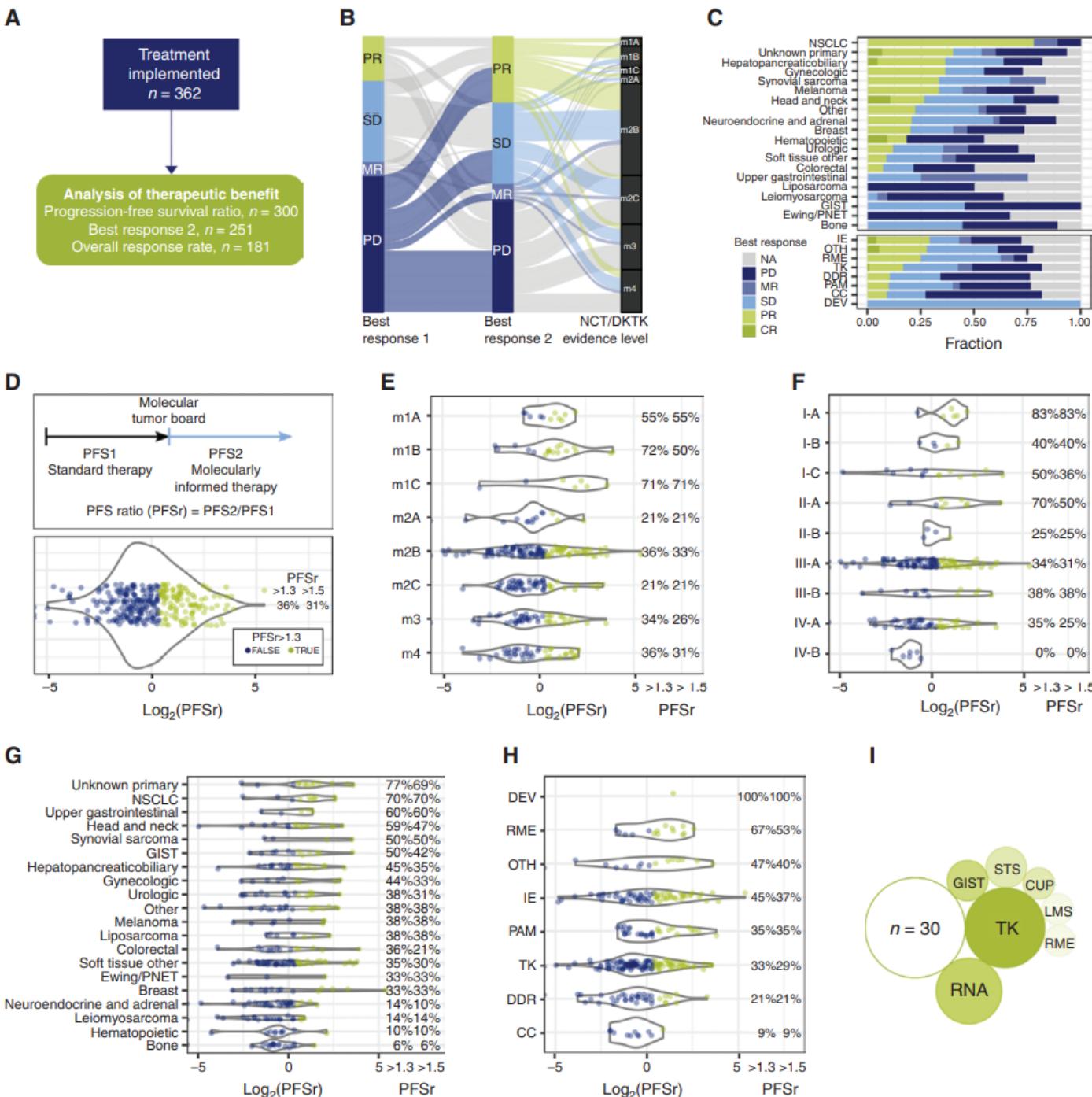
A, Among 55 cases of cancer of unknown primary (CUP) origin sequenced, 28 (50.9%) were reclassified to a definitive diagnosis through RNA sequencing tissue of origin predictor. An additional 4 cases in the MET1000 cohort with presumed known diagnoses at study entry were also reclassified. B, Sequencing results were highly informative for patients with CUP, with a total of 34 of 55 CUP cases (61.8%) having at least 1 of the following: (1) a change in cancer

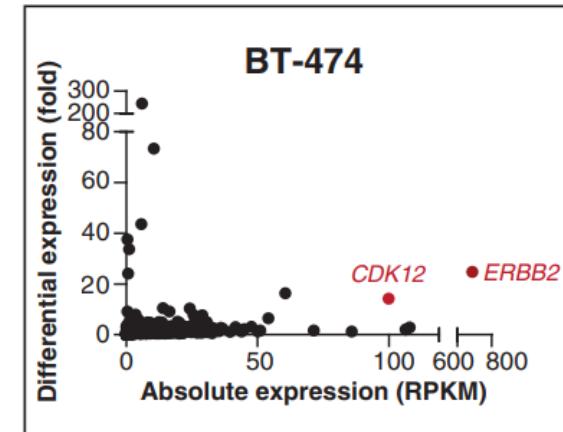
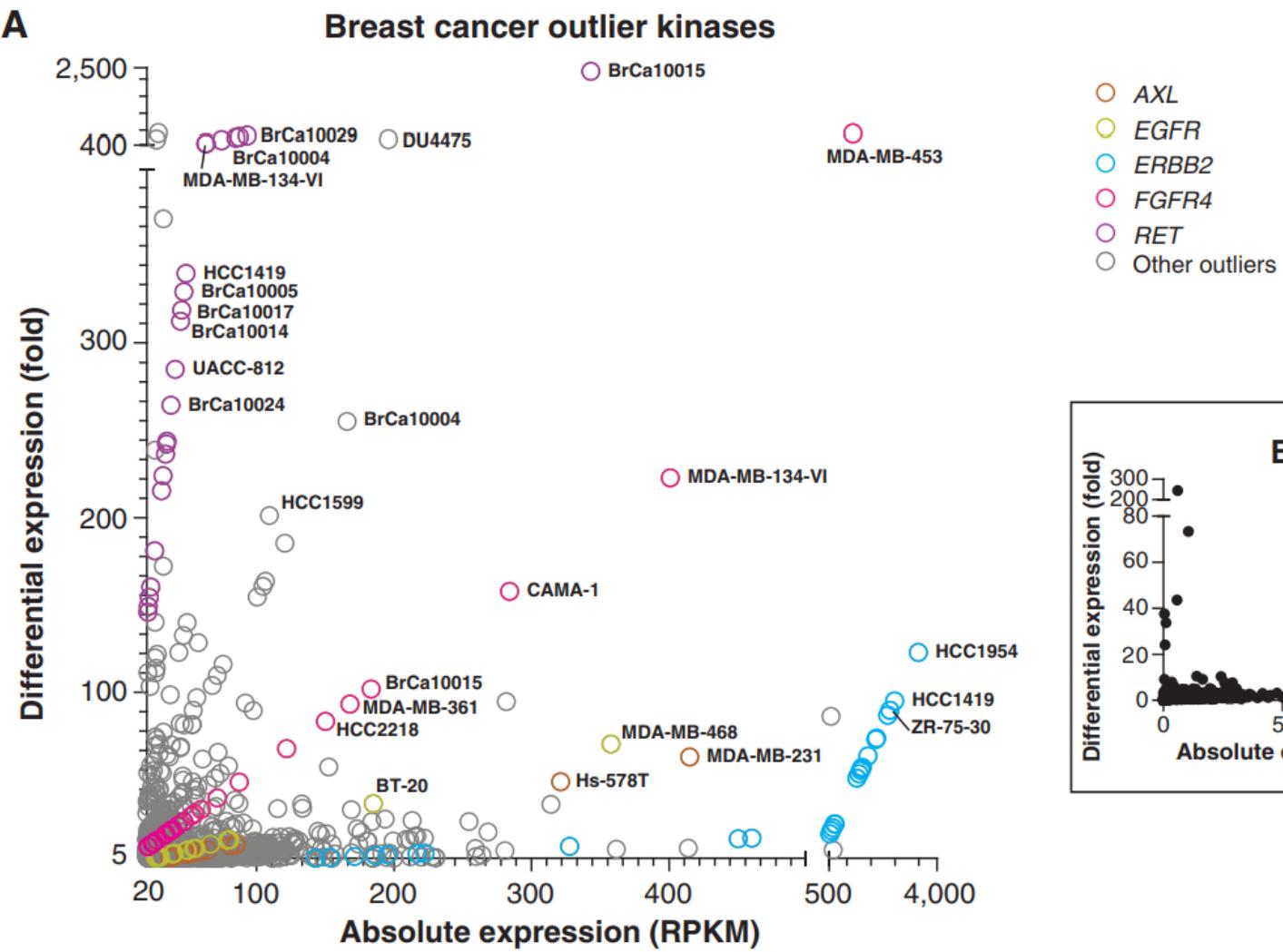
diagnosis (28 patients [50.9%]), (2) receipt of sequencing-directed therapy (SDT) (13 patients [23.6%]), or (3) identification of a pathogenic germline variant (PGV) conferring increased cancer risk (8 patients [14.5%]). NET indicates neuroendocrine tumor; NSCLC, non-small cell lung cancer; and SCC, squamous cell carcinoma.









A

Trends

- Reflex NGS (small panels) vs. comprehensive tests (palliative setting / negative tests)
- Expand from SNV mutational analysis (mutational signatures, fusion genes, CNV etc.)
- Oncogenetics
- Basket trials



AWESOMENESS

When I Get Sad, I Stop Being Sad and Be Awesome Instead.