

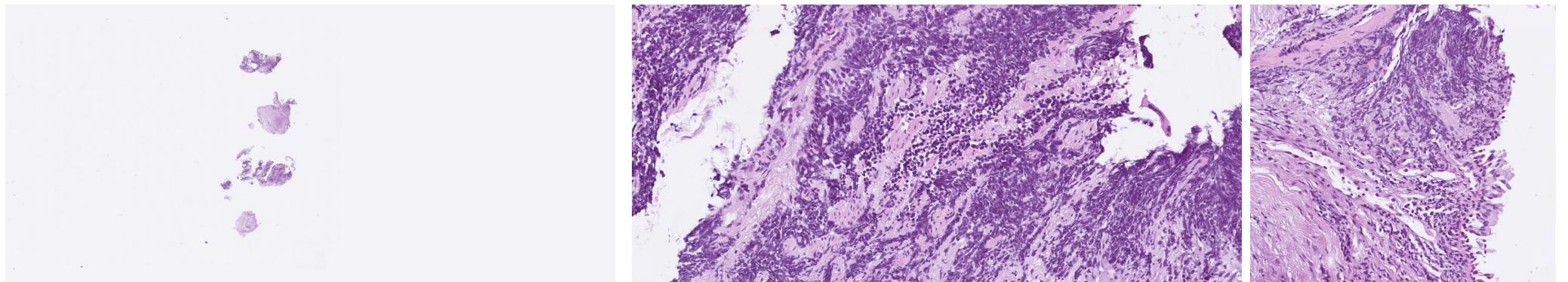
# Genomic profiling of solid tumors – what is the clinical impact?

**Felix Haglund de Flon**

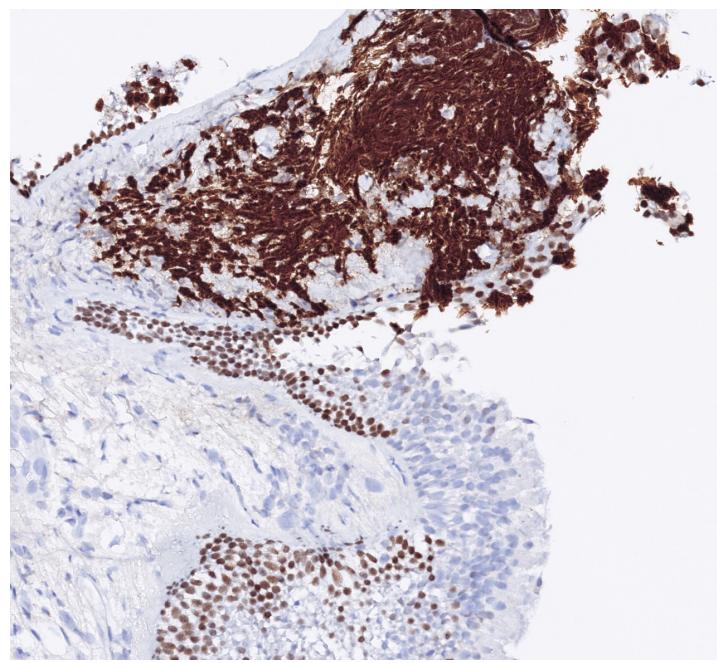
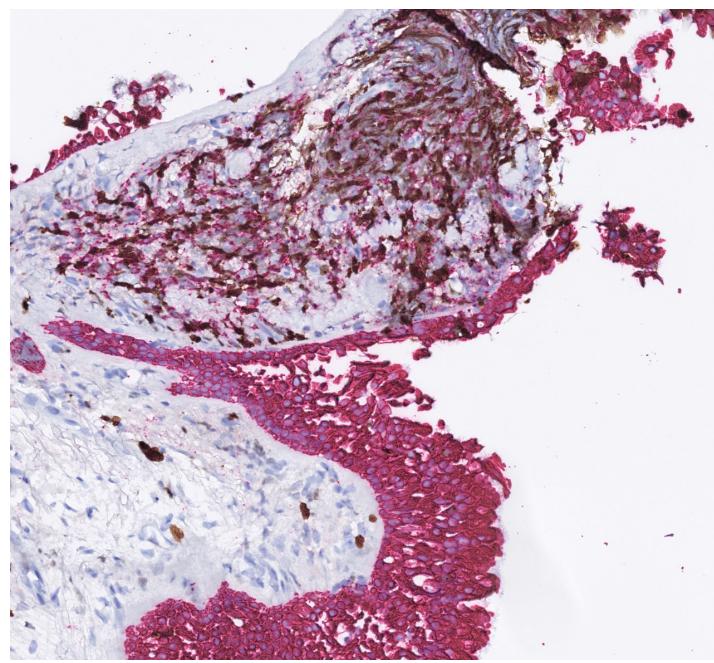
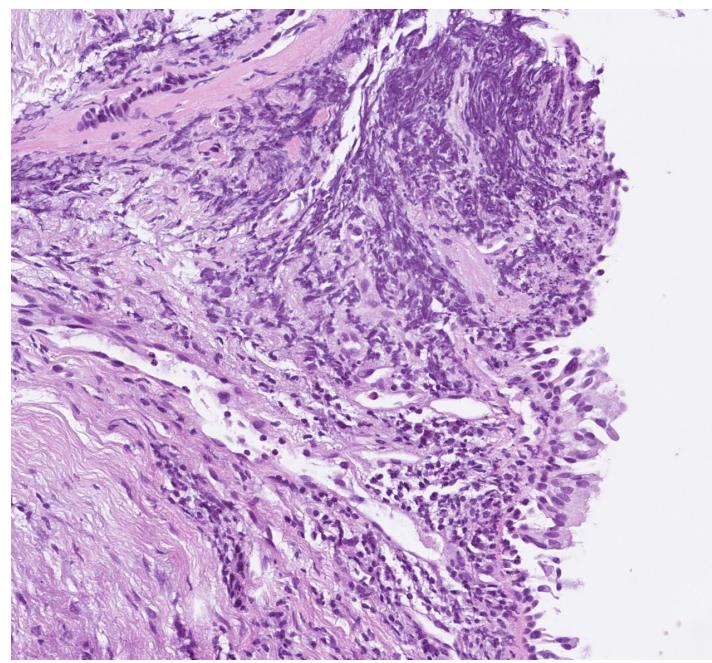
Associate Professor, Dept. Oncology-Pathology, KI

What has molecular pathology ever done for us?

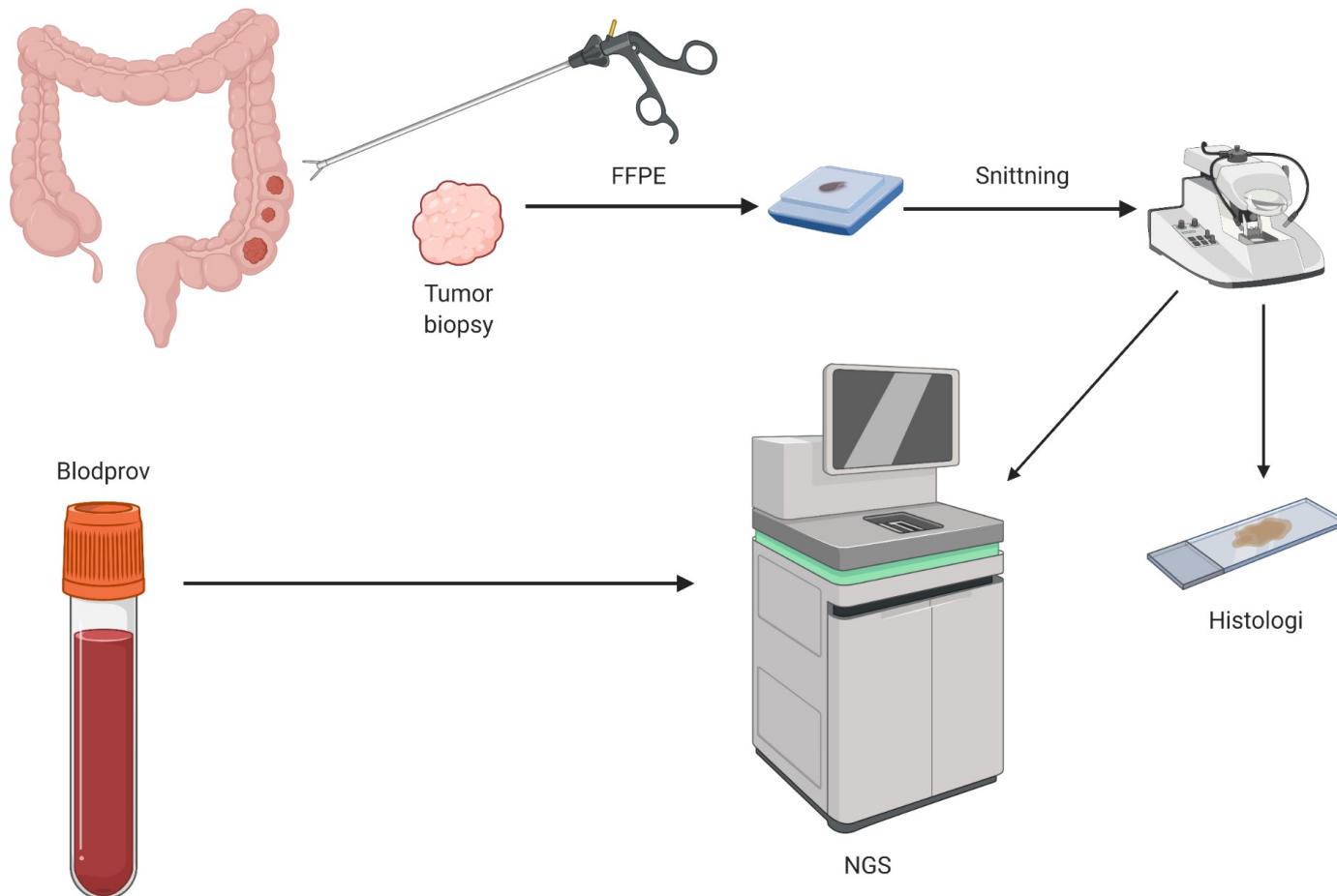




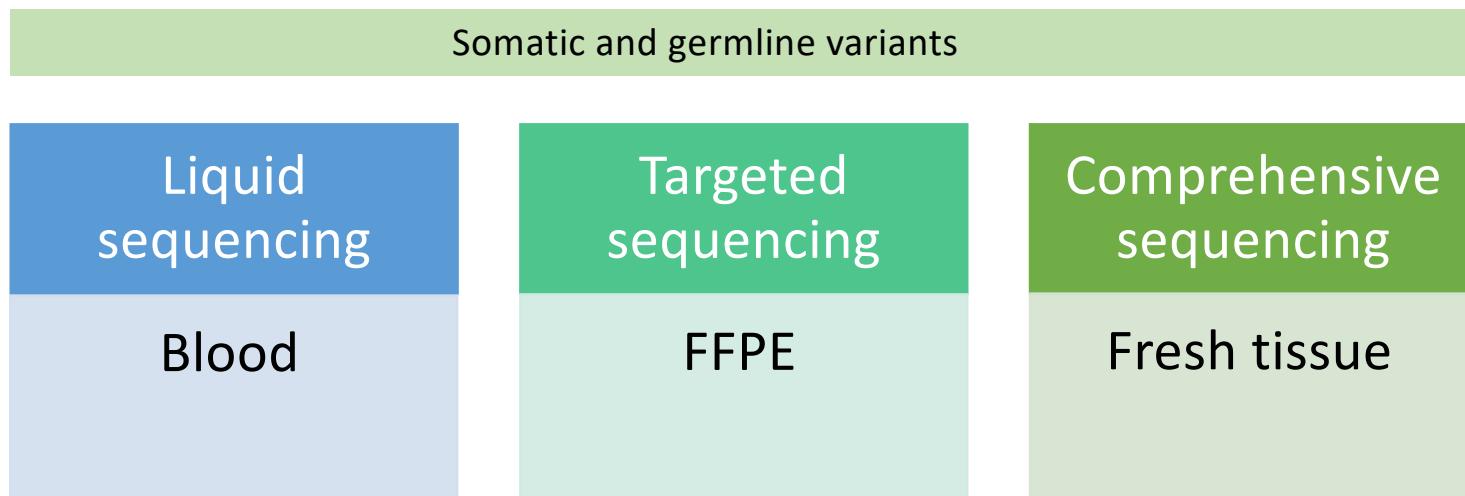
TP53 mutation (VAF 22%) – diagnosis?



# Clinical implementation of genomic profiling



# Genomic profiling of cancer patients

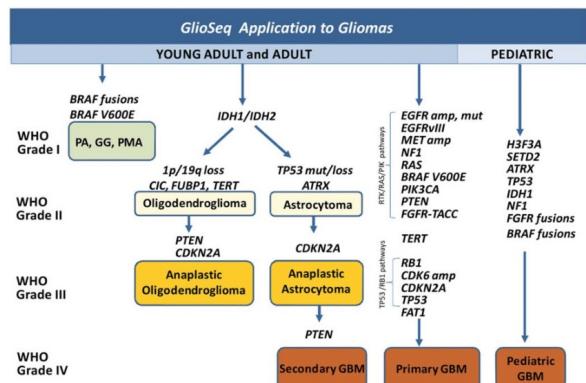


# Metodval?

|  | Purity  |         |         |         |         |                 |
|--|---------|---------|---------|---------|---------|-----------------|
|  | 100%    | 50%     | 20%     | 10%     | 1%      | 0.1%            |
| Required coverage                          | 100x    | 100x    | 500x    | >1000x  | >2000x  | >5000x          |
| Cost with WGS                              | € 5 000 | € 5 000 | -       | -       | -       | -               |
| Cost with targeted sequencing              | € 1 500 | € 1 500 | € 1 500 | € 1 500 | € 1 500 | -               |
| Minimal target and tailored bioinformatics | -       | -       | -       | -       | -       | €1 500 - €2 000 |

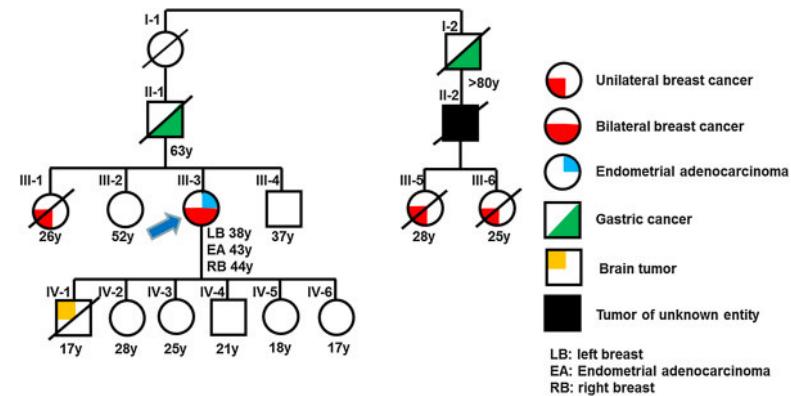
# Tumor genome

## Tumor classification

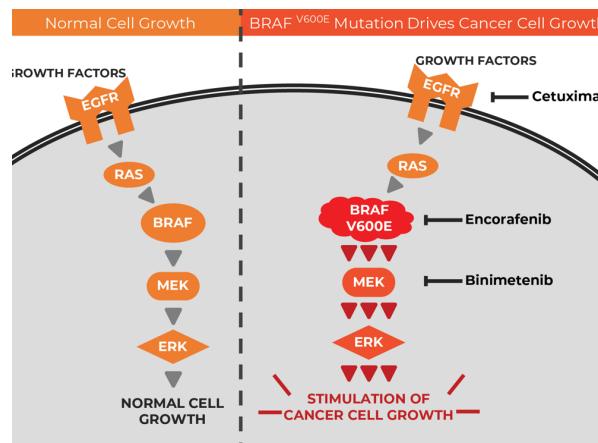


# Germline genome

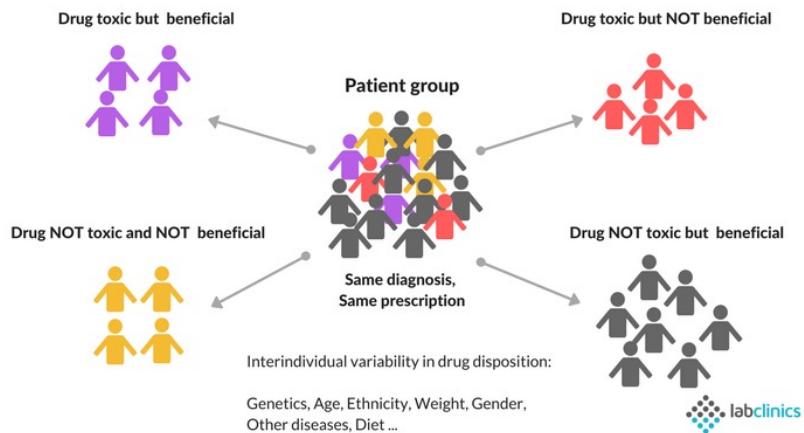
## Oncogenetics

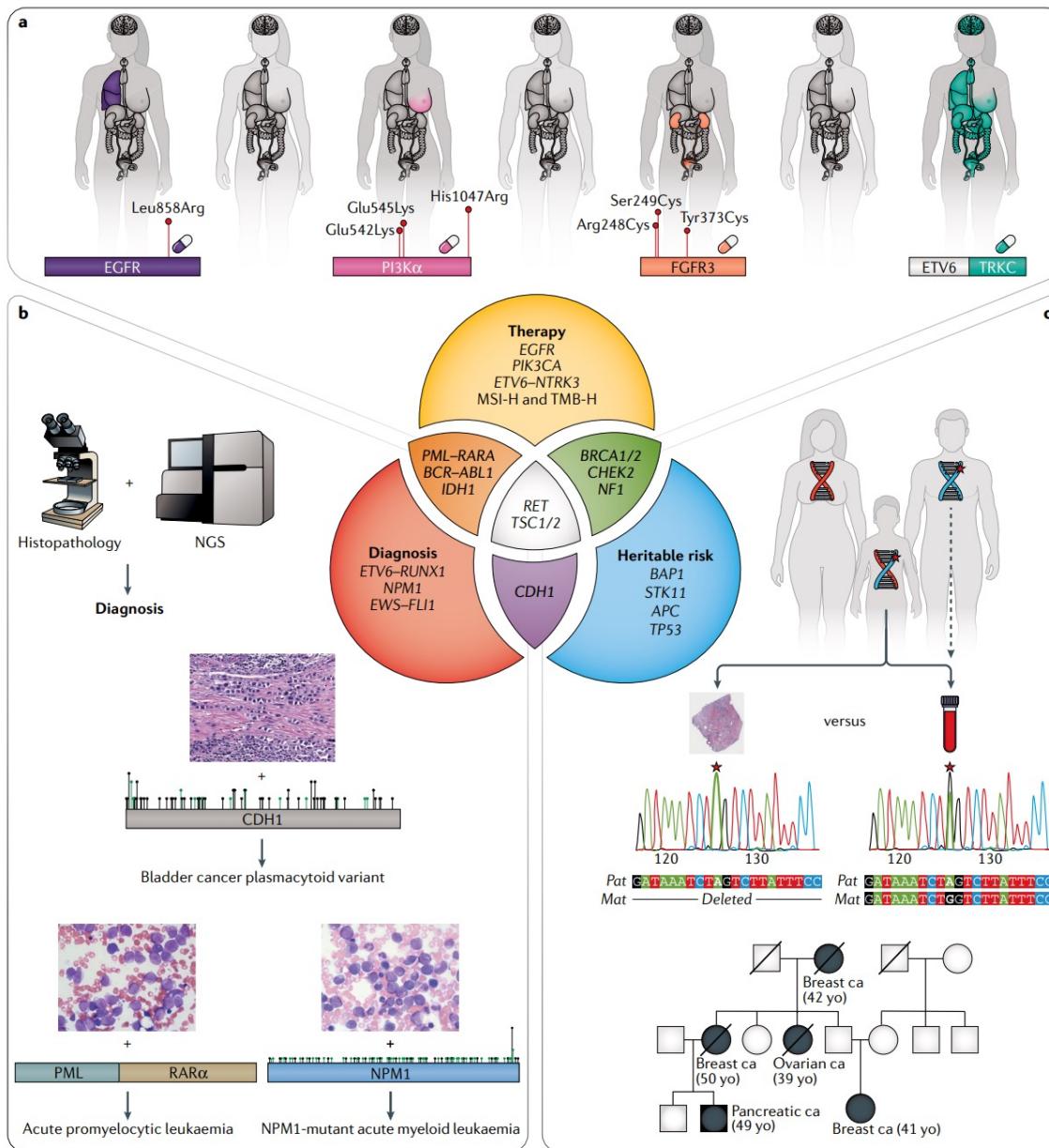


# Pharmacogenomics

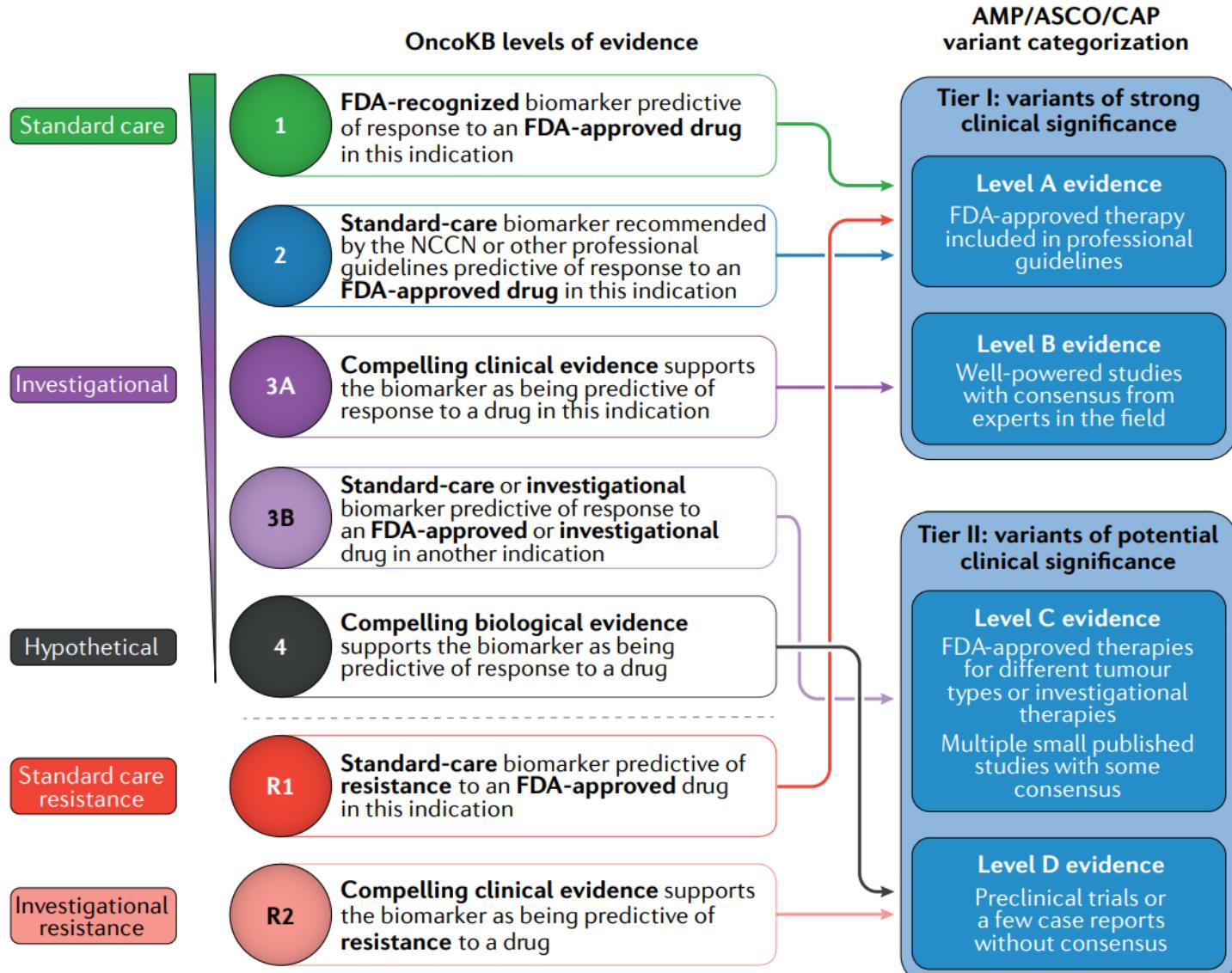


# Pharmacogenetics

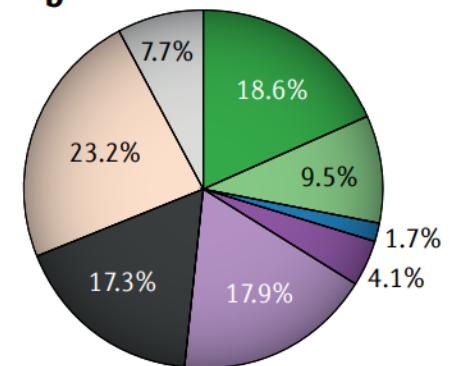




**a Mapping between the OncoKB levels of evidence and the AMP/ASCO/CAP consensus recommendation**

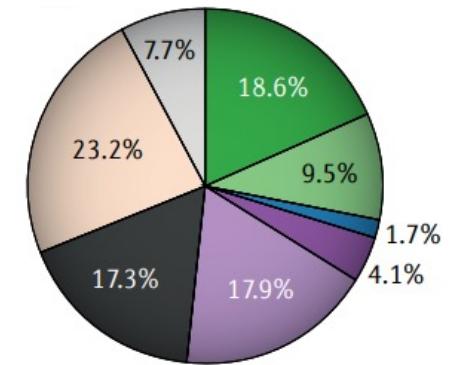


**b**



- Level 1 (incl. MSI-H)
- Level 1 (only TMB-H)
- Level 2
- Level 3A
- Level 3B
- Level 4
- Drivers without actionability
- Only VUS

| Therapeutic Levels                                 | Diagnostic Levels                             | Prognostic Levels                                 | FDA Levels  |
|--|---|---|---|
| ① Level 1<br>FDA-approved drugs<br><b>43 Genes</b> | ② Level 2<br>Standard care<br><b>24 Genes</b> | ③ Level 3<br>Clinical evidence<br><b>27 Genes</b> | ④ Level 4<br>Biological evidence<br><b>25 Genes</b> |
|  |   |   |   |
| ⑤ Level R1/R2<br>Resistance<br><b>11 Genes</b>     |   |   |   |

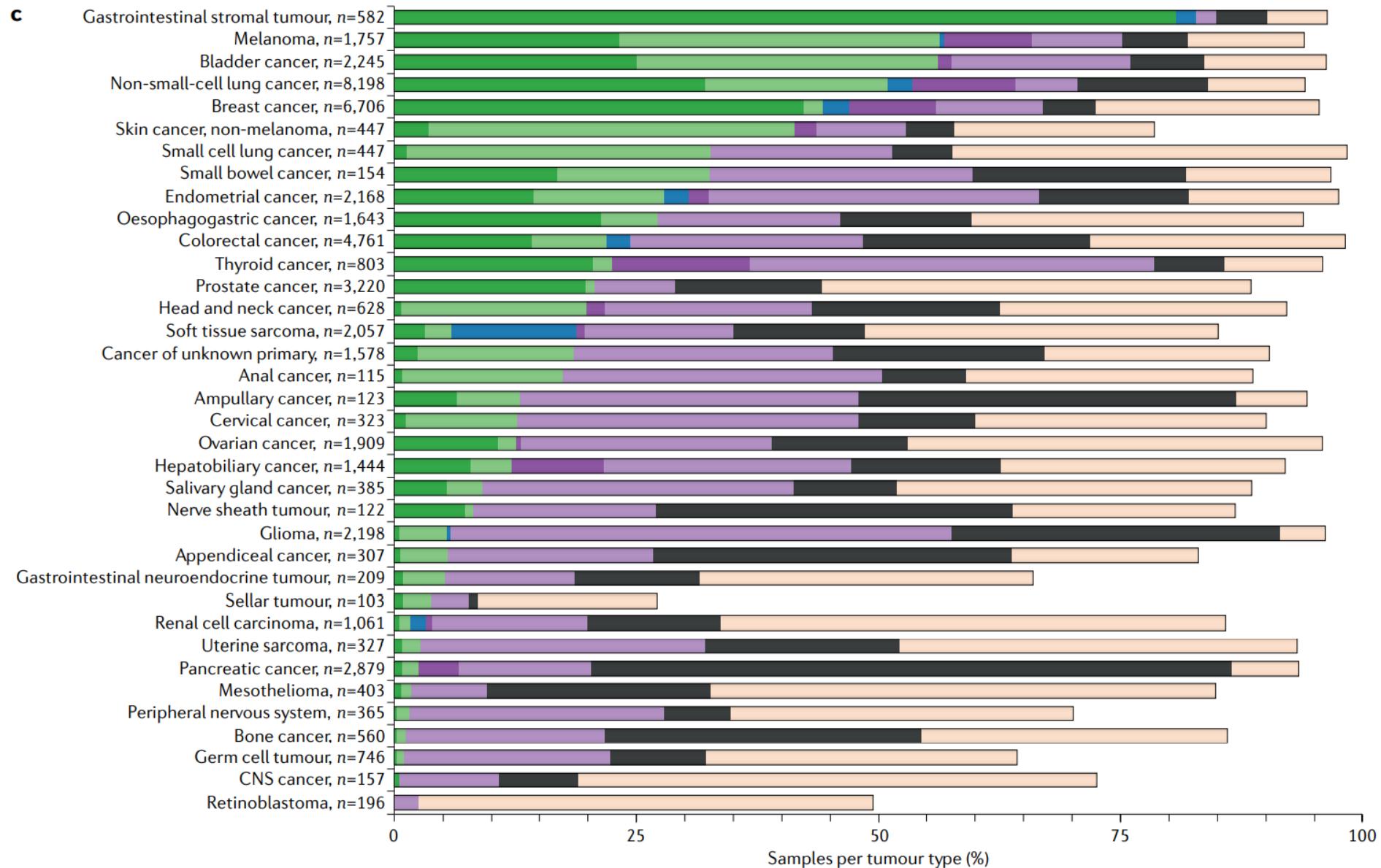


Metastatic solid tumors sequenced at MSK:

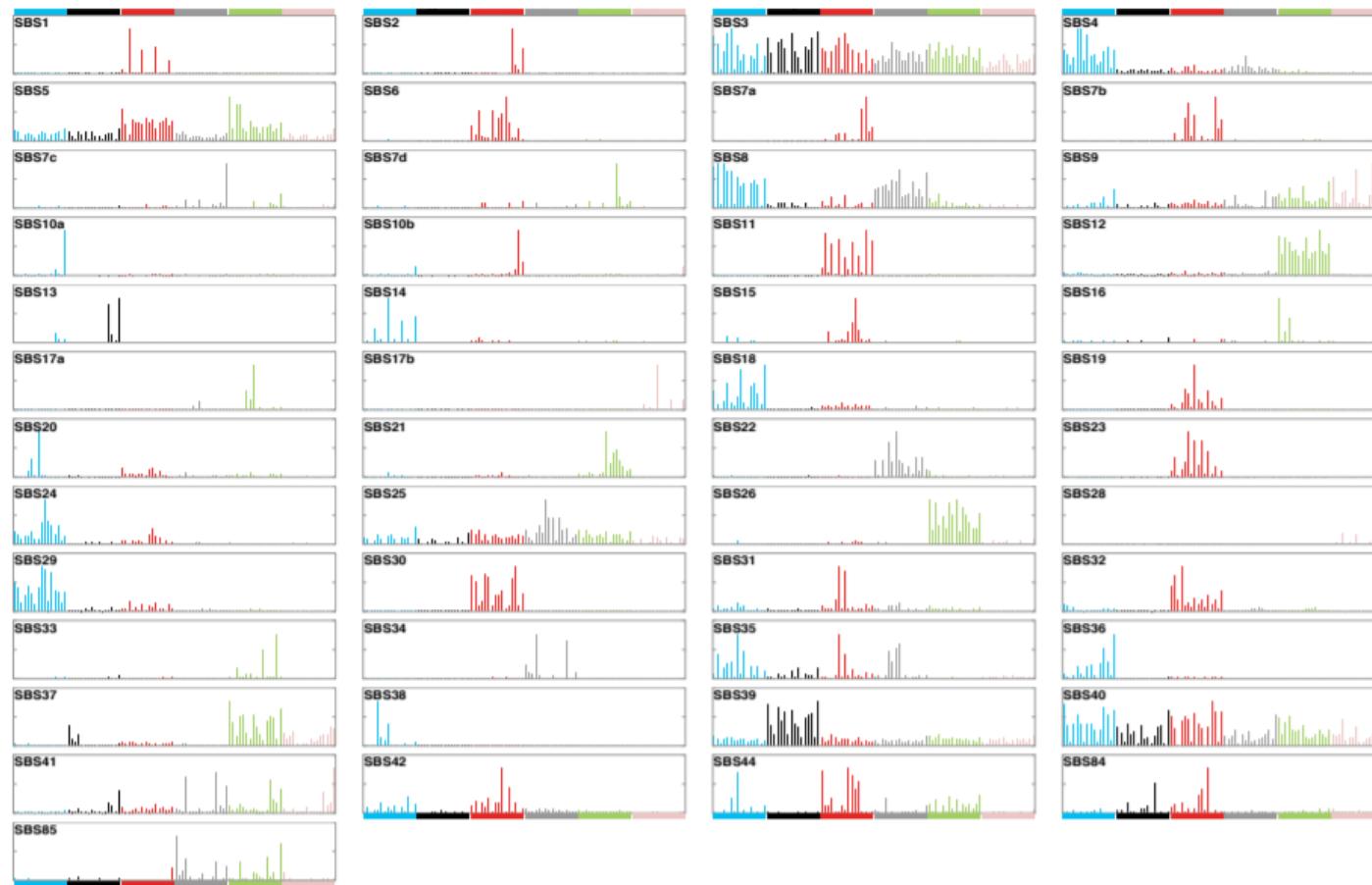
2017: 9% ESCAT I-II

2021: 34% ESCAT I-II

- Level 1 (incl. MSI-H)
- Level 1 (only TMB-H)
- Level 2
- Level 3A
- Level 3B
- Level 4
- Drivers without actionability
- Only VUS

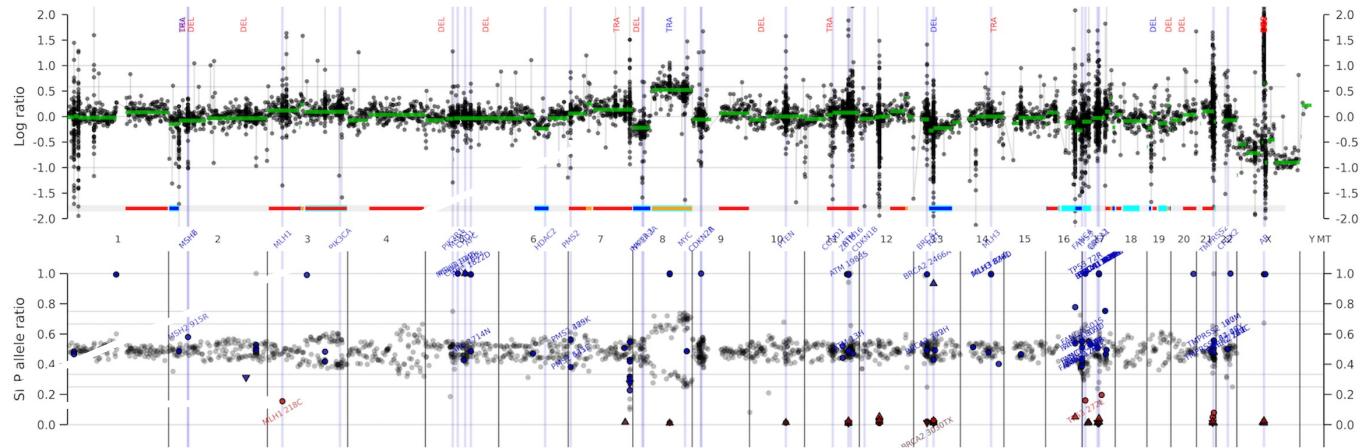


# Mutational signatures

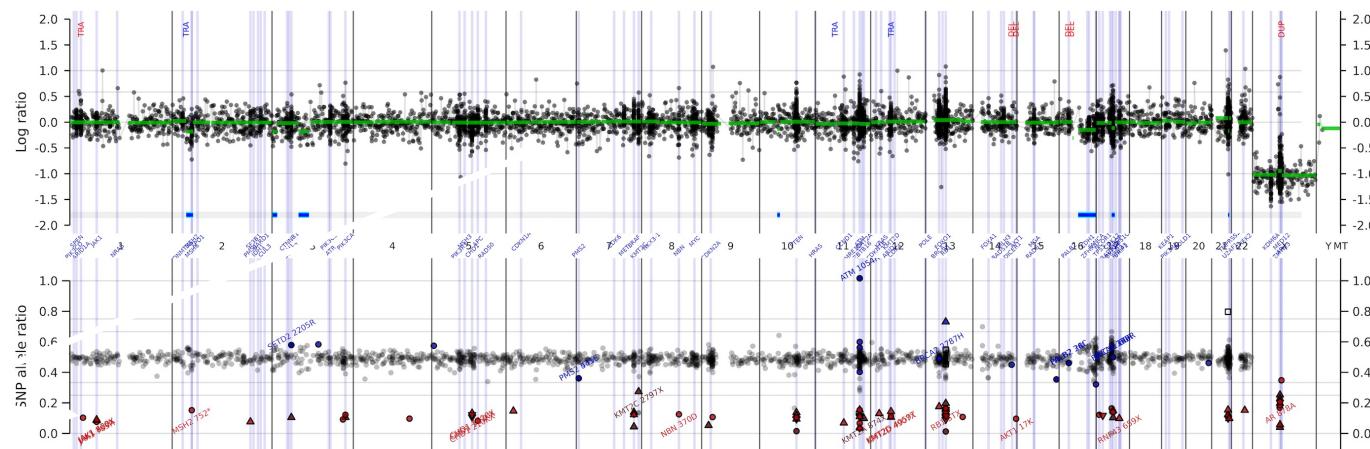


## MSI+ vs MSI- case

# MSI- case



# MSI+ case





## AUTOSEQ CURATION REPORT

### ABOUT THE TEST

The iPCM profile consists of a RUO next-generation sequencing assay, analysis pipeline and curation procedure.

| SPECIMENS | RECEIVED DATE | REPORT DATE |
|-----------|---------------|-------------|
| FFPE      | 2022-07-11    |             |
| EPM DNR   | 2021-00135    |             |

### PATIENT

| STUDY ID      |                   |
|---------------|-------------------|
| DATE OF BIRTH | NA                |
| DISEASE       | Colorectal cancer |
| HOSPITAL      | NA                |

### SPECIMEN AND ASSAY

| SPECIMEN    | ANALYTE | ASSAY                                    | QUALITY |
|-------------|---------|--|---------|
| FFPE        | DNA     | Pan-Cancer comprehensive panel (GMCK) v1 | Pass    |
| Whole blood | DNA     | Pan-Cancer comprehensive panel (GMCK) v1 | Pass    |

### GENOME-WIDE FINDINGS

| CATEGORY                     | RESULT | ASSESSMENT POSSIBLE | COMMENT   |
|------------------------------|--------|---------------------|---|
| FRACTION OF CANCER DNA       | 0.36   | Yes                 | Excellent sensitivity to detect all types of somatic alterations. |
| PLOIDY                       | 2.43   | Yes                 |   |
| MSI STATUS                   | MSS    | Yes                 |   |
| TUMOR MUTATIONAL BURDEN      | Low    | Yes                 |   |
| OTHER GENOMIC PHENOTYPE      | No     | Yes                 |   |
| PATHOGENIC GERMLINE VARIANTS | No     | Yes                 |   |

### SMALL VARIANTS

| GENE   | SOURCE   | VARIANT DETAILS       | CONSEQUENCE        | CLONALITY | SECONDHIT | IMPACT  | TRANSCRIPT ID   | HGVSP          |
|--------|----------|-----------------------|--------------------|-----------|-----------|---------|-----------------|----------------|
| APC    | somatic  | chr5:112175272, C>T   | stop_gained        | CLONAL    | LOH       | HIGH    | ENST00000457016 | Gln1328Ter     |
| KRAS   | somatic  | chr12:25398284, C>A   | missense_variant   | CLONAL    | AMP       | HOTSPOT | ENST00000256078 | Gly12Cys       |
| LZTR1  | somatic  | chr22:21347142, G>A   | missense_variant   | CLONAL    | INDEL     | UNKNOWN | ENST00000215739 | Gly404Arg      |
| PIK3CA | somatic  | chr3:178936090, G>A   | missense_variant   | CLONAL    | NO        | HOTSPOT | ENST00000263967 | Glu545Lys      |
| RET    | somatic  | chr10:43609026, G>A   | missense_variant   | CLONAL    | NO        | UNKNOWN | ENST0000035710  | Glu595Lys      |
| SOX9   | somatic  | chr17:70120243, C>T   | stop_gained        | CLONAL    | NO        | HIGH    | ENST00000245479 | Gln416Ter      |
| KRAS   | somatic  | chr12:25398283, C>A   | missense_variant   | SUBCLONAL | -         | HOTSPOT | ENST00000256078 | Gly12Val       |
| LZTR1  | somatic  | chr22:21341831, C>A   | missense_variant   | SUBCLONAL | -         | UNKNOWN | ENST00000215739 | His120Gln      |
| MEN1   | somatic  | chr11:6457327, C>T    | missense_variant   | SUBCLONAL | -         | UNKNOWN | ENST00000337652 | Arg360Gln      |
| LZTR1  | germline | chr22:21346012, CTA>C | frameshift_variant | -         | SNV       | -       | ENST00000215739 | Tyr297CysTer18 |

### STRUCTURAL REARRANGEMENTS

| GENE 1                        | GENE 2 | SOURCE | VARIANT DETAILS | CONSEQUENCE | CLONALITY | SECONDHIT |
|-------------------------------|--------|--------|-----------------|-------------|-----------|-----------|
| No relevant variants detected |        |        |                 |             |           |           |

### COPY NUMBER ALTERATIONS

| GENE                                | SOURCE  | VARIANT DETAILS         | CONSEQUENCE | COPY-NUMBER |
|-------------------------------------|---------|-------------------------|-------------|-------------|
| ETV6, GPR19, CDKN1B, GRIN2B, ATF7IP | somatic | chr12:12028041-15957472 | FOCAL AMP   | 4           |
| RB1, LPAR6                          | somatic | chr13:48966615-49023728 | FOCAL AMP   | 4           |
| BRCA1                               | somatic | chr17:41247590-41253945 | HOM DEL     | 1           |



## AUTOSEQ CURATION REPORT

| SPECIMENS | RECEIVED DATE | REPORT DATE |
|-----------|---------------|-------------|
| FFPE      | 2022-08-16    |             |
| EPM DNR   | 2021-00135    |             |

### PATIENT

| STUDY ID      |                   |
|---------------|-------------------|
| DATE OF BIRTH | NA                |
| DISEASE       | Colorectal cancer |
| HOSPITAL      | NA                |

### SPECIMEN AND ASSAY

| SPECIMEN    | ANALYTE | ASSAY                                    | QUALITY |
|-------------|---------|--|---------|
| FFPE        | DNA     | Pan-Cancer comprehensive panel (GMCK) v1 | Pass    |
| Whole blood | DNA     | Pan-Cancer comprehensive panel (GMCK) v1 | Pass    |

### GENOME-WIDE FINDINGS

| CATEGORY                     | RESULT | ASSESSMENT POSSIBLE | COMMENT   |
|------------------------------|--------|---------------------|---|
| FRACTION OF CANCER DNA       | 0.48   | Yes                 | Excellent sensitivity to detect all types of somatic alterations.   |
| PLOIDY                       | 2      | Yes                 |   |
| MSI STATUS                   | MSI-H  | Yes                 |   |
| TUMOR MUTATIONAL BURDEN      | High   | Yes                 | 57.14 single nucleotide mutations per megabase of coding sequence and 37.14 indel mutation per megabase of coding sequence.               |
| OTHER GENOMIC PHENOTYPE      | Yes    | Yes                 |   |
| PATHOGENIC GERMLINE VARIANTS | Yes    | Yes                 | MLH1 pDNA variant: chr3:37045934-37045935; GNOMAD minor allele frequency 3.978e-06; Clinvar annotation: pathogenic; dbSNP ID: rs63750781. |

### SMALL VARIANTS

| GENE | SOURCE   | VARIANT DETAILS    | CONSEQUENCE      | CLONALITY | SECONDHIT | IMPACT | RSID       | TRANSCRIPT ID   | HGVSP     |
|------|----------|--------------------|------------------|-----------|-----------|--------|------------|-----------------|-----------|
| MLH1 | germline | chr3:37045934, C>T | missense variant | -         | LOH       | -      | rs63750781 | ENST00000231790 | Thr117Met |

### STRUCTURAL REARRANGEMENTS

| GENE 1                        | GENE 2 | SOURCE | VARIANT DETAILS | CONSEQUENCE | CLONALITY | SECONDHIT |
|-------------------------------|--------|--------|-----------------|-------------|-----------|-----------|
| No relevant variants detected |        |        |                 |             |           |           |

### COPY NUMBER ALTERATIONS

| GENE | SOURCE | VARIANT DETAILS | CONSEQUENCE | COPY-NUMBER                   |
|------|--------|-----------------|-------------|-------------------------------|
|      |        |                 |             | No relevant variants detected |



## Tumor Suppressor

Highest level of evidence: Level 1 ① · FDA Level 2 ②

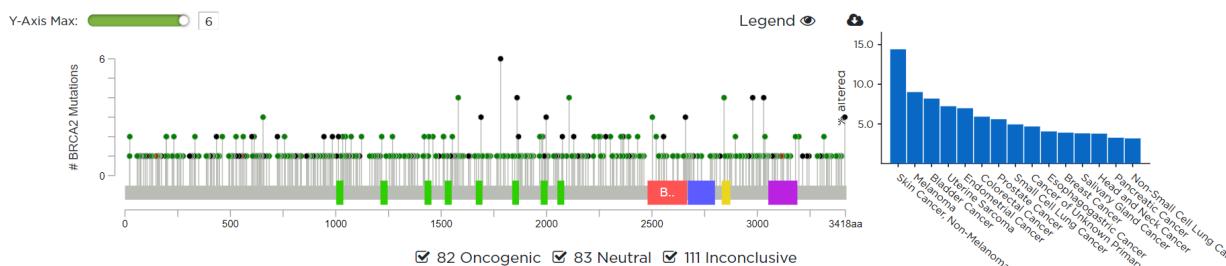
Also known as FANCD1, XRCC11, FAD1

BRCA2, a tumor suppressor involved in the DNA damage response, is mutated in various cancer types.

[Show BRCA2 background ③](#)

|                    |  |
|--------------------|--|
| NCBI Gene          | 675  |
| Ensembl Gene       | ENSG00000139618 (GRCh37/GRCh38)                                      |
| Location           | Chr13:32889611-32973805 (GRCh37)<br>Chr13:32315086-32400268 (GRCh38) |
| Ensembl Transcript | ENST00000380152 (GRCh37/GRCh38)                                      |
| RefSeq             | NM_000059.3 (GRCh37/GRCh38)  |

## Annotated Mutations in MSK-IMPACT Clinical Sequencing Cohort (Zehir et al., Nat Med 2017)

[Annotated Alterations](#)[Therapeutic](#)[FDA-Recognized Content](#)

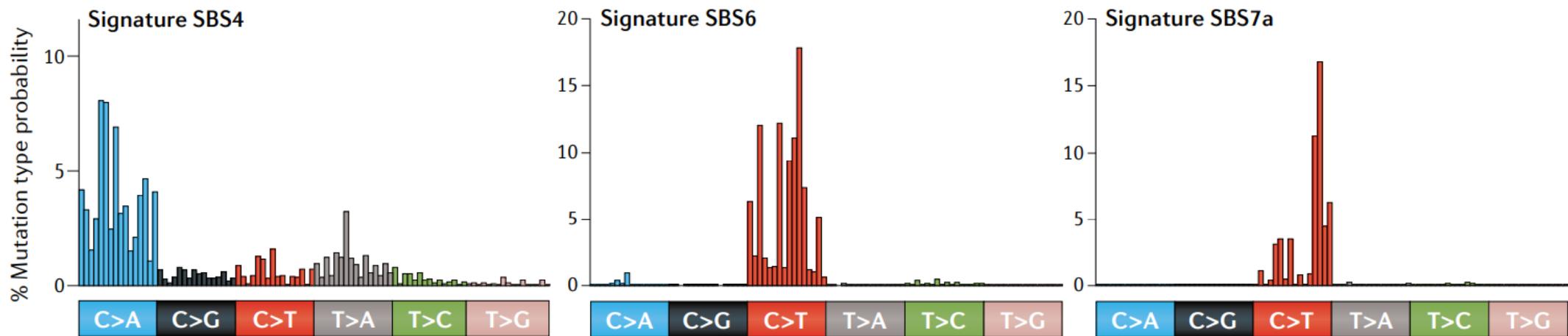
A list of the cancer type-specific BRCA2 alterations that may predict response to a targeted drug and the corresponding OncoKB level of evidence assigning their level of [clinical actionability](#).

If you notice any mistakes or omissions, please reach out to us.

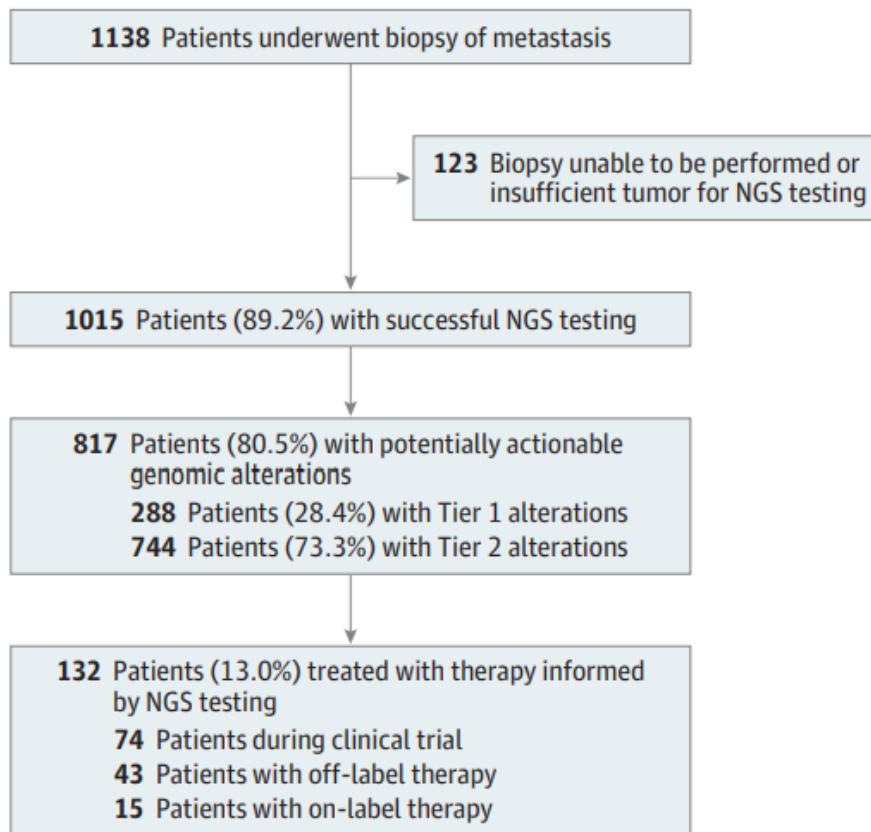
 Search ...

| Level | Alterations         | Level-associated cancer types ⑤                                   | Drugs                            | Citations |
|-------|---------------------|---|----------------------------------|-----------|
| ①     | Oncogenic Mutations | Ovary/Fallopian Tube, Ovarian Cancer, Peritoneal Serous Carcinoma | Niraparib                        | 3         |
| ①     | Oncogenic Mutations | Ovary/Fallopian Tube, Ovarian Cancer, Peritoneal Serous Carcinoma | Olaparib + Bevacizumab, Olaparib | 5         |
| ①     | Oncogenic Mutations | Ovary/Fallopian Tube, Ovarian Cancer, Peritoneal Serous Carcinoma | Rucaparib                        | 4         |
| ①     | Oncogenic Mutations | Prostate Cancer, NOS, Prostate Cancer                             | Olaparib                         | 2         |
| ①     | Oncogenic Mutations | Prostate Cancer, NOS, Prostate Cancer                             | Rucaparib                        | 2         |

**d Mutation signatures**



**Figure 1. CONSORT Diagram of Patients in the MET1000 Cohort**



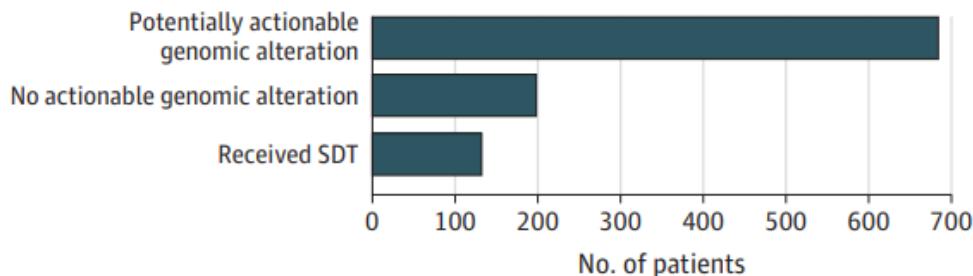
NGS indicates next-generation sequencing.

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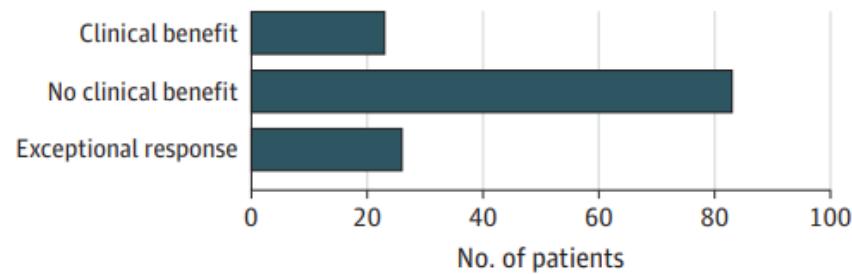
**Figure 3. Patients Receiving Sequencing-Directed Therapy (SDT) in MET1000 Cohort and Exceptional Responses**

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**A** All patients



**B** Received SDT



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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.

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**Figure 4. Pathogenic Germline Variants (PGVs) Observed in the METI000 Cohort**

