# Precision Medicine: A Case-based Approach

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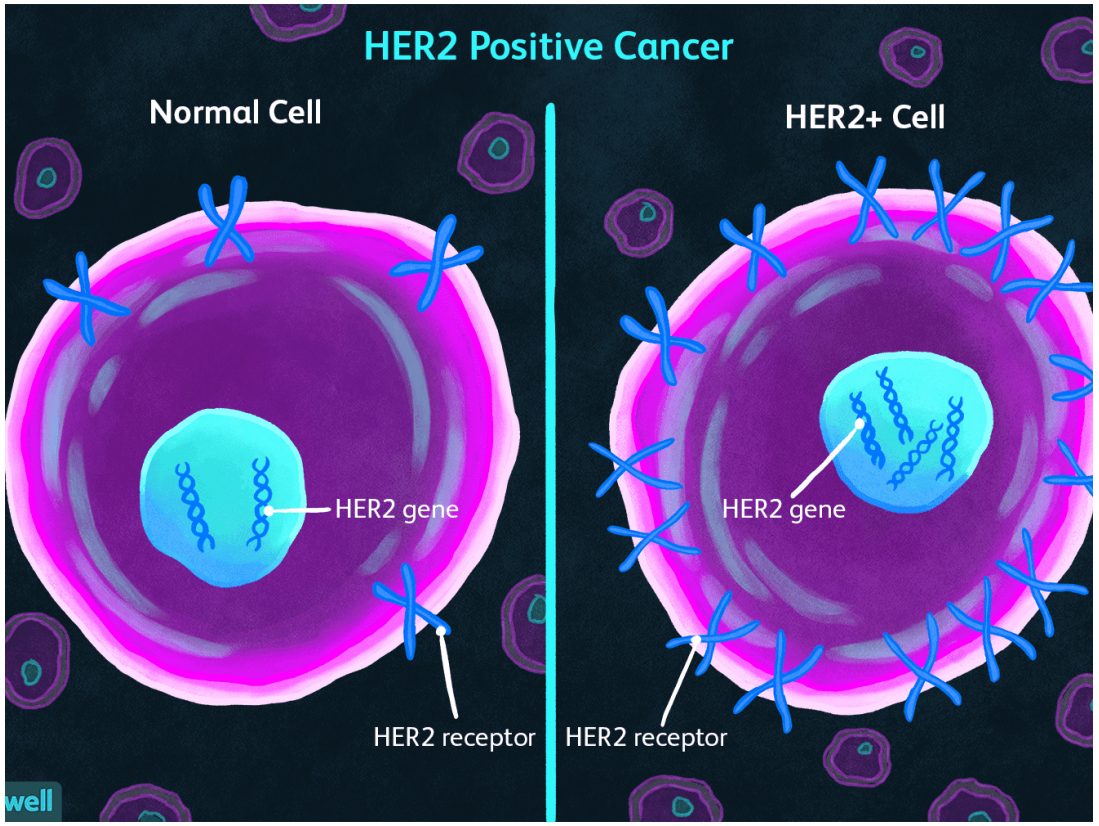
# What and why: Genomic sequencing?

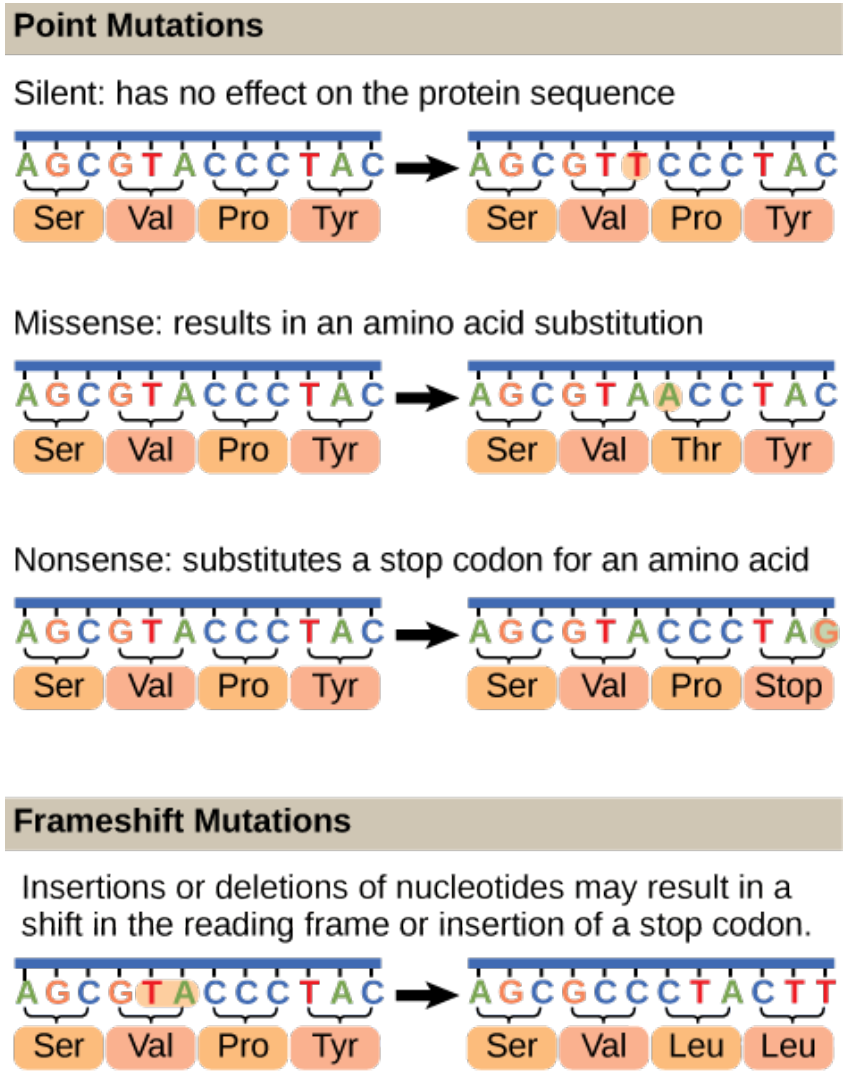
- Sequencing the DNA in tumor cells either by tissue analysis or blood
- The goal is to determine which genomic variants are present in the tumor which may guide future therapeutic treatment options
- Treatment options could either be an FDA approved drug which targets a particular gene variant for a particular disease (e.g. BRCA1/BRCA2 in prostate cancer – Olaparib) or to find clinical trial opportunities with novel targeted oncolytics

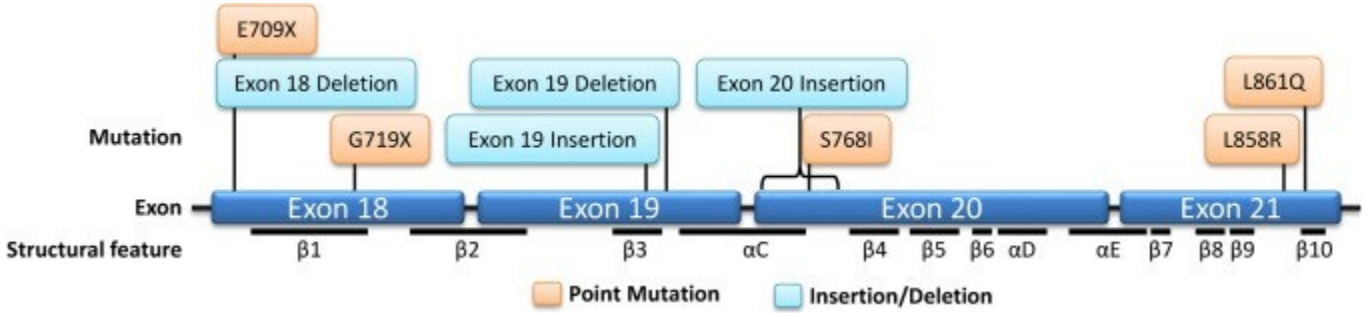
# Amplification



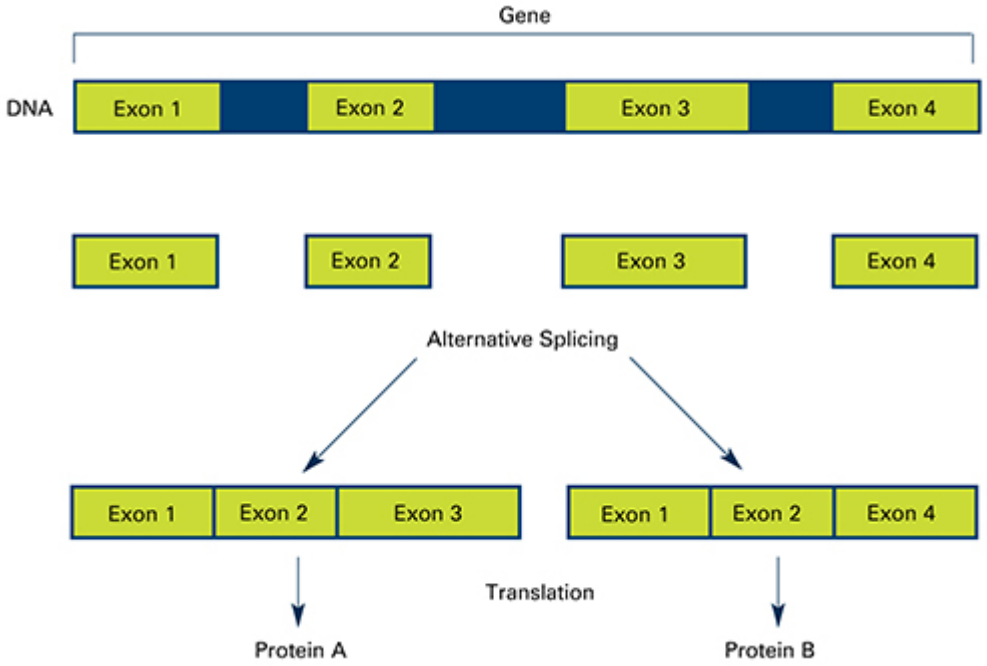

- Amplification can occur at the gene level or by increased transcription
- Gene copy number is evaluated by FISH
- Protein expression is evaluated by immunohistochemistry
- Gene expression (RNA) is identified by some NGS assays

# Point Mutations and Frameshift Mutations



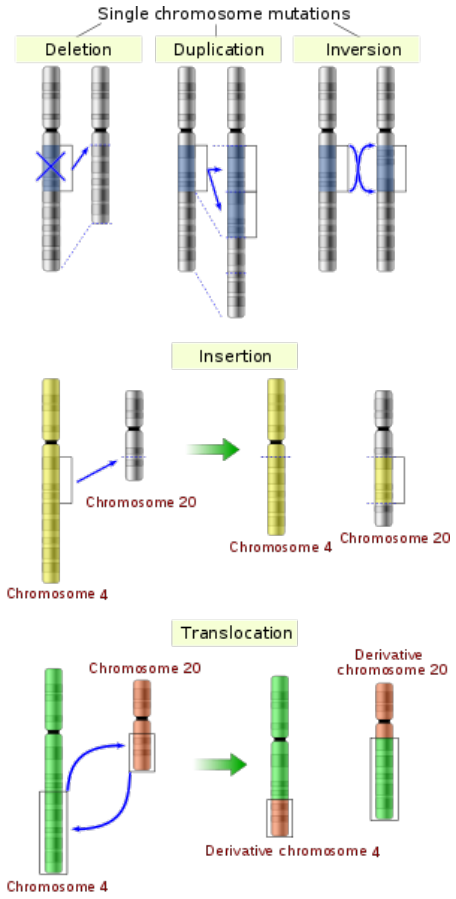



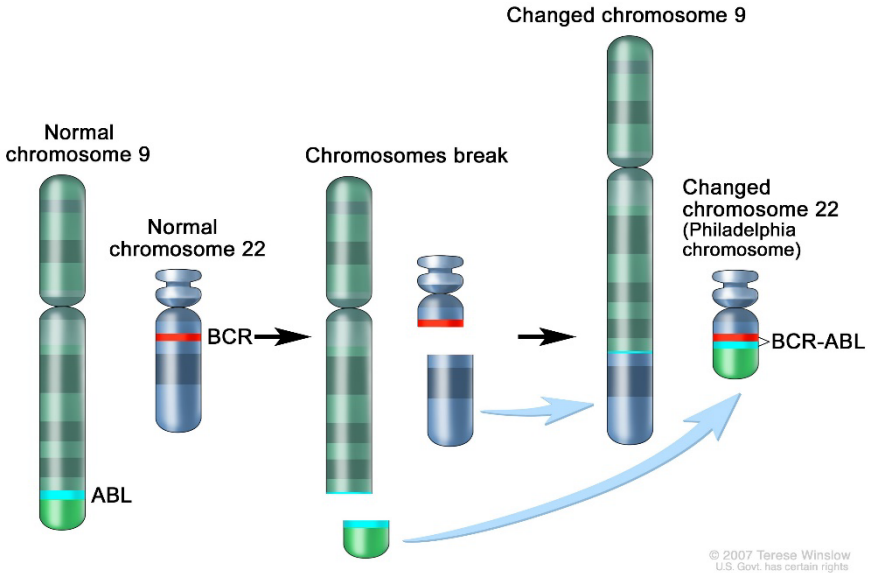
# Splicing Mutations

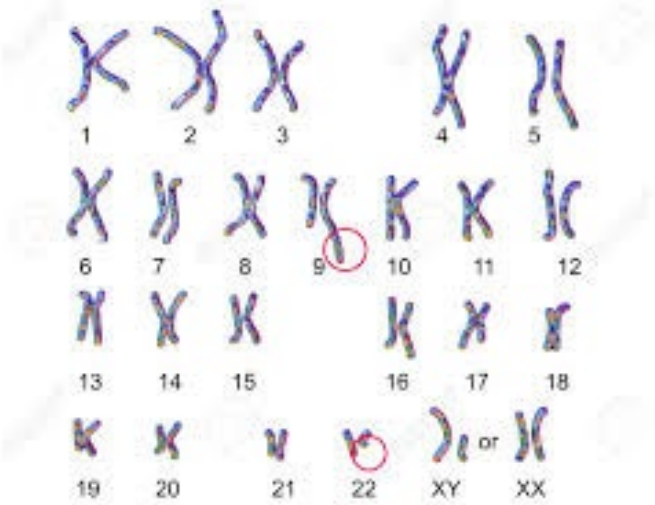



- One variant, several transcripts
- GENE:Location:Sequence Change

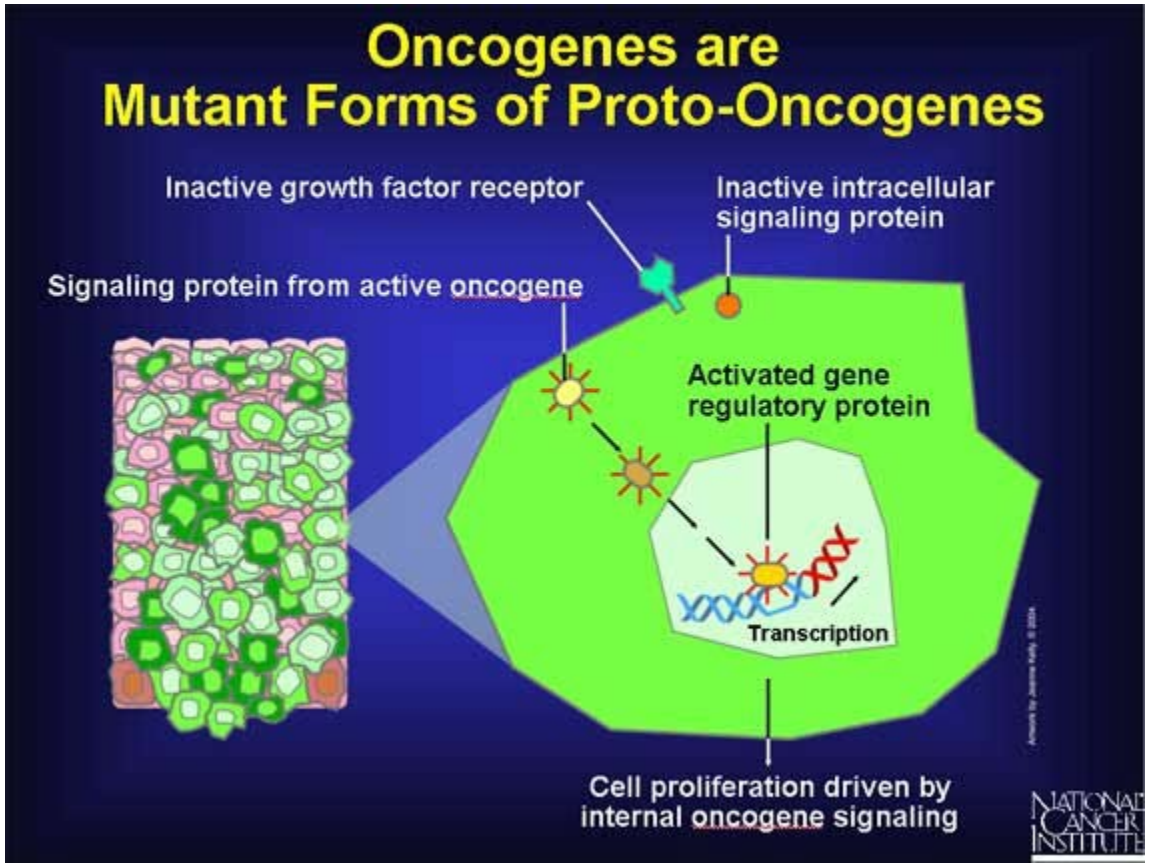
# Chromosome Level Mutations = New Fusion Genes



# Oncogenes and Mechanisms of Activation




Point Mutations

- EGFR
- KRAS
- BRAF

Chromosomal Translocation

- Philadelphia chromosome (eg; BCR ABL)

Gene Amplification

HER2

C-MYC

Usually druggable

KRAS has proven to be a challenge over time

Transcription factors also difficult to target

**EMMANUEL N. KONTOMANOLIS et al. Anticancer Res 2020;40:6009-6015**

# Tumor Suppressor Genes

Tumor suppressor genes prevent cancer

When they get mutated, cancer can occur

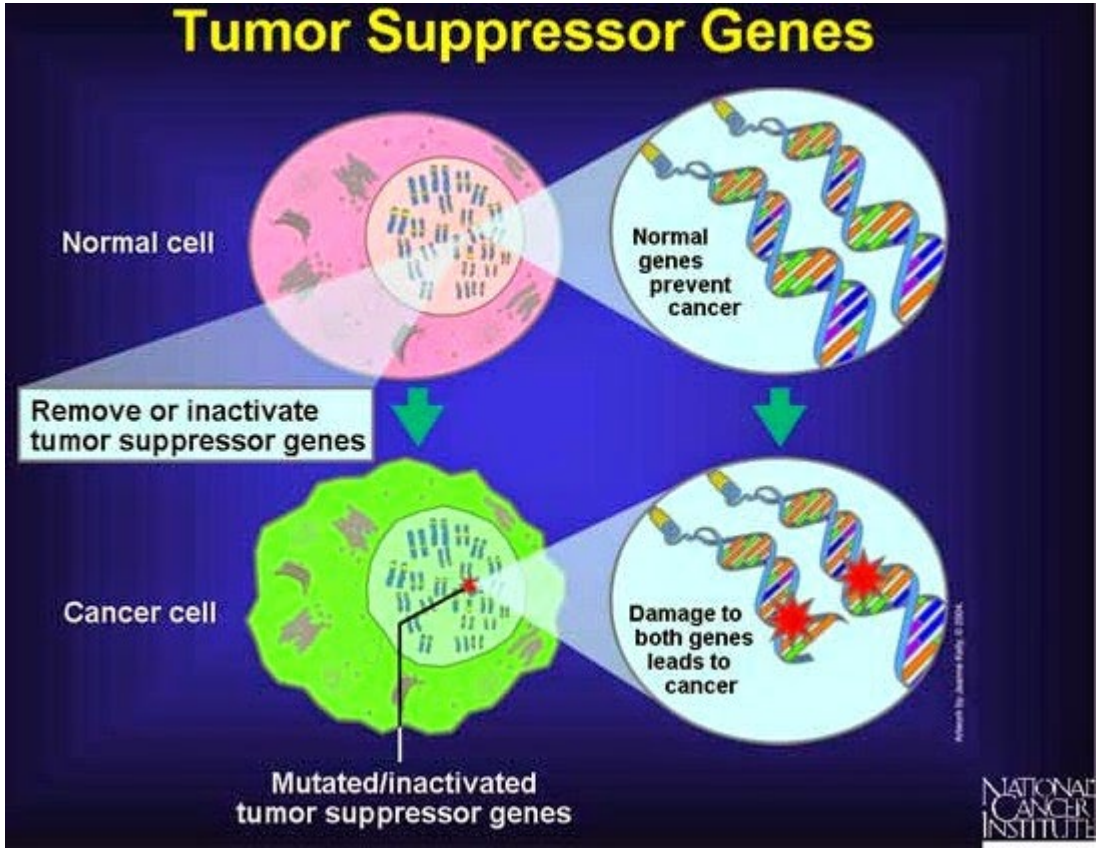
<u>Examples</u>

- PTEN
- TP53

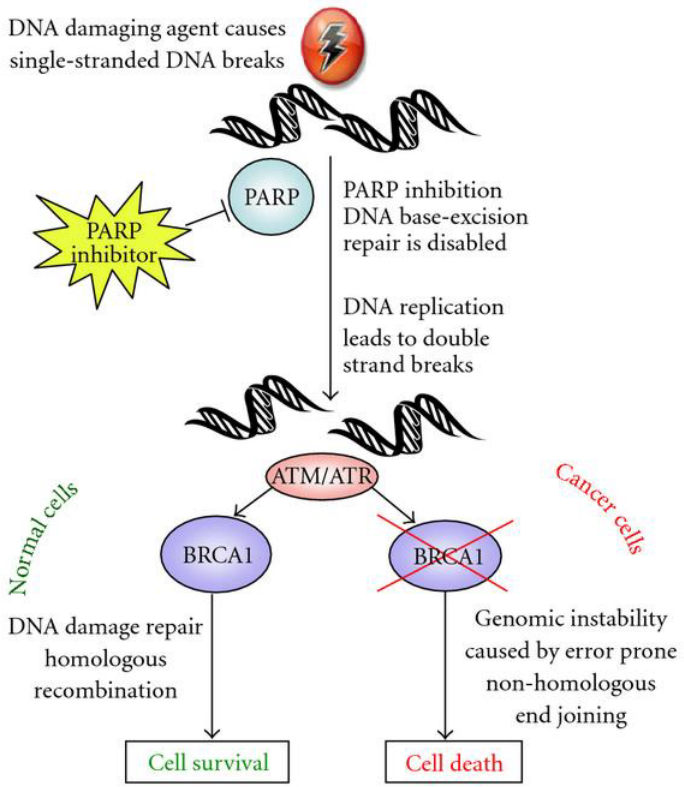
Many are involved in DNA repair

Bad News = Hard to target

Notable exception, synthetic lethality



# Synthetic Lethality




- Inhibiting PARP impacts base excision repair
- BRCA1 mutation impacts double strand DNA repair
- PARP inhibition in BRCA1 mutant patient a highly effective strategy
- Ongoing clinical trials combining PARP inhibitors with ATM and ATR inhibitors

# Common NGS Assays

| Platform | Genes | Sequencing Strategy | FDA Approval | Use |
|---|---|---|---|---|
| FoundationOne CDX | 324 | Capture | Yes | Substitutions, insertion and deletion alterations (indels), and copy number alterations (CNAs) |
| Foundation Liquid | 324 | Capture | Yes (NSCLC, Prostate, Ovarian, Breast) | Substitutions, insertion and deletion alterations (indels), and copy number alterations (CNAs) |
| Caris Molecular Intelligence CDX | ~20,000<br>592 reported | Exome (DNA and RNA) | No | Whole exome and transcriptome, pretty much everything |
| Guardant 360 | 73 | Capture | Yes (NSCLC) | Substitutions, insertion and deletion alterations (indels), and copy number alterations (CNAs) + fusions |

# Common NGS Assays

| Platform | Coverage | Error rate (positive and negative, sensitivity and specificty) | LoD (limitation of detection at 100% sensitivity) | Notes |
|---|---|---|---|---|
| FoundationOne CDX | 250X | <1% | Most ~ 2.5% | |
| Foundation Liquid | 250X | <1% | Most ~0.5% | Concordance was 100% to another liquid assay |
| Caris Molecular Intelligence CDX | 1000X for 720 clinical genes, > 500X, for others | <1% false positive, <5% SNVs and indels | 0.1% | >95% concordance with Sanger sequencing |
| Guardant 360 | | <1% SNV and indels | 0.25% | Concordance 92%-100% to tissue |

# How Are The Sequencing Reports Utilized to Generate Clinical Recommendations?

# Translating NGS Results into Individualized Therapy Recommendations

- Start with the individual themselves:
  - Cancer diagnosis and stage
  - Prior therapies
  - Goals of care
  - Other important comorbidities or considerations

- NGS tests results have limited patient specific information
- Goal is to translate the findings into realistic treatment options for each individual patient
  - Consider current and future therapies
  - Summarize multiple genomic tests → tumors can change over time

# Common Components of NGS Reports

- “Front Page” findings
- Detailed individual gene descriptions
- Clinical trials
- Variants of uncertain significance
- References
- Appendix information:
  - Test methodology
  - Genes and alterations assessed
  - Lower limits of detection

# CARIS MiProfile

High Impact Results

| BIOMARKER | METHOD | RESULT | THERAPY ASSOCIATION | | BIOMARKER LEVEL* |
|---|---|---|---|---|---|
| BRCA1 | NGS | Mutated, Pathogenic Exon 23 \| p.R1835* | BENEFIT | olaparib, talazoparib | Level 1 |
| | | | BENEFIT | carboplatin, cisplatin | Level 3A |
| ER | IHC | Positive \| 3+, 90% | BENEFIT | endocrine therapy | Level 1 |
| | | | BENEFIT | abemaciclib, palbociclib, ribociclib | Level 2 |
| | | | BENEFIT | everolimus | Level 2 |
| PR | IHC | Positive \| 2+, 3% | BENEFIT | endocrine therapy | Level 1 |
| | | | BENEFIT | abemaciclib, palbociclib, ribociclib | Level 2 |
| ERBB2 (Her2/Neu) | CISH | Not Amplified | LACK OF BENEFIT | ado-trastuzumab emtansine (T-DM1), lapatinib, neratinib, pertuzumab, trastuzumab | Level 1 |
| | IHC | Negative \| 1+, 10% | | | |

**CANCER TYPE RELEVANT BIOMARKERS**

| Biomarker | Method | Result |
|---|---|---|
| MSI | NGS | Stable |
| Mismatch Repair Status | | Proficient |
| Tumor Mutational Burden | | Intermediate \| 11 Mutations/Mb |
| AKT1 | NGS | Mutation Not Detected |
| AR | IHC | Positive \| 2+, 90% |
| BRCA2 | NGS | Mutation Not Detected |
| ERBB2 (Her2/Neu) | NGS | Mutation Not Detected |
| ESR1 | NGS | Mutation Not Detected |
| PD-L1 | SP142 IHC | Negative \| 0 |

**CANCER TYPE RELEVANT BIOMARKERS (cont)**

| Biomarker | Method | Result |
|---|---|---|
| PIK3CA | NGS | Mutated, Pathogenic |
| | | Exon 21 \| p.H1047R |
| PTEN | IHC | Positive \| 1+, 100% |
| | NGS | Mutation Not Detected |

**OTHER FINDINGS** (see page 2 for additional results)

| Biomarker | Method | Result |
|---|---|---|
| ARID1A | NGS | Mutated, Pathogenic |
| | | Exon 3 \| p.P517fs |



# FoundationOne® CDx/ Heme / Liquid CDx

## Companion Diagnostic (CDx) Associated Findings

| GENOMIC FINDINGS DETECTED | FDA-APPROVED THERAPEUTIC OPTIONS |
|---|---|
| *Tumor Mutational Burden (TMB)* ≥ 10 Muts/Mb | Keytruda® (Pembrolizumab) |

**OTHER ALTERATIONS & BIOMARKERS IDENTIFIED**

Results reported in this section are not prescriptive or conclusive for labeled use of any specific therapeutic product. See *professional services* section for additional information.

***Microsatellite status*** MS-Stable §
***Tumor Mutational Burden*** 11 Muts/Mb §
***FGFR3*** S249C
***MLL2*** Q2898*
***PIK3CA*** E545K
***STK11*** Q152*
***TGFBR2*** S295*

*§ Refer to appendix for limitation statements related to detection of any copy number alterations, gene rearrangements, BRCA1/2 alterations, LOH, MSI, or TMB results in this section.*

*Please refer to appendix for Explanation of Clinical Significance Classification and for variants of unknown significance (VUS).*

# TEMPUS xT®

## GENOMIC VARIANTS

**Somatic - Potentially Actionable** — Variant Allele Fraction

- **TP53** p.R196* Stop gain - LOF — 61.4%
- **AR** Copy number gain
- **CDKN2A** Copy number loss
- **TMPRSS2 - ERG** Chromosomal rearrangement

**Somatic - Biologically Relevant**

- **CDKN2B** Copy number loss

**Germline - Pathogenic / Likely Pathogenic**

No pathogenic variants were found in the limited set of genes on which we report.

## IMMUNOTHERAPY MARKERS

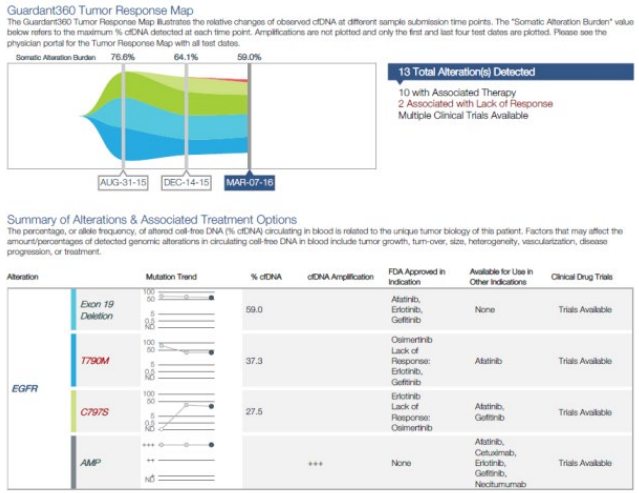
**Tumor Mutational Burden**

**2.1 m/MB** 40th percentile

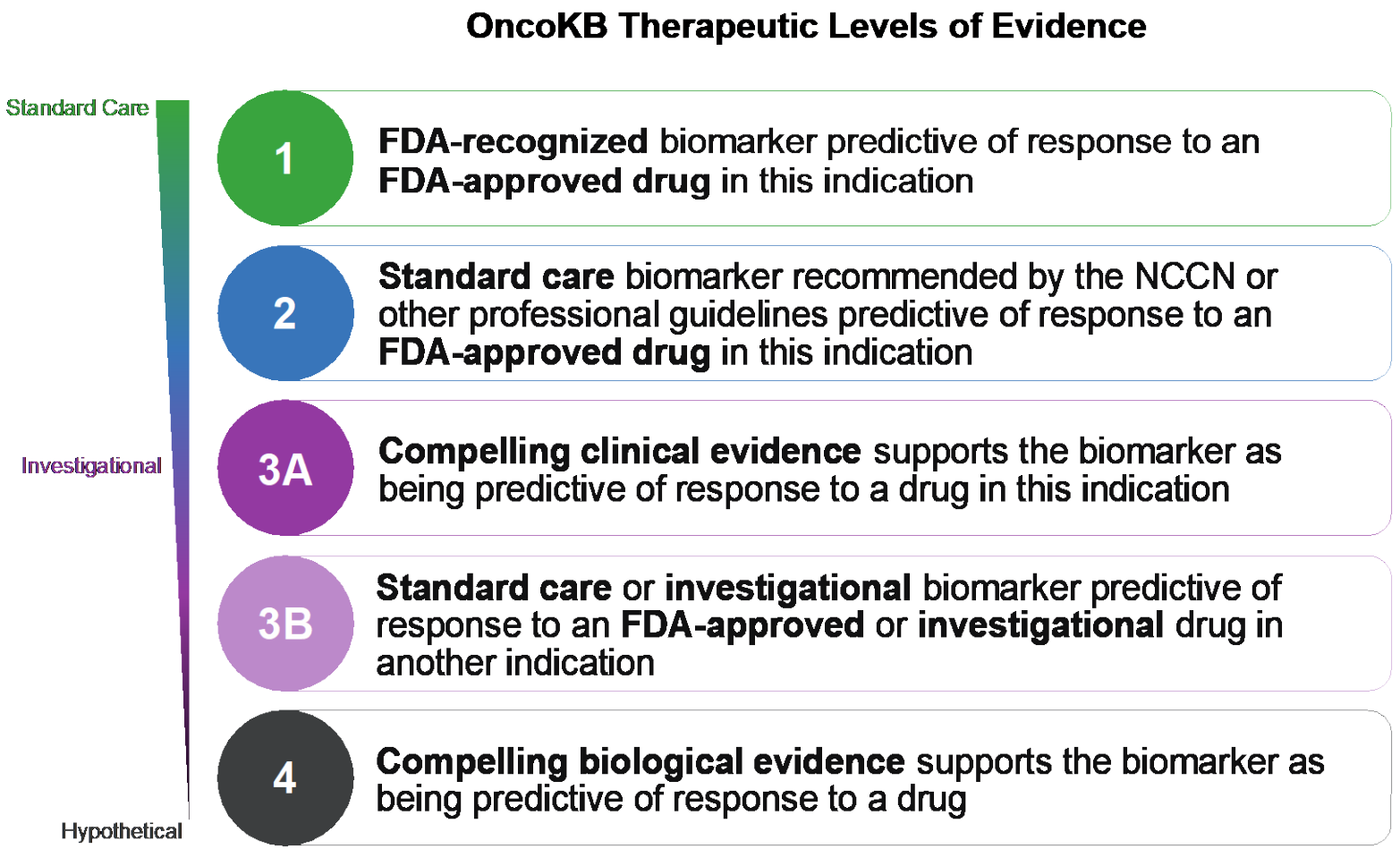
**Microsatellite Instability Status**

**Stable** | Equivocal | High

# Guardant360®



# MSKCC/OncoKb Levels of Evidence




JCO Precison Oncol. 2017 Jul;2017 (epub 2017 May 16)

# Translating Results into Patient Care

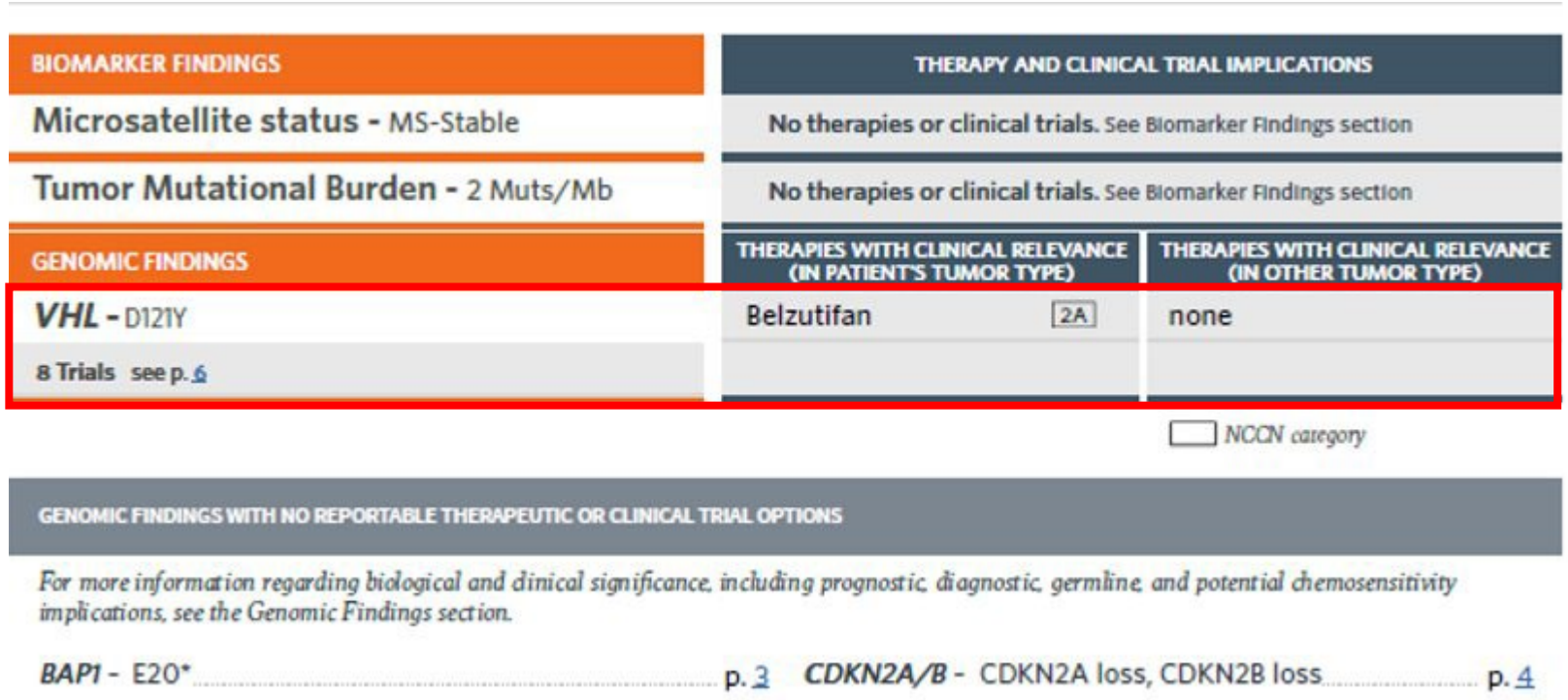
- Which gene mutations could be driving the cancer?

- Which gene mutations do we likely not want to target (passenger mutations)?

# Case #1

- Patient is a 69 y/o female with renal clear-cell carcinoma; former smoker 20 pack years
- April 2012 - underwent a total nephrectomy on the R side. Pathologic diagnosis at that time was that of an 8.5 cm firm and grade 4/4 T3a N0 M0 clear-cell carcinoma. The tumor was present in large muscular line branches of the renal vein within the renal sinus.
- May 2014 - surveillance CT scans reveal several scattered small pulmonary nodules, the largest now being up to 11 mm in the R pleural-based region. There have been some small nodules in the RP, slightly more prominent in the L periaortic area measuring size 12 mm.
- November 2021 - had what she thought was recurrent sciatica. MRI revealed an S1 mass with encroachment on thecal sac. Steroid injection w/o relief requiring oxycodone and supine position for such. No bowel or bladder changes. No other obvious lesions by MRI lumbar.
- December 2021 – underwent CT-guided bx of sacral mass. Path + for RCC - Received palliative RT to sacrum 300Gy x 5
- March 2022 – received 5 cycles nivolumab/cabozantinib with improvement then developed enterocolitis vs diverticulitis, drained abscess

# Case #1 – Foundation CDx Somatic Tissue Testing



| BIOMARKER FINDINGS | THERAPY AND CLINICAL TRIAL IMPLICATIONS |
|---|---|
| **Microsatellite status -** MS-Stable | **No therapies or clinical trials.** See Biomarker Findings section |
| **Tumor Mutational Burden -** 2 Muts/Mb | **No therapies or clinical trials.** See Biomarker Findings section |

| GENOMIC FINDINGS | THERAPIES WITH CLINICAL RELEVANCE (IN PATIENT'S TUMOR TYPE) | THERAPIES WITH CLINICAL RELEVANCE (IN OTHER TUMOR TYPE) |
|---|---|---|
| ***VHL* -** D121Y | Belzutifan 2A | none |
| **8 Trials** see p. 6 | | |

NCCN category

**GENOMIC FINDINGS WITH NO REPORTABLE THERAPEUTIC OR CLINICAL TRIAL OPTIONS**

*For more information regarding biological and clinical significance, including prognostic, diagnostic, germline, and potential chemosensitivity implications, see the Genomic Findings section.*

***BAP1*** - E20* ..... p. 3

***CDKN2A/B*** - CDKN2A loss, CDKN2B loss ..... p. 4

# Case #2

- Patient is a 49 y/o male with newly diagnosed pancreatic cancer; hx DM2, HTN, irregular heart beat
- 8/22/2022 – presented to PCP with c/o intermittent RUQ abdominal pain x 3 months.
- 9/2/2022 – US concerning for abdominal mass
- 9/7/2022 – CTAP showed 8cm pancreatic mass, multiple liver masses, splenic infarct, hiatal hernia
- 9/14/2022 –EGD/EUS showed multiple metastatic liver lesions, a mass in the pancreatic body and tail, and many hypoechoic lesions in the peritoneal cavity. TxNxM1. FNA of liver lesions c/w pancreatic ductal adenocarcinoma.
- 9/20/2022 – presented at IUSCC pancreatic tumor board. Stage IV. Recommend clinical trial vs first line palliative systemic chemo.
- 9/27/2022 – CT chest showed few tiny pulmonary nodules are nonspecific. No LAD.
- 10/4/2022 – started FOLFIRINOX chemotherapy
- 10/5/2022 – presented to ED with vomiting. CT unchanged.

# Case #2 – Foundation CDx – Somatic Tissue Testing

| GENOMIC FINDINGS | THERAPIES WITH CLINICAL RELEVANCE (IN PATIENT'S TUMOR TYPE) | THERAPIES WITH CLINICAL RELEVANCE (IN OTHER TUMOR TYPE) |
|---|---|---|
| ***BRCA2*** – W2626C<br>10 Trials see p. 12 | Olaparib 2A | Rucaparib 2A<br>Niraparib<br>Talazoparib |
| ***CCNE1*** – amplification<br>4 Trials see p. 14 | none | none |
| ***FGFR4*** – amplification<br>10 Trials see p. 15 | none | none |
| ***KRAS*** – Q61L<br>3 Trials see p. 17 | none | none |
| ***MYC*** – amplification<br>5 Trials see p. 18 | none | none |
| ***PIK3CA*** – amplification - equivocal<br>10 Trials see p. 19 | none | none |
| ***TP53*** – Y220C<br>1 Trial see p. 21 | none | none |

☐ NCCN category

**VARIANTS TO CONSIDER FOR FOLLOW-UP GERMLINE TESTING IN SELECT CANCER SUSCEPTIBILITY GENES**

*Findings below have been previously reported as pathogenic germline in the ClinVar genomic database and were detected at an allele frequency of >10%. See appendix for details.*

***BRCA2*** – W2626C ..... p. 2

This report does not indicate whether variants listed above are germline or somatic in this patient. In the appropriate clinical context, follow-up germline testing would be needed to determine whether a finding is germline or somatic.

**GENOMIC FINDINGS WITH NO REPORTABLE THERAPEUTIC OR CLINICAL TRIAL OPTIONS**

*For more information regarding biological and clinical significance, including prognostic, diagnostic, germline, and potential chemosensitivity implications, see the Genomic Findings section.*

***CDKN2A/B*** – CDKN2A loss exon 1, CDKN2B loss ..... p. 7

***PARK2*** – loss exons 2-4 ..... p. 8

# Case #3

- Patient is a 33 y/o female with recurrent WHO grade 4 astrocytoma
- 2008 – presented w/seizures. Originally diagnosed w/grade 3 astrocytoma. Underwent resection in Bloomington then radiation and temozolomide for about a year.
- 2011 – recurrent disease s/p second resection in Bloomington. Completed some adjuvant temozolomide but ultimately lost to follow up w/out completing a full course
- 2012 – underwent surgery for exposed hardware
- Late October 2022 – presented with seizures. MRI w/concerns for HGG in L frontal lobe, but on vimpat and lamotrigine, discharged w/plans for coordinated surgery with neurosurgery and ENT given surgical history and need for wound flap
- 12/6/2022 – underwent resection #3. Pathology showed WHO grade 4 astrocytoma, IDH1 mutant, NTRK2 fusion present. Post op course complicated by aphasia and R hemiparesis. Prolonged hospital stay discharged to AR on 12/22/2022.
- Plans for re-irradiation with concurrent chemo to begin soon locally.

# Case #3 Caris Somatic Tissue Testing

## Results with Therapy Associations

| BIOMARKER | METHOD | ANALYTE | RESULT | THERAPY ASSOCIATION | | BIOMARKER LEVEL* |
|---|---|---|---|---|---|---|
| **NTRK2** | **Seq** | **RNA-Tumor** | **Pathogenic Fusion** | **BENEFIT** | **entrectinib, larotrectinib** | **Level 2** |
| MGMT | PyroSeq | DNA-Tumor | Methylated | | | Level 2 |
| IDH1 | Seq | DNA-Tumor | Pathogenic Variant Exon 4 \| p.R132S | BENEFIT | temozolomide | Level 3 |

## Genomic Signatures

| Biomarker | Method | Analyte | Result |
|---|---|---|---|
| Microsatellite Instability (MSI) | Seq | DNA-Tumor | Stable |
| Tumor Mutational Burden (TMB) | Seq | DNA-Tumor | Result: Low 2 — Low 10 High |
| Genomic Loss of Heterozygosity (LOH) | Seq | DNA-Tumor | Low - 15% of tested genomic segments exhibited LOH (assay threshold is ≥ 16%) |

## MGMT Promoter Methylation

| Assay: Pyrosequencing | Result: Methylated |
|---|---|

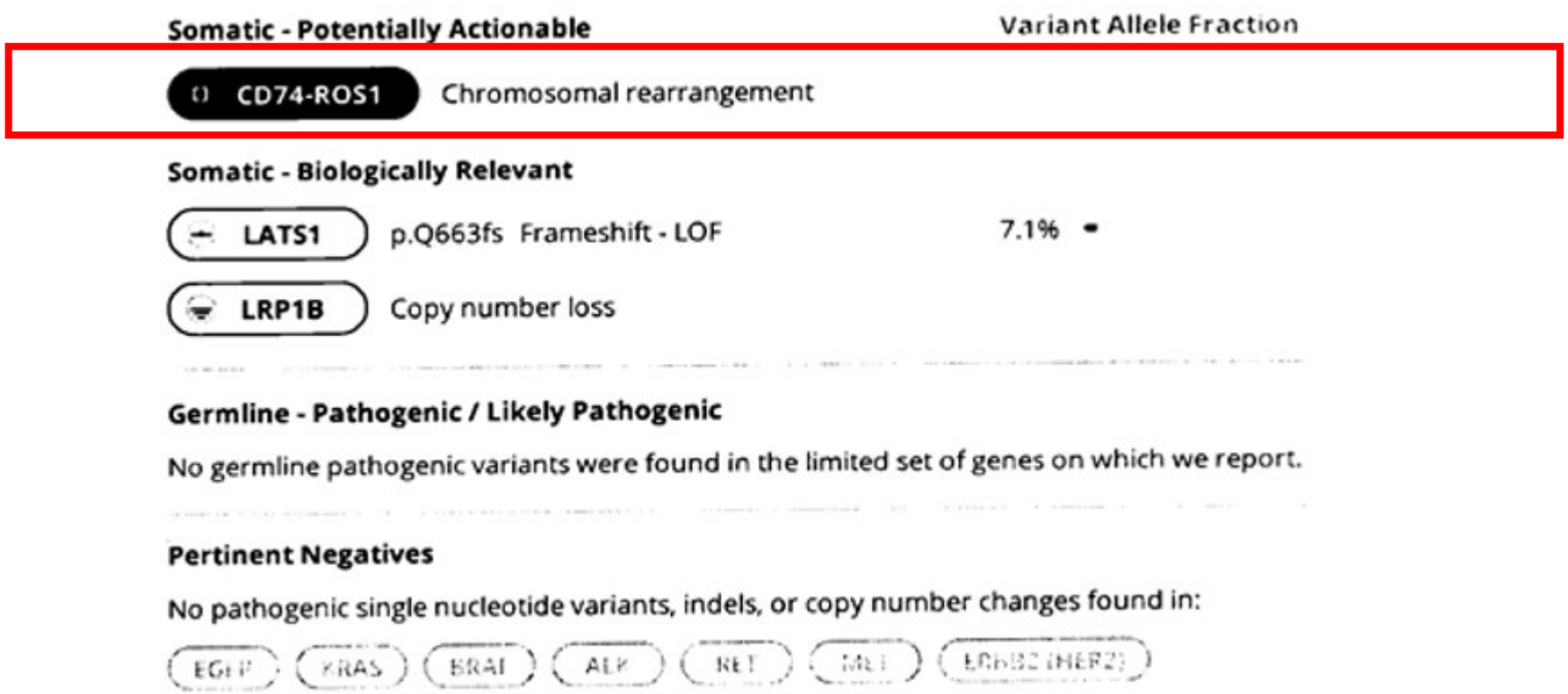
## Genes Tested with Pathogenic or Likely Pathogenic Alterations

| Gene | Method | Analyte | Variant Interpretation | Protein Alteration | Exon | DNA Alteration | Variant Frequency % |
|---|---|---|---|---|---|---|---|
| IDH1 | Seq | DNA-Tumor | Pathogenic Variant | p.R132S | 4 | c.394C>A | 43 |
| MET | Seq | RNA-Tumor | Likely Pathogenic Fusion | PTPRZ1-MET | 2 | - | - |
| | CNA-Seq | DNA-Tumor | Amplified | - | - | - | - |

# Case #4

- 35 yo woman with newly diagnosed NSCLC
- 7/23 - Presented to ER with lower back pain/chest pain with deep inspiration; imaging concerning for RLL and perihilar mass/pathologic fracture T7; biopsy endobronchial lesion – poorly differentiated adenocarcinoma; MRI brain shows multiple brain mets
- 8/23 - Started carboplatin/pemetrexed/zoledronic acid – XRT to brain/consideration for kyphoplasty

# Case #4 Tempus Somatic Tissue Testing



**Somatic - Potentially Actionable** Variant Allele Fraction

CD74-ROS1 Chromosomal rearrangement

**Somatic - Biologically Relevant**

LATS1 p.Q663fs Frameshift - LOF 7.1%

LRP1B Copy number loss

**Germline - Pathogenic / Likely Pathogenic**

No germline pathogenic variants were found in the limited set of genes on which we report.

**Pertinent Negatives**

No pathogenic single nucleotide variants, indels, or copy number changes found in:

EGFR KRAS BRAF ALK RET MET ERBB2 (HER2)

# Case #5

- 47 yo man with history of germ cell tumor

- 6/97 - B-HCG – 81,215/AFP 3,525; 10 x 16cm retroperitoneal mass/multiple bilateral pulmonary metastases – poor risk metastatic testicular cancer; BEP x 4 followed by RPLND – revealing teratoma; post-surgery – rapid increase in B-HCG – 2 x VeIP with subsequent rapid rise in B-HCG (platinum refractory); High-dose chemotherapy/autologous SCT x 2 – CR for 20 + years

- 3/23 - New onset pain in L posterior rib – imaging revealed a mass in the area; CT chest/abd/pelvis otherwise normal; B-HCG/AFP - normal; biopsy – well-differentiated adenocarcinoma consistent with germ cell tumor with malignant transformation along endodermal elements/intestinal phenotype; i12p (-)

- 6/23 - Later relapse of teratoma/de-differentiated into adenocarcinoma, well-differentiated; plan for surgical resection

# Case #5 –Guardant360 Liquid Biopsy

**Summary of Detected Somatic Alterations, Immunotherapy Biomarkers & Associated Treatment Options**

KEY ✓ Approved in indication ○ Approved in other indication ⊗ Lack of response

| Detected Alteration(s) / Biomarker(s) | Associated FDA-approved therapies | Clinical trial availability (see page 3) | % cfDNA or Amplification |
|---|---|---|---|
| *FGFR3-TACC3* Fusion | ○ Erdafitinib | Yes | 0.09% |
| *APC* Q1444* | None | No | 0.2% |
| *SMAD4* S154* | None | No | 0.2% |

# Case #5 – Caris Somatic Tissue Testing

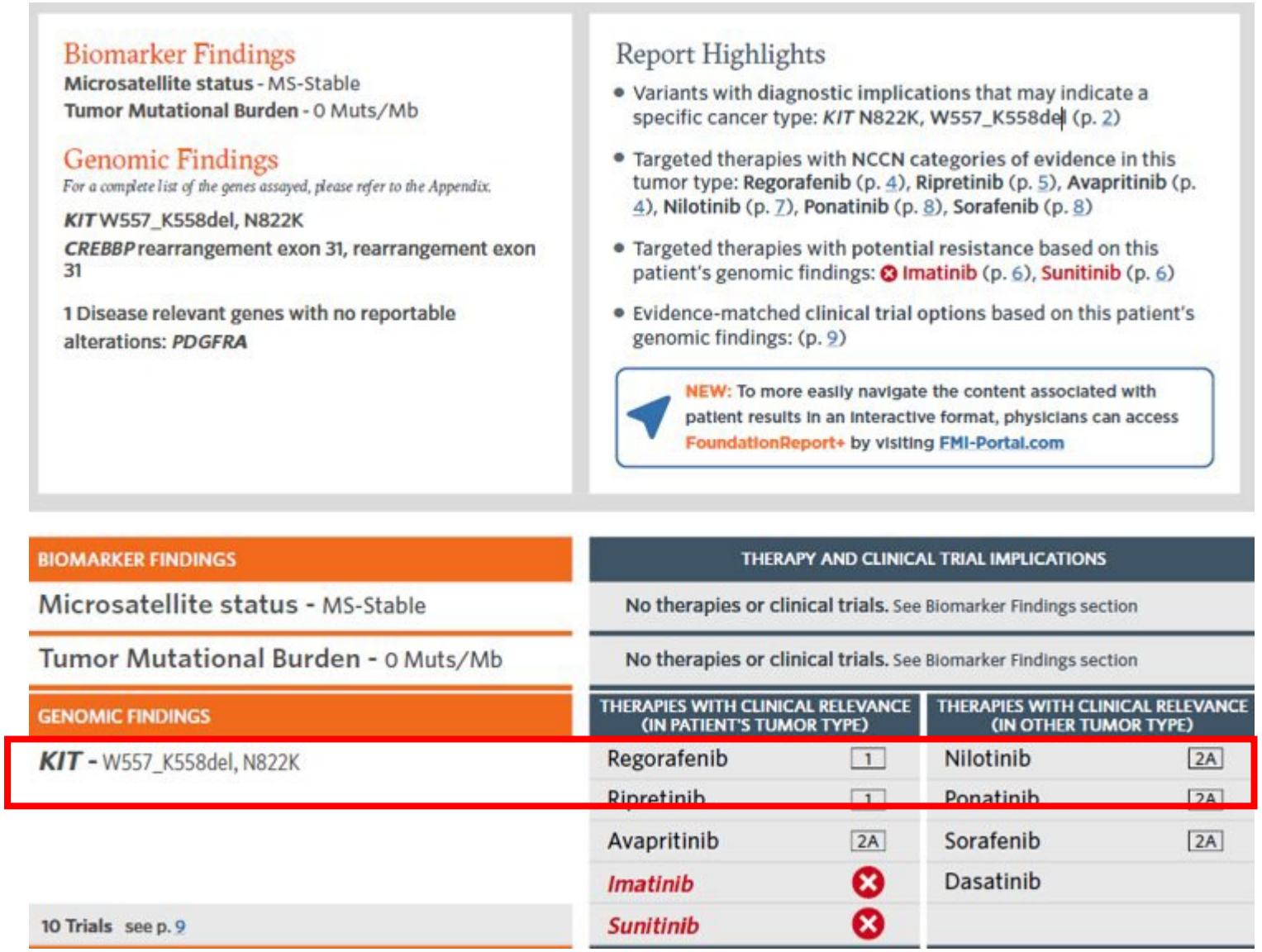
## Genes Tested with Pathogenic or Likely Pathogenic Alterations

| Gene | Method | Analyte | Variant Interpretation | Protein Alteration | Exon | DNA Alteration | Variant Frequency % |
|---|---|---|---|---|---|---|---|
| APC | Seq | DNA-Tumor | Pathogenic Variant | p.Q1444* | 16 | c.4330C>T | 44 |
| FGFR3 | Seq | RNA-Tumor | Pathogenic Fusion | FGFR3-TACC3 | 17 | - | - |
| SMAD4 | Seq | DNA-Tumor | Pathogenic Variant | p.S154* | 5 | c.461C>G | 44 |

# Case #6

- 2011-Patient was found to have GIST tumor
- She was initially worked up for iron deficiency anemia and was diagnosed with small-bowel GIST.
- 2011: She underwent surgical resection and was found to have a 7.5 cm GIST tumor connected to the small-bowel with high mitotic rate (high risk), Grade 2, tumor was ruptured, felt to be stage pT3NxM0. It was c-KIT positive (no molecular testing)
- After surgical resection, she was started on Imatinib and took it from 06/2010 – 02/2015.
- 09/06/2016: Routine imaging revealed disease recurrence with a 7 cm mesenteric mass in the right lower quadrant. She underwent surgical resection of an 8 cm mesenteric mass on 09/29/2016 and path consistent with GIST, grade 2, with high mitotic rate.
- She was restarted on imatinib postoperatively and continued on 400 mg daily.
- 6/2023 Routine imaging revealed a new 1.4 cm omental nodule, suspicious for recurrence.
- 7/10/23 She underwent omental lesion biopsy - consistent with GIST. Molecular testing revealed exon 11 mutation, but also an exon 17 mutation (Asn822Lys) that predicts resistance to imatinib
- She was referred to see surgery and is planned to have omental lesion resected.  Plan is to start sunitinib.

# Case #6 Foundation CDx Somatic Tissue Testing



## Biomarker Findings

**Microsatellite status** - MS-Stable
**Tumor Mutational Burden** - 0 Muts/Mb

## Genomic Findings

*For a complete list of the genes assayed, please refer to the Appendix.*

***KIT*** **W557_K558del, N822K**
***CREBBP*** **rearrangement exon 31, rearrangement exon 31**

**1 Disease relevant genes with no reportable alterations: *PDGFRA***

## Report Highlights

- Variants with diagnostic implications that may indicate a specific cancer type: *KIT* N822K, W557_K558del (p. 2)
- Targeted therapies with NCCN categories of evidence in this tumor type: **Regorafenib** (p. 4), **Ripretinib** (p. 5), **Avapritinib** (p. 4), **Nilotinib** (p. 7), **Ponatinib** (p. 8), **Sorafenib** (p. 8)
- Targeted therapies with potential resistance based on this patient's genomic findings: **Imatinib** (p. 6), **Sunitinib** (p. 6)
- Evidence-matched clinical trial options based on this patient's genomic findings: (p. 9)

**NEW:** To more easily navigate the content associated with patient results in an interactive format, physicians can access **FoundationReport+** by visiting **FMI-Portal.com**

| BIOMARKER FINDINGS | THERAPY AND CLINICAL TRIAL IMPLICATIONS |
|---|---|
| Microsatellite status - MS-Stable | No therapies or clinical trials. See Biomarker Findings section |
| Tumor Mutational Burden - 0 Muts/Mb | No therapies or clinical trials. See Biomarker Findings section |

| GENOMIC FINDINGS | THERAPIES WITH CLINICAL RELEVANCE (IN PATIENT'S TUMOR TYPE) | | THERAPIES WITH CLINICAL RELEVANCE (IN OTHER TUMOR TYPE) | |
|---|---|---|---|---|
| ***KIT*** - W557_K558del, N822K | Regorafenib | 1 | Nilotinib | 2A |
| | Ripretinib | 1 | Ponatinib | 2A |
| | Avapritinib | 2A | Sorafenib | 2A |
| | *Imatinib* | ⊗ | Dasatinib | |
| 10 Trials see p. 9 | *Sunitinib* | ⊗ | | |

# Case #7

- 60-year-old postmenopausal woman with metastatic estrogen receptor positive breast cancer.
- 2009 when she was originally diagnosed with a stage I ER positive invasive ductal carcinoma of the right breast. She was treated with lumpectomy with sentinel lymph node biopsy finding 0.7 cm of grade 1 disease and 0 of 2 lymph nodes involved. She also underwent a left- sided excisional biopsy for symmetry. She received adjuvant radiation and tamoxifen for approximately 3 months
- 2015 when she presented with a right pleural effusion and pleural-based nodularity. A PET-CT at that time showed FDG avid bilateral hilar adenopathy and some diffuse uptake in the endometrium. Cytology from thoracentesis confirmed adenocarcinoma that was ER positive 91%, PR positive 76%, HER2 equivocal by IHC as well as by FISH with a copy number of 4.8 and a ratio of 1.0. Pleural-based biopsy- ER positive 93%, PR positive 93% and HER2 negative with a ratio of 1.1 and a copy number of 3.9.
- started on letrozole and palbociclib when she was seen at Vanderbilt. She opted to stop her therapy 2017 to pursue alternative dietary therapies.
- PET-CT 2020 with new liver lesion as well as enlarging pleural- based nodularity and a new pleural-based paraesophageal nodularity. Started back on palbociclib and letrozole in October 2020.
- 1/2021, POD in liver. she declined enrollment on the PACE trial and was started on fulvestrant monotherapy.
- 5/2022, POD and declined chemotherapy and was recommended exemestane with everolimus. Patient declined and pursued integrative medicine.
- growth in the liver and s/p cyberknife in Chicago.

# Case #7 – Foundation CDx Somatic Tissue Testing

| HISTORIC PATIENT FINDINGS | | FoundationOne® 29 Jul 2015 TRF103385 | FoundationOne®Liquid CDx 30 Aug 2023 ORD-1701966-01 VAF% |
|---|---|---|---|
| **Blood Tumor Mutational Burden** | | Not Tested | 1 Muts/Mb |
| **Microsatellite status** | | Cannot Be Determined | MSI-High Not Detected |
| **Tumor Fraction** | | Not Tested | Elevated Tumor Fraction Not Detected |
| ***ESR1*** | ● Y537S | Not Detected | 0.25% |
| ***CBFB*** | ● splice site 79-1G>A | Detected | 0.41% |
| ***DNMT3A*** | ● T257fs*59 | Not Detected | 0.61% |
| ***GATA3*** | ● splice site 925-3_925-2delCA | Detected | Not Detected |
| ***KMT2C (MLL3)*** | ● Q1105* | Detected | Not Tested |
| ***MCL1*** | amplification | Detected | Not Detected |

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