What, when, how for somatic panel test?

울산의대 서울아산병원 병리과
조 영미
What kind of sequencing?

Whole genome sequencing:
- Sequencing region: whole genome
- Sequencing Depth: >30X
- Covers everything—can identify all kinds of variants including SNPs, INDELS and SV.

Whole exome sequencing:
- Sequencing region: whole exome
- Sequencing Depth: >50X ~ 100X
- Identify all kinds of variants including SNPs, INDELS and SV in coding region.
- Cost effective

Targeted sequencing:
- Sequencing region: specific regions (could be customized)
- Sequencing Depth: >500X
- Identify all kinds of variants including SNPs, INDELS in specific regions
- Most Cost effective

Table:

<table>
<thead>
<tr>
<th>Panel test</th>
<th>No. of targeted genes</th>
<th>Tumor mutation burden</th>
<th>FDA approval</th>
</tr>
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<tbody>
<tr>
<td>Oncomine Dx Target Test</td>
<td>23 genes</td>
<td>-</td>
<td>Yes</td>
</tr>
<tr>
<td>MSK-IMPACT</td>
<td>468 genes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
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<td>FoundationOne CDx</td>
<td>324 genes</td>
<td>Yes</td>
<td>Yes</td>
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<tr>
<td>NCC Oncopanel</td>
<td>114 genes</td>
<td>-</td>
<td>-</td>
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<td>Todai OncoPanel</td>
<td>464 genes</td>
<td>-</td>
<td>-</td>
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<tr>
<td>CANCERPLEX</td>
<td>435 genes</td>
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<td>-</td>
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<tr>
<td>OncoPrime</td>
<td>223 genes</td>
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<td>PleSSision</td>
<td>160 genes</td>
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<td>OmniSeq Advance</td>
<td>144 genes</td>
<td>Yes</td>
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<tr>
<td>P5 report</td>
<td>52 genes</td>
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What tissues?

Fresh-frozen tissue

Formalin-fixed paraffin-embedded tissue
Cancer cell proportion & mutated-allele

- Normal cells 50%
  - 25% oncogenic allele
  - 75% wild type allele

- Normal cells 90%
  - 5% oncogenic allele
  - 95% wild type allele

- Tumor cells 50%
  - 25% oncogenic allele
  - 75% wild type allele

- Tumor cells 10%
  - 5% oncogenic allele
  - 95% wild type allele
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<td>Emerging</td>
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<td>• PD-L1 IHC</td>
<td>• <strong>FGFR2/3 mutation/fusion:</strong> Erdafitinib</td>
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<td><strong>Predictive- Solid tumor</strong></td>
<td></td>
<td>• dMMR/MSI\textsuperscript{high}/TMB\textsuperscript{high}: Pembrolizumab</td>
<td>Emerging</td>
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<td>• <strong>NTRK1/2/3 fusions:</strong> Larotrectinib, Entrectinib</td>
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DNA Damage Repair

Proteins
- PARP1
- XRCC1
- LIGASE 3
- BRCA1
- BRCA2
- PALB2
- DNA-PK
- KU70/80
- ATM
- CHEK1
- CHEK2
- RAD51

Proteins
- NHEJ
- BER
- Homologous recombination

Proteins
- NER
- ERCC4
- ERCC1
- Mismatch repair

Proteins
- Direct reversal
- MGMT
- Base alkylations
- Base mismatches, insertions and deletions
- Bulky adducts
- Double-strand break
- Single-strand break

DNA Damage Repair

Cause:
Mutation → Protein loss

Dysfunction

Outcome:
Phenotype

MMR gene alteration:
MLH1, MSH2, MSH6, PMS2

dMMR (defective mismatch repair)

HR gene alteration:
BRCA1/2 etc.

HRD (homologous recombination deficiency)

Genomic scarring:
• LOH (loss of heterozygosity)
• TAI (telomeric allelic imbalance)
• LST (large scale state transition)

NGS

PCR

IHC

Outcome:
• MSI
• Hypermutation
• High Ins/Del

NGS
[AMC] I-index: (# of InDel mutations / # of total mutations)*100

207 colorectal cancer

MSI Diagnosis : NGS at AMC
Tumor Mutation Burden (TMB)

- Smoking
- APOBEC
- MSI
- Aging
- UV

MHC Diversity

TCR repertoire

Epigenetic modulation

T-effector Cell

Neoadtigen Processing

High TMB

Tumor Cell

- Synonymous coding mutation
- Non-Synonymous coding mutation
- Oncogenic drivers
- Germline mutation

WES = Exome (∼38Mb)

Foundation One = Foundation One

MSK-IMPACT = ∼1.5Mb

OncoPanel AMC v4 = 0.64 Mb

Prostate Cancer: DNA Double Strand Break Repair

**Genomic instability**

**Inability to repair DNA**

**HRD**

**Genetic mutations in HRR pathway** (eg, BARD1, BRCA1, BRCA2, PALB2, RAD51C)\(^1\)

**Unidentified causes**

**HRD**

**Inability to repair DNA**

**Genomic instability**

**Altered gene expression (ie, promoter methylation)**

- Genetic mutations in HRR pathway (eg, BARD1, BRCA1, BRCA2, PALB2, RAD51C)
- Unidentified causes
- HRD
- Inability to repair DNA
- Genomic instability

**Prostate Cancer: DNA Double Strand Break Repair**

- Genetic mutations in HRR pathway
  - BARD1
  - BRCA1
  - BRCA2
  - PALB2
  - RAD51C

**Unidentified causes**

**HRD**

**Inability to repair DNA**

**Genomic instability**

- Genetic mutations in HRR pathway
- Unidentified causes
- HRD
- Inability to repair DNA
- Genomic instability
Molecular Pathology in Prostate Cancer

ISUP 2020

Recommendations of the Working Group were the following:

- In combination with appropriate genetic counseling, germline panel testing for DNA repair gene alterations should be offered (if clinically indicated) to patients with:
  - Localized Grade Group ≥ 4 tumors.
  - Any Grade Group with PSA ≥ 20.
  - Known metastatic disease.

- Somatic tumor DNA testing should be offered to all patients with the known metastatic disease if clinically indicated. It can be performed on metastatic tissue or, if unavailable, primary tissue. Testing should include:
  - **Defective MMR assessment** via MMR IHC for MSH2, MSH6, MLH1, PMS2 with or without MSI testing and/or sequencing of MMR genes (and tumor mutation burden estimate).
  - **Defective HR assessment** via sequencing for *BRCA1*, *BRCA2* at a minimum, with the ability to detect copy number alterations.

Germline testing may be considered in patients with a personal history of prostate cancer in the following scenarios:

- By Prostate Cancer Tumor Characteristics (diagnosed at any age)
  - intermediate-risk prostate cancer with *intraductal/cribriform histology*

- By prostate cancer and a prior personal history of any of the following cancers:
  - exocrine pancreatic, colorectal, gastric, melanoma, pancreatic, upper tract urothelial, glioblastoma, biliary tract, and small intestinal
Experience in PROfound Trial

- 4425 Patients entered screening
- 4047 Patients with samples tested & reported
- 2792 Successful (69%)
- 1255 Failed (31%)

Experience in PROfound Trial

RP → BCR → Metastasis → Death
≈ 2 yrs → ≈ 8 yrs → ≈ 5 yrs

EDTA

Organ tissue site

Sample age

Proportion of samples with successful test (%)

Bone (n=204)  Prostate (n=4522)  Liver (n=87)  Lung (n=43)  Lymph node (n=328)  Other (n=147)

Proportion of samples with successful test (%)

≤1 year (n=368)  1–3 years (n=1133)  3–5 years (n=1139)  5–10 years (n=1446)  >10 years (n=727)
Therascreen FGFR RGQ RT-PCR Kit (TCGA)

- FGFR3 mutation: S249C (7.9%), Y373C (2.0%), G370C (1.2%), R248C (0.7%)
- FGFR3/2 fusion: FGFR3-TACC3 (2.0%)/BAIAP2L1, FGFR2-BICC1/CASP7
Bladder Cancer: FGFR3 Alterations for Erdafitinib
Bladder Cancer: TERT Promoter Mutation

- 60% to 80% of UC
- C228T > C250T > C242T/C243T > C228A
- Positive: squamous cell carcinoma, glandular differentiation, sarcomatoid, plasmacytoid, micropapillary variants
- Negative: benign urothelial mimics, prostatic adenocarcinoma, enteric-type adenocarcinomas, urachal carcinomas
# Kidney Cancer: WHO 5th Edition

## Chapter 2: Tumours of the kidney

### 3.1: Renal cell tumours
- 3.1.0: Renal cell tumours: Introduction
- 3.1.1: Clear cell renal tumours
  - 3.1.1.1: Clear cell renal cell carcinoma
- 3.1.2: Papillary renal tumours
  - 3.1.2.1: Renal papillary adenoma
  - 3.1.2.2: Papillary renal cell carcinoma
- 3.1.4: Oncocytic and chromophobe renal tumours
  - 3.1.4.1: Oncocytoma of the kidney
  - 3.1.4.2: Chromophobe renal cell carcinoma
- 3.1.4.3: \[Other oncocytic tumours of the kidney\]
- 3.1.5: Collecting duct tumours
  - 3.1.5.1: Collecting duct carcinoma
- 3.1.6: Other renal tumours
  - 3.1.6.1: Clear cell papillary renal cell tumour
  - 3.1.6.2: Mucinous tubular and spindle cell carcinoma
  - 3.1.6.3: Acquired cystic disease-associated renal cell carcinoma
  - 3.1.6.3: Eosinophilic solid and cystic renal cell carcinoma
  - 3.1.6.4: Renal cell carcinoma NOS
- 3.1.7: Molecularly defined renal carcinomas
  - 3.1.7.1: TFE3-rearranged renal cell carcinomas
  - 3.1.7.2: TFE3-rearranged renal cell carcinomas
  - 3.1.7.3: ELOC (formerly TCEB1)-mutated renal cell carcinoma
  - 3.1.7.4: Fumarate hydratase-deficient renal cell carcinoma
  - 3.1.7.5: Succinate dehydrogenase-deficient renal cell carcinoma
  - 3.1.7.6: ALK-rearranged renal cell carcinomas
  - 3.1.7.7: SMARCB1-deficient renal medullary carcinoma

### 3.2: Metanephric tumours
- 3.2.0: Metanephric adenoma
- 3.2.2: Metanephric adenofibromas
- 3.2.3: Metanephric stromal tumour

### 3.3: Mixed epithelial and stromal renal tumours
- 3.3.0: Mixed epithelial and stromal tumour of the kidney

### 3.4: Renal mesenchymal tumours
- 3.4.1: Adult renal mesenchymal tumours
  - 3.4.1.1: Classic angiomylipoma / PEComa of the kidney
  - 3.4.1.2: Epithelioid angiomylipoma / epithelioid PEComa of the kidney
  - 10.9.2.2: Renal haemangioendothelioma
  - 3.4.3.1: Juxtaglomerular cell tumour
  - 3.4.14: Renomedullary interstitial cell tumour

### 3.4.2: Paediatric renal mesenchymal tumours
- 3.4.2.2: Osseous renal tumour of infancy
- 3.4.2.1: Congenital mesoblastic nephroma
- 3.4.2.3: Rhabdoid tumour of the kidney
- 3.4.2.4: Clear cell sarcoma of the kidney

### 3.5: Embryonal neoplasms of the kidney
- 3.5.1: Nephroblastoma
  - 3.5.1.1: Nephrogenic rests
  - 3.5.1.2: Paediatric cystic nephroma
  - 3.5.1.3: Cystic partially differentiated nephroblastoma
  - 3.5.1.4: Nephroblastoma

### 3.6: Miscellaneous renal tumours
- 3.6.2: Germ cell tumours of the kidney
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경청해 주셔서 감사합니다!