AACC Better health through laboratory medicine.

PEARLS OF LABORATORY MEDICINE

Pearl Title: Introduction to Cancer Genetics

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Application of Molecular testing

- Diagnosis
- Prognostic: risk markers
- Therapeutic
  - Selecting therapeutic targets
  - Monitoring treatment response

Solid tumors with clinically significant molecular biomarkers

- Lung
- Colorectal carcinoma
- Melanoma
- Brain Tumors
- Breast
- GIST
- Thyroid
- Sarcomas

Lung carcinoma

Gene	Prevalence	Histology	Clinical characteristics	Available targeted therapy
EGFR	10-35%	Adenocarcinoma with bronchoalveolar features	East Asian, women, never smokers	TKIs- Geftinib, erlotinib
KRAS	25-30%	Adenocarcinomas, poorly differentiated, mucinous, bronchiolalveolar	Smokers Non-Asians > Asians	Negative predictor of response to EGFR TKIs
EML-ALK4 fusions	5%	Solid/ acinar, signet ring adenocarcinoma	Non/ light smokers Younger age	Response to Crizotinib
BRAF	2-3%	Adenocarcinoma, micropapillary, papillary	Current/former smokers M=F	Resistance to EGFR inhibition. Benefit from MEK inhibitors
ROS1 fusions			Never smokers, Asian, younger	Response to Crizotinib

EGFR

- Mutations seen in 25-30% of NSCLC
- EGFR TK domain mutations: Most reliable predictor of response to TKIs

Sensitive to TKIs	Resistant to TKIs
Exon 19 deletion (codons 746-750)	Insertions in exon 20
L858R (exon 21)	T790M (secondary resistance)
G719 (exon 18)	S768I, L747S, D761Y and T854A
L861 (exon 21)	

Other mutations

- *KRAS*
  - Mutually exclusive of *EGFR*
  - G12C:
    - More common in smokers
    - Reduced sensitivity to Cisplatin
    - Better response to Paclitaxel and Pemetrexed
  - G12D
    - Never smokers
- *EML4-ALK*
  - FISH Dual color break apart probe
  - Other partner genes: *KIF5B*, *KLC-1*, *TFG*
- *BRAF*
  - V600E (exon 15)- most common mutation
  - G469A (exon 11)- 2nd most common
- *ROS1* fusions
  - Fusion partners- *SLC34A2*, *CD74*, *TPM3*, *SD4*, *EZR*, *LRIG3*

ASCO recommendations/ Algorithm

- *EGFR* should get priority over other testing
- On limited specimens *EGFR* and *ALK* testing can be performed when an adenocarcinoma cannot be excluded
- In resected specimens, *EGFR* and *ALK* testing is not recommended if there is no adenocarcinoma

Colorectal Carcinoma (CRC)

- 3 distinct pathways
  - FAP (suppressor) (chromosomal instability pathway)
    - APC/β -catenin/Wnt signaling pathway
  - Serrated pathway (aberrant CpG island methylation-CIMP)
    - Microsatellite stable (MSS)
    - Microsatellite instability high (MSI-H): epigenetic silencing (hypermethylation) of *MLH1*
  - Hereditary MSI (Lynch syndrome)
    - Germline mutation in *MSH2*, *MLH1*, *MSH6*, or *PMS2*

Microsatellite Stability

- Mismatch repair (MMR)
  - Sporadic
    - MSI- Most show CpG methylation of MLH1 promoter
    - 3/4 of these will have *BRAF* mutation
  - Germline
    - < 1/3 of MSI/ MMR deficient- germline mutation of 1 of the 4 MMR genes: Lynch syndrome- AD

MSI- Clinical Significance

- MSI-H
  - Better prognosis
  - Resistant to 5-FU, alkylating agents, and platinum compounds
  - More sensitive to irinotecan
  - Early data: better response to anti- PD-1 /PD-L1 immune checkpoint inhibitor therapy

Colorectal Cancer: Mutation profile

- *EGFR* mutation is very rare in CRC
- EGFR monoclonal Ab resistance
  - *KRAS* mutations
  - *BRAF* V600E
- *KRAS* ~ 40%
  - Never smokers- G12D, G>A transitions (G13D, G12S)
  - Smokers- G12C, G>T transversion (G13C , G12V)
- *BRAF* V600E ~4%
- *PIK3CA* ~ 3%
- *NRAS* ~ 2%
- *MEK1*, *AKT* ~ 0.5%

CRC testing recommendations

- *KRAS* and *NRAS* codons
  - 12 and 13 (exon 2)
  - 59 and 61 (exon 3)
  - 117 and 146 (exon 4)
- *BRAF*
  - V600E: poor outcomes, decreased response to EGFR-targeted therapy
- *PIK3CA*- poor response rate and progression free survival
  - E542, E545, H1047 (exons 9, 20)
- *EGFR*- no role for testing
- CAP guidelines: *KRAS* codons 12/13/61/146 and *NRAS*

Melanoma

- *BRAF*~ 40—60%
  - Intermittently sun damaged skin
  - V600E (70-85%), V600K (5-30%)
  - Vemurafenib- active against BRAF
- *NRAS* (15-20%)
  - Nodular melanomas, sun damaged skin
  - Mutually exclusive of *BRAF* alterations
  - Codon 61- most common
- *KIT*
  - Acral and mucosal melanoma
- *GNAQ*/*GNA11*: mutually exclusive
  - Uveal melanoms (83%)
  - Blue nevus like melanomas

Brain: Oligodendroglioma

- Oligodendroglioma
  - 1p/19q co-deletion
    - Chemosensitive and radiation sensitive
    - Favorable prognosis
  - *IDH* mutations
  - WHO Classification- *IDH* mutations and 1p/19q co-deletion required for grade II and III oligodendrogliomas
  - No *EGFR* amplification

Brain

- *EGFR*
  - Amplified/ mutated in 40-45% of high grade gliomas
  - Constitutive TK activation
  - Does not predict response to EGFR therapy.
- *IDH1*/*IDH2* (exon 4)
  - ~75% of grade II and III gliomas
  - Diagnostic
    - Tumor vs reactive gliosis
    - Pilocytic astrocytoma vs. diffuse astrocytoma or oligodendroglioma
  - Favorable prognosis
  - *IDH1* R132H- most common

Breast Cancer

- *ERBB2* (HER2) amplification- ~20%
  - Higher grade, metastatic tumors
- Response to trastuzumab and lapatinib
- Testing: IHC and/ or FISH
- Familial breast cancer
  - *BRCA1*, *BRCA2*
  - *TP53* - Li-Fraumeni syndrome
  - *STK11* - Peutz-Jeghers syndrome
  - *PTEN* - Cowden syndrome
  - *CHEK2*
  - *ATM*
  - *PALB2*
  - *BRIP1*

Gene expression profiles

- Oncotype DX
  - Predicts a recurrence score which can be used to guide treatment decisions
  - 21 genes (16 cancer related, 5 reference), PCR based
  - Women recently diagnosed with invasive breast cancer (stage I-IIIa), ER+, HER2-
  - Recurrence score: low (<18)/intermediate (18-30)/high risk (>31)
- MammaPrint
  - Predicts likelihood to benefit from adjuvant chemotherapy
  - 70 genes
  - FDA approved for node-negative, treatment naive breast cancer patients with stage I or II disease
  - Classification into low or high risk
- PAM50
  - 50 genes to identify the intrinsic subtype of breast cancer
- Theros (Biotheranostics Breast Cancer Index)

GIST

- *KIT*- 95%, spindled
  - Exon 11 (gastric)
    - p.W557del and/or K558del - worse prognosis
  - Exon 9 (small intestine and colon)
    - Relatively resistant to imatinib (higher dose)
- *PDGFRA*- 5%, epithelioid
  - Gastric, extra-GI
  - D842V- resistant to imatinib
- Imatinib resistance-
  - Primary- *KIT* WT, exon 9, *PDGFRA* D842V
  - *KIT* exon 13 K642E, *KIT* exon 17 Y823D

Thyroid

- *BRAF* V600E
  - PTC - 35-70%
  - Tall cell variant, classic
- *RET/PTC* rearrangement
  - Sporadic PTC - 10-20%
  - Radiation exposure, younger age
  - Lymph node metastases
- *RAS*
  - Papillary (follicular variant) and Follicular
- *PAX8*/peroxisome proliferator-activated receptor (*PPARγ*) rearrangements
  - Follicular
  - Younger, smaller size, solid/nested growth
- *RET* mutations
  - Medullary thyroid carcinomas

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