Genomics in the Cancer Clinic

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January 23, 2020
Genetics vs. Genomics-1

Oncologists utilize both GENETIC AND GENOMIC information to treat patients

GENETICS: The DNA a person is born with (HEREDITY)

- Inherited DNA mutations predispose to cancer (BRCA1/2)
- Detected from the blood or saliva
- May or may not be known before a cancer diagnosis

Oncologists follow national guidelines on testing e.g. NCCN (National Comprehensive Cancer Network)

Results may affect how the cancer is treated
Genetics vs. Genomics-2

- **GENOMICS**: The DNA profile of a cancer:
  - “How does the cancer DNA differ from normal?”
  - Mutations acquired as a normal cell becomes a cancer cell
  - Present only in the cancer, not the germline DNA
  - Detected from a tumor biopsy > bloodstream
  - Have important implications for the treatment of cancer
  - Oncologists order “genomic profiling” from companies or their institution
CANCER DEVELOPS BY ACCUMULATING DNA CHANGES: Captured by Genomic Profiling
THERAPEUTIC OPTIONS FOR THE PATIENT WITH ADVANCED CANCER

- CHEMOTHERAPY - TARGET RAPIDLY DIVIDING CELLS
- IMMUNOTHERAPY - PATIENT’S IMMUNE CELLS ATTACK CANCER
- TARGETED THERAPY - BIND “DRIVER MUTATIONS” IN A CANCER CELL TO HALT GROWTH AND SPREAD
- DRIVERS FOUND BY GENOMIC PROFILING
- COMBINATIONS OF THE ABOVE
GENOMIC PROFILING CLASSIFIES CANCER BY DRIVER MUTATIONS

Lung Adenocarcinoma

2003

2012

KRAS
EGFR
ALK fusions
HER2
MAP2K1
AKT1
P1K3CA
BRAF
NRAS
ROS1 fusions
RET fusions
Unknown

# Genomic Profiling Identifies Gene Targets To Personalize Therapy

<table>
<thead>
<tr>
<th>Genomic Alterations Detected</th>
<th>FDA Approved Therapies (in patient’s tumor type)</th>
<th>FDA Approved Therapies (in another tumor type)</th>
</tr>
</thead>
<tbody>
<tr>
<td>EGFR L858R</td>
<td>Erlotinib</td>
<td>Cetuximab</td>
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<tr>
<td></td>
<td>Gefitinib</td>
<td>Lapatinib</td>
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<tr>
<td></td>
<td>Afatinib</td>
<td>Panitumumab</td>
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<tr>
<td>ALK EML4-ALK fusion</td>
<td>Crizotinib</td>
<td>None</td>
</tr>
<tr>
<td>TSC2 splice site 3285-1 G&gt;A</td>
<td>None</td>
<td>Everolimus</td>
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<tr>
<td></td>
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<td>Temsirolimus</td>
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<tr>
<td>BRAF V600E</td>
<td>None</td>
<td>Vemurafenib</td>
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<td>Trametnib</td>
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<td>Dabrafenib</td>
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Lung Ca Patient Treated With an EGFR Inhibitor

6 FEB 2002

13 FEB 2002
TARGETED THERAPY VS. CHEMOTHERAPY IN LUNG CANCER

A. Patients in Intention-to-Treat Population

<table>
<thead>
<tr>
<th></th>
<th>Median Progression-free Survival</th>
<th>No. of Patients</th>
<th>Progression-free Survival</th>
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</thead>
<tbody>
<tr>
<td>Osimertinib</td>
<td>10.1 (95% CI: 8.3–12.3)</td>
<td>279</td>
<td></td>
</tr>
<tr>
<td>Platinum–pemetrexed</td>
<td>4.4 (95% CI: 4.2–5.6)</td>
<td>140</td>
<td></td>
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</table>

Hazard ratio for disease progression or death, 0.30 (95% CI: 0.23–0.41)
P<0.001

No. at Risk

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<tr>
<td></td>
<td>279</td>
<td>140</td>
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<td>Month</td>
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</tbody>
</table>

MOK TS, ET AL. NEJM 2016
**Targeted Cancer Therapies are Exploding**

- Worldwide dollars spent on targeted oncology drugs:
  - 2002: $2.0 bn
  - 2011: $21.7 bn

- **Pharma Pipeline**
  - >950 clinical trials
  - 470 targeted therapies

- **Progress in molecular biology** continues to underpin explosive growth in the number of targets, targeted therapeutics, and their utilization.

- Source: Tufts Center for the Study of Drug Development

1. *Worldwide dollars spent on targeted oncology drugs*
Potential State Role

Genetic Testing

- Mandate that insurers cover the cost for testing of any individuals who meet national testing guidelines for hereditary cancers

Genomic Testing

- Mandate that insurers cover the cost of at least one “Genomic Profile” for each patient with advanced, incurable cancer.
PANCREATIC CANCER LACKS THERAPEUTIC OPTIONS

• **CHEMOTHERAPY**: *TARGET RAPIDLY DIVIDING CELLS*

• **IMMUNOTHERAPY** - PATIENT’S IMMUNE CELLS ATTACK CANCER

• **TARGETED THERAPY** - BIND “DRIVER MUTATIONS” IN A CANCER CELL TO HALT GROWTH AND SPREAD, DRIVERS FOUND BY GENOMIC PROFILING

• **COMBINATIONS OF THE ABOVE**
Projected Annual US Cancer Deaths

- Lung and bronchus
- Colon and rectum
- Liver
- Pancreas
- Breast
- Bladder
- Leukemia
- Liver and intrahepatic bile duct
- Prostate

Rahib et al., Cancer Res 2014
Pancreatic Cancer

High-Risk Groups Under Study:

- Hereditary Genetic/Familial: 10%
- Sporadic (no known cause): 90%
- High-Risk: Age 50+ with new-onset diabetes mellitus (12 months)
Fasting Blood Glucose Levels Provide Estimate of Duration and Progression of Pancreatic Cancer before Diagnosis

Predicted duration of invasive PDAC before diagnosis (Sojourn time)

Lead time: 30-36 months

Hyperglycemia

Diabetes

PDAC diagnosis

Mean FBG (mg/dl)

Time to Diagnosis (months)
Early Detection Protocol in New-Onset Diabetes >50 yo

Define a high risk group

Enrich a high risk group

Find the lesion

Biopsy

Imaging

Biomarker/ Clinical phenotype

Clinical indicators

General population

New-onset diabetes

Blood test

MRI

EUS