Benefits of Genomic Medicine: What to Tell the Patient

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No Conflict of Interest to Disclose
Outline

• Background in head and neck squamous cell carcinoma (HNSCC)
• Current approaches to the management of HNSCC
  – Prognostic factors
• Future approaches to personalized therapy in HNSCC
  – Genomics-based predictive biomarkers
  – Barriers to a clinical implementation
• Summary
Background: HNSCC

- The 5th most common cancer worldwide
- Median age of Dx: 53-57
- Gender: Male Predominance (M:F=3:1)
- Approximately 2/3 of the cases are advanced stage III/IV at presentation
- Risk factors
  - Tobacco, Alcohol
  - Human Papillomavirus (HPV): oropharynx
  - Epstein-Barr Virus (EBV): nasopharynx
Common sites of squamous cell carcinoma

- Oral Cavity: oral tongue, floor of mouth, etc.
- Nasopharynx: base of tongue, soft palate, tonsil
- Oropharynx: pyriform sinus, post-cricoid, posterior pharyngeal wall
- Hypopharynx: pyriform sinus, post-cricoid, posterior pharyngeal wall
- Larynx: Supraglottis, glottis, subglottis

Sinonasal tumors
Salivary gland tumors
Lymphoma
Mucosal melanoma
Sarcoma
Thyroid, etc.
Overall Survival by HPV Status

log-rank p<0.001

5-year difference ~30%

Patients at Risk
HPV Pos. 206 HPV Neg. 117
0 1 2 3 4 5
Years after Randomization

Patients at Risk
0 1 2 3 4 5

Overall Survival (%)
Case #1: Mrs. H.

- 63 year old woman
- 3 months of toothache, 20 lbs of weight loss from pain with chewing
- SHx: Librarian, 2 packs of cigarette x 40 years, 3 glasses of wine every night x 30 years
- T4N2bM0: locally advanced stage IV
- HPV status: negative
Stage IV oral cavity SCC
Case #2: Mr. S.

- 36 year old man
- Sore throat and a neck mass for 3 months
- Treated with antibiotics for 2 weeks by primary care doctor but did not get better
- SHx: Truck Driver, Married with two children, non-smoker, 6 packs of beer only in weekends
- T2N2cM0 : locally advanced stage IV
- HPV status: positive
Stage IV oropharyngeal SCC
Treatment for Stage IV HNSCC in Mrs. H. and Mr. S.

- Concurrent chemoradiation
  - radiation therapy daily over 7 weeks
  - cisplatin Q 3 week X 3 cycles
Outcome

• Mrs. H. is disease free for 5 years
  – Severe fibrosis of oral cavity and neck requiring a G-tube

• Mr. S. died of disease
  – Developed widely metastatic disease in bones, lungs and liver
  – Received 2 courses of palliative radiation therapy to the bone metastasis to control pain
  – Surgical decompression of metastasis around the spinal cord
  – Received 2 courses of palliative chemotherapy
  – Died under the care of hospice within 2 year
Overall Survival by HPV Status

Overall Survival (%)

Years after Randomization

Patients at Risk
HPV Pos. 206
HPV Neg. 117

log-rank p<0.001

HPV Positive

HPV Negative

Patients at Risk
HPV Pos. 206
HPV Neg. 117

Ang, et al. NEJM 2010
Prognostic and Predictive Molecular Markers

• **Prognostic markers** distinguish the differences in patient outcomes regardless of given treatment
  → HPV alone is not sufficient

• **Predictive markers** distinguish the differences in patient outcomes based on a specific therapy
  → Need a predictive biomarker for a less toxic, more effective therapy for each patient
<table>
<thead>
<tr>
<th>Study</th>
<th>Disease</th>
<th>Marker</th>
<th>Treatment</th>
<th>HR</th>
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</thead>
<tbody>
<tr>
<td>Heinrich (2003) JCO</td>
<td>GIST</td>
<td>C-kit mutation</td>
<td>Imatinib</td>
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<td>Kantarjian (2004) CCR</td>
<td>CML</td>
<td>t(9;22)</td>
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<td>Rosell (2009) NEJM</td>
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<td>EGFR mutation (L858R)</td>
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<td>Shaw (2011) Lancet Onc</td>
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<td>EML4/ALK translocation</td>
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<td>Chapman (2011) NEJM</td>
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<td>B-raf mutation (V600E)</td>
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<td>Karapetis (2008) NEJM</td>
<td>Colon cancer</td>
<td>K-ras wild type</td>
<td>Cetuximab</td>
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<tr>
<td>Coiffier (2002) NEJM</td>
<td>Diffuse large B cell lymphoma</td>
<td>CD20</td>
<td>Rituximab</td>
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<td>Schulz (2007) JNCI</td>
<td>Follicular lymphoma</td>
<td>CD20</td>
<td>Rituximab</td>
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<td>Bang (2010) Lancet</td>
<td>Gastric cancer</td>
<td>HER2 overexpression</td>
<td>Trastuzumab</td>
<td>1.5</td>
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<tr>
<td>Slamon (2001) NEJM</td>
<td>Breast cancer</td>
<td>HER2 overexpression</td>
<td>Trastuzumab</td>
<td>1.3</td>
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</table>
Whole exome sequencing of HNSCC

<table>
<thead>
<tr>
<th></th>
<th>HPV-positive</th>
<th>HPV-negative</th>
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</thead>
<tbody>
<tr>
<td># of mutations</td>
<td>19</td>
<td>576</td>
</tr>
<tr>
<td># of tumors</td>
<td>4</td>
<td>28</td>
</tr>
<tr>
<td>Average # of mutations per tumor</td>
<td>4.8</td>
<td>20.6</td>
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Agrawal, et al. Science 2011
Mutational Spectrum in HPV(-) vs HPV(+)

HPV(-): Mostly tumor suppressors – TP53, CDKN2A, NOTCH1

HPV(+): More oncogenes – PIK3CA, FGFR2/3

Kech, et al, ASCO 2013
“All happy families are alike; each unhappy family is unhappy in its own way.”

- Leo Tolstoy, Anna Karenina
Case #3: Mr. A.

- 49 yo WM with T2 N2b M0 HPV+ OPSCC
  - Bilateral tonsillectomy by transoral robotic resection and right neck dissection
  - Post-op weekly cisplatin + RT X 6 weeks
  - Recurrence in the spine in 14 months
  - Cisplatin/docetaxel/cetuximab X 6 cycles
  - Disease progression within 3 months of completing the chemotherapy
Clinical Report

**ABOUT THE TEST:**
FoundationOne™ is a next-generation sequencing (NGS) based assay which identifies genomic alterations within hundreds of cancer-related genes.

**PATIENT RESULTS**

- 4 genomic alterations
- 4 therapies associated with potential clinical benefit
- 0 therapies associated with lack of response
- 6 clinical trials

**TUMOR TYPE: HEAD AND NECK SQUAMOUS CELL CARCINOMA (HNSCC)**

Genomic Alterations Identified
- MET L1112F
- PIK3CA E542K, amplification
- SOX2 amplification

**THERAPEUTIC IMPLICATIONS**

<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>
<th>Potential Clinical Trials</th>
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<tbody>
<tr>
<td>MET L1112F</td>
<td>None</td>
<td>Cabozantinib, Crizotinib</td>
<td>Yes, see clinical trials section</td>
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<tr>
<td>PIK3CA E542K, amplification</td>
<td>None</td>
<td>Everolimus, Temsirolimus</td>
<td>Yes, see clinical trials section</td>
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<tr>
<td>SOX2 amplification</td>
<td>None</td>
<td>None</td>
<td>Yes, see clinical trials section</td>
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JOHNS HOPKINS MEDICINE
No therapies FDA approved in this patient’s tumor type

<table>
<thead>
<tr>
<th>THERAPIES</th>
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<tr>
<td>There are no therapies FDA approved in this patient’s tumor type that are:</td>
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<tr>
<th>ADDITIONAL THERAPIES – FDA APPROVED IN OTHER TUMOR TYPES</th>
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<tr>
<td>THERAPY</td>
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<tr>
<td>---------</td>
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<tr>
<td>Cabozantinib</td>
</tr>
<tr>
<td>Crizotinib</td>
</tr>
<tr>
<td>Everolimus</td>
</tr>
<tr>
<td>Temsirolimus</td>
</tr>
</tbody>
</table>

FDA approved in other tumor types

- Cabozantinib
- Crizotinib
- Everolimus
- Temsirolimus

MET inhibitor

- Cabozantinib
- Crizotinib

mTOR inhibitor

- Everolimus
- Temsirolimus
Limitations:
Lack of Trial Options and Cost

- PI3KCA E542K/amp, SOX2 amp, MET L1112F
- Not eligible to PI3K inhibitor trials due to lack of measurable disease (bone mets only)
- Lack of clinical trials with appropriate combinations
- Cost of the assay: $5,700
- Cost of current cancer medications (everolimus ~$8,000 and cabozantinib ~4,000 per month)
- Who pays for this?
Case #4: Mr. S.

- 60 yo WM with HPV- oral cavity SCC
  - T2N0M0: Partial glossectomy and neck dissection
  - Recurrence within 3 months: Total glossectomy and post-op chemoRT
  - Recurrence within 3 months with lung mets
Limitations: Lack of Treatment

- TP53 R213*, MYC amp, NKX2-1
- Lack of treatment for tumor suppressor genes and untargetable mutations/aberrations
- Limited data regarding biological and clinical significance of genetic aberration
- Turn around time of the assays
  - Planned to enroll on the Wee1 inhibitor trial but performance status declined rapidly and passed away before the trial
Case #5: Mr. F.

- 60 yo WM with HPV+ T3N1M0 OPSCC
  - Cisplatin, 5FU and XRT
  - Recurrence in tonsil after 2 years: salvage resection
  - Recurrence in the neck nodes in 6 months: neck dissection
  - Solitary lung met in 3 months: wedge resection
  - Recurrence in the neck nodes again in 2 months: neck dissection → carbo/taxol and XRT
  - Recurrence to subcarinal and hilar LN in 5 months → MAGE vaccine trial but progressed
  - Dermal met in 6 months: Local resection and reconstruction
  - Within a month, new dermal mets along the surgical scar
ERBB2 (HER-2) amp
RICTOR amp
MLL2 E766*
FGF10 amp
HER-2 IHC and FISH

Courtesy of Dr. Robert Palermo at Greater Baltimore Medical Center
Before
Therapy

Trastuzumab and Paclitaxel X 2 cycles

After Therapy
Treatment Course of Mr. F.

• Trastuzumab and Paclitaxel X 8 cycles (6 months) – complete response
• Developed toxicities from paclitaxel and treated on trastuzumab alone (3 months) – disease progression in the lymph nodes while bone mets were still under control
Limitations: Heterogeneity

B Vogelstein et al. Science 2013;339:1546-1558
Limitations:
Tumor heterogeneity and toxicities

- Tumor heterogeneity and emergence of resistant clones
- Toxicities, especially with combination regimens
- Repeat biopsies and cost
- Surveillance methods
NCI-Precision Medicine Initiatives

• Incorporate genomics to clinical trials for precision medicine

• Multiple single arm trials
  – Exceptional Responders Initiatives
  – MATCH: Molecular Analysis for Therapy Choice
  – ALCHEMIST: Adjuvant Lung Cancer Enrichment Marker Identification and Sequencing Trial
  – Lung-MAP (S1400 Lung Master Protocol)

• Patients undergo pre- and post-tx biopsies to obtain genomic data

• Enroll patients to appropriate targeted agent arms based on their genomic data
What to tell the patient

• Genomic testing is NOT a standard of care for HNSCC
• Yes, there are scientific evidence that results of genomic testing MAY help the outcome in HN cancer
• But there is NO data to support that the treatment based on the testing results prolongs survival in HN cancer and the trials are ongoing
• May not have targetable genomic aberrations
• May not have access to medication
• Expensive and no cost-benefit analysis is available
• While the technology is here, clinical research, health care policy, insurance policy and ethics guidelines have not caught up yet
Conclusions

• While genomics data reveal a complex genome, the biological and clinical significance of genetic aberrations are largely unknown.

• While they are powerful discovery tools, each finding must be vigorously validated before broad clinical application.

• In addition to response prediction research, toxicity prediction deserves more attention.

• There are many unresolved issues beyond Science and Medicine (i.e. regulatory, financial, etc.).