Precision Oncology: 
Current Applications of –omics

ACP Arizona Chapter Scientific Meeting, 2014
Arizona State University in Tempe, Arizona
Alan Bryce, MD
Disclosures

None
### The Diseases and Casualties this Week

<table>
<thead>
<tr>
<th>Disease</th>
<th>Cases</th>
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<tbody>
<tr>
<td>Impothesis</td>
<td>11</td>
</tr>
<tr>
<td>Infants</td>
<td>16</td>
</tr>
<tr>
<td>Killed by a fall from the Belfrey at Allhallows the Great</td>
<td>1</td>
</tr>
<tr>
<td>King's Evil</td>
<td>2</td>
</tr>
<tr>
<td>Lethargy</td>
<td>1</td>
</tr>
<tr>
<td>Paralyse</td>
<td>1</td>
</tr>
<tr>
<td>Plague</td>
<td>716</td>
</tr>
<tr>
<td>Rickets</td>
<td>17</td>
</tr>
<tr>
<td>Rising of the Lights</td>
<td>11</td>
</tr>
<tr>
<td>Scouring</td>
<td>5</td>
</tr>
<tr>
<td>Scurvy</td>
<td>2</td>
</tr>
<tr>
<td>Spleen</td>
<td>2</td>
</tr>
<tr>
<td>Spotted Fever</td>
<td>102</td>
</tr>
<tr>
<td>Stillborn</td>
<td>17</td>
</tr>
<tr>
<td>Stone</td>
<td>2</td>
</tr>
<tr>
<td>Stopping of the Stomach</td>
<td>9</td>
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<tr>
<td>Strangury</td>
<td>1</td>
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<tr>
<td>Suddenly</td>
<td>1</td>
</tr>
<tr>
<td>Surfeit</td>
<td>49</td>
</tr>
<tr>
<td>Teeth</td>
<td>121</td>
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<tr>
<td>Thrush</td>
<td>5</td>
</tr>
<tr>
<td>Timpany</td>
<td>1</td>
</tr>
<tr>
<td>Tiffick</td>
<td>1</td>
</tr>
<tr>
<td>Vomiting</td>
<td>3</td>
</tr>
<tr>
<td>Winde</td>
<td>3</td>
</tr>
<tr>
<td>Wormes</td>
<td>15</td>
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<table>
<thead>
<tr>
<th>Gender</th>
<th>Cases</th>
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<tbody>
<tr>
<td>Males</td>
<td>4095</td>
</tr>
<tr>
<td>Females</td>
<td>4202</td>
</tr>
<tr>
<td>In all</td>
<td>8297</td>
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</table>

**Increased in the Burials this Week**: 607

**Parishes clear of the Plague**: 4

**Parishes Infected**: 126

---

The Asize of Bread set forth by Order of the Lord Mayor and Court of Aldermen.

A penny Wheaten Loaf to contain Nine Ounces and a half, and three half-penny White Loaves the like weight.
NSCLC
Clinical Application of NGS

- Real time application of NGS to clinical practice is challenging
  - Time from biopsy to return of results
  - Development of Bioinformatic infrastructure for interpretation of results
  - Acquisition of drugs

- Pilot study was begun in the third quarter of 2010 to address these challenges

- Genomic Tumor Board for return results begun May 2012
Study Design

- Two parallel protocols were opened
  - Institutionally funded protocol for rare cancers (Stewart)
  - Self Pay protocol (Borad)

- Patients must have
  - Advanced Malignancy refractory to standard therapy
  - Biopsiable lesion
  - Life Expectancy >3 months
Genetic Counselor visit

Four 18 gauge core biopsy samples
Serum for germline DNA

Whole genome, exome and RNA sequencing

Clinical Genomics Tumor Board

CLIA validation

Consensus recommendation to treating physician

Results discussed with patient, physician and genetic counselor
Cholangiocarcinoma
Graphical Overview
ERRFI1 (Mig6) inactivating mutation
ERRFI1 mutation treated with erlotinib

Baseline

3 months
Detected fusions in cholangiocarcinomas
FGFR2 and FGFR3 IHC
FGFR2:MGEA5 fusion and FGFR3 amplification treated with ponatinib
HPV 18 integration
# Extramedullary Myeloma

## Table 1. Summary of clinically relevant SNVs

<table>
<thead>
<tr>
<th>Chr</th>
<th>hg19 position</th>
<th>SNV</th>
<th>Gene</th>
<th>SIFT</th>
<th>Polyphen2</th>
<th>Effect</th>
<th>Amino acid</th>
<th>dbSNP</th>
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<tr>
<td>3</td>
<td>3195747</td>
<td>C&gt;T</td>
<td>CRBN</td>
<td>Tolerated</td>
<td>Benign</td>
<td>Not</td>
<td>R283K</td>
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<tr>
<td>3</td>
<td>3215822</td>
<td>G&gt;A</td>
<td>CRBN</td>
<td>Predicted</td>
<td>Predicted</td>
<td>STOP gained</td>
<td>Q99*</td>
<td></td>
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<tr>
<td>3</td>
<td>178936082</td>
<td>G&gt;A</td>
<td>PIK3CA</td>
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<td>Damaging</td>
<td>Nonsynonymous coding</td>
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<td>NR3C1</td>
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<td>Nonsynonymous coding</td>
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<tr>
<td>18</td>
<td>12720612</td>
<td>G&gt;A</td>
<td>PSMG2</td>
<td>Tolerated</td>
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<td>Nonsynonymous coding</td>
<td>E171K</td>
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</table>
Precision Oncology at MCA Challenges

- Cost and Time of testing
- Bioinformatics
- Staff- Medical Geneticists and Genetic Counselors
- Drug Acquisition
  - Need new Paradigms for Trials
  - RAPID
- Number Needed to Screen
  - Routine Testing of all patients is needed
Eroom’s Law
THE CLINICAL-TRIAL CLIFF

Drug companies are removing more compounds from the pipeline at all levels of testing than ever before.

For projects started between 1990 and 2004, the United States, Europe and Japan have seen sharp rises in the attrition of drugs tested in trials.

Most of the product failures in phase II and III trials are because researchers are unable to demonstrate efficacy or sufficient safety.

- **Phase II 2008–10**
  - Efficacy
  - Safety
  - Strategic
  - Pharmacokinetics/bioavailability
  - Commercial/financial
  - Not disclosed

- **Phase III 2007–10**
  - Efficacy
  - Safety
  - Strategic
  - Pharmacokinetics/bioavailability
  - Commercial/financial
  - Not disclosed
New Paradigms

- Target Discovery/Validation through Genome directed therapy studies
  - FGFR inhibitor studies being initiated at MCA (Board)

- Histology Specific trials of multiple molecular aberrations

- Basket Studies of tumor agnostic aberration specific therapy
  - RAPID
**RAPID (Modular Design)**

- **GENOMIC PROFILING**
- **TARGET ID**
- **CLINOMICS BOARD**
- **Treatment Plan**
- **EFFICACY OUTCOME AND SAFETY OUTCOME**
- **CIM GENOMIC OUTCOMES DATABASE**

**Sponsor 1 Drug 1**
- **Sponsor 1 Drug 2**
- **Sponsor 2 Drug 1**
- **Sponsor 2 Drug 2**
- **Sponsor N Drug n**
- **Sponsor N Drug n+1**
CIM at MCA today
Oncology

1. Genomic Oncology Clinic
2. BEAUTY- Breast Cancer Pharmcagenomics Trial
3. PROMOTE- Prostate Cancer PGX Trial
4. SU2C- Randomized trial of genome directed therapy versus chemotherapy
BEAUTY

Old Model – Surgery First

tumor → surgery → disease free → chemo → observe

New Model

tumor → chemo → nothing → surgery → disease free → observe

response / outcome known here
Von Minckwitz G. et al. JCO 2012; 30: 1796-1804
BEAUTY Project
Breast Cancer Genome Guided Therapy

Women with invasive breast cancer

HER2+
Paclitaxel + Trastuzumab
AC or FEC

HER2-
Paclitaxel
AC or FEC

Tumor biopsy
Magnetic Resonance Imaging
Molecular Breast Imaging
Mouse “avatars” (xenografts)

Tumor biopsy
Magnetic Resonance Imaging

Tumor biopsy
Molecular Breast Imaging

Surgery
5 year observation

Tumor tissue
Mouse “avatars” (xenografts)
Tumor Biopsies from BEAUTY Patients

Breast Tumor samples

- Baseline (before chemotherapy), during and after chemotherapy
  - All 3 biopsies go for sequencing
  - Baseline biopsy and any residual disease goes for xenografts

Multiple sequencing approaches

- Tumor DNA—Exome Sequence
- Tumor RNA-Seq
- Tumor Methylation 450K Illumina
- Germline DNA—Exome Sequence
- Germline SNP Array
- RPPA

Xenografts

- Determine functional implications of genetic alterations
- Study new drugs, and drug combinations, to identify best regimens to move forward in specific tumor subtypes
CIM at MCA
Non Oncology

1. Service Line 2 - Diagnostic Odyssey
2. TAILOR-PCI - Clopidogrel Pharmacogenomics
3. Pharmacogenomics Task Force-Development of EMR based tools
Pharmacogenomics Program

Ensure we give the **right drug** at the **right dose** at the **right time** based on the **individual patient**

- Abacavir
- Carbamazepine
- Interferon
- Thiopurines

Embed in EMR
Educate physicians
Improve care
Reduce costs
<table>
<thead>
<tr>
<th>Phenotype: Metabolizer Group</th>
<th>Genotype and Examples</th>
<th>Effect on CYP2D6 activity</th>
<th>Effect on Codeine metabolism</th>
<th>Recommended Action</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Ultrarapid Metabolizer</strong></td>
<td>Two or more copies of functional alleles or two copies of increased function alleles *1/*1xN *2A/*2AxN (*1/*2A)xN *2A/*2A</td>
<td>Increased</td>
<td>Increased morphine formation leading to increased risk of toxicity</td>
<td>Avoid Codeine due to toxicity Consider alternatives that are not similarly CYP2D6 dependant- i.e. avoid Tramadol</td>
</tr>
<tr>
<td><strong>Extensive Metabolizer</strong></td>
<td>Two functional alleles*1/*1</td>
<td>Normal</td>
<td>Normal morphine formation</td>
<td>Standard dosing</td>
</tr>
<tr>
<td><strong>Intermediate Metabolizer</strong></td>
<td>One functional and one absent functional allele or 2 reduced function alleles *1/*4 *10/*10</td>
<td>Reduced</td>
<td>Reduced morphine formation and possible insufficient pain relief</td>
<td>Standard dosing Monitor for lack of efficacy If no response use alternative that is not similarly CYP2D6 dependant- i.e. avoid Tramadol</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Increased dosing is not recommended.</td>
<td></td>
</tr>
<tr>
<td><strong>Poor Metabolizer</strong></td>
<td>No functional alleles *4/*4 *4/*5</td>
<td>Absent</td>
<td>Minimal morphine formation and insufficient pain relief. Side effects of codeine are reported.</td>
<td>Avoid Codeine due to lack of efficacy Consider alternatives that are not similarly CYP2D6 dependant- i.e. avoid Tramadol</td>
</tr>
</tbody>
</table>
CYP2D6 Event Rule
Ver. 1.0 6/28/13

New Lab Result on EMR interface

Lab is 2D6 result

Yes

Lab Key Type and Key Sub Type = 'LAB'

Yes

LAB is 2D6 result received

Yes

Populate ProblemList

Scan problem list for xxPOORxx, xxNORMALxx, xxINTERMEDIATExx or xxULTRARAPIDxx codes (active, inactive and resolved codes), to check if there is more than one problem list code to determine Inbox Message Content

Send inbox alert:
Inpatient recipient: Ordering service,
Outpatient recipient: Provider
Msg - Patient has a poor, intermediate or ultrapid level (based on the problem list code) and may be at risk of reduced efficacy or side effects. AME link for specifics. If more than one problem list code exists for the patient, then the alert includes that in this message.

Log Patient and rule result Information

Exit
# Acknowledgements

<table>
<thead>
<tr>
<th>CIM</th>
<th>MCA</th>
<th>TGEN</th>
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<td>Gianrico Farrugia</td>
<td>Mitesh Borad</td>
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<td>Richard Caselli</td>
<td>Katherine Hunt</td>
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<td>Kostas Lazaridis</td>
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