Getting to the Right Patient, with the Right Drug(s) at the Right Time(s)

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October 20, 2016

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Precision Medicine and the Paradigm Shift

Treatment landscape in prostate cancer. Courtesy of William K. Oh, MD.
Mission
MD Anderson will provide Personalized Cancer Therapy for all of our patients, and define the new standard of patient care by improving outcomes and reducing costs.

Vision
MD Anderson will be the leader in implementing Personalized Cancer Therapy, based on an analysis of each patient’s cancer that will integrate information across DNA, RNA, proteins and metabolomics in the context of the tumor in its microenvironment, the patient’s immune system and the patient’s own genotype.

Approach
We will provide assays and tools that enable clinical investigators to genetically and molecularly interrogate a patient’s tumor, in order to facilitate assignment of experimental or approved therapies most likely to benefit the patient.
Who is Our Patient Population?

- Standard of Care
- No Standard Treatment Available or Remaining
- Everyone Else
NGS Cost Decrease Leads to Increases in Data Generation

• Beltran et al (2015, JAMA Oncology): EXaCT-1 (Exome) = 5%

• Meric-Bernstam et al (2014): 46-50 gene panel = 11%

~500 gene
~50 gene

~125 “actionable” genes

NGS “Big” Data are necessary, but insufficient, to drive precision medicine.
Why:
1. Solid tumors – light microscopy sufficient for most diagnoses. Leukemia/lymphoma – molecular subtyping in addition to light microscopic examination.
2. Accessibility – peripheral blood/bone marrow vs. surgical/biopsy; Timing of data.
3. Attitudes of oncologists(?) and Payers?
Why are We (All) so “Bad” at This?

- This = figuring out which patients should get tested
- This = using molecular data to impact patient care
- This = demonstrating that data changes outcome
- This = deciding how much of the genome we should sequence
- This = how we should pay for it
Percentage of Patients with Mutation in ‘Actionable’ Gene

- Potentially actionable somatic mutations: 789 (39.45%)
- Non-actionable somatic mutations: 414 (20.70%)
- Likely germline variants: 205 (10.25%)
- No mutation/variant: 592 (29.60%)
- Total: 2000 (100.00%)
Clinical Trials Categorized by Type of “Match”

- **Genotype-selected trials**: Trials requiring a specific genomic status for enrollment
  - eg trials for patients with BRAF V600E-mutant tumors

- **Genotype-relevant trials**: Trial with a drug that directly or indirectly targets product of an gene that is altered, but does not require biomarker for eligibility
  - Indirectly: eg inhibiting downstream signaling
  - Eg enrolling a patient with BRAF V600E-mutant tumors on a MEK inhibitor trial

- **Genotype-matched trials**: Genotype selected or relevant
Enrollment on Genotype Matched Trials

Underwent Genomic Testing
N = 2000

Mutation in Potentially Actionable Gene

Yes (789)  No (1211)

Genotype-matched trial after genomic testing?

Yes (83)  No (706)

Genotype-Selected Trial N = 54
Genotype-Relevant Trial N = 29

4% of patients tested were ultimately treated with “matched” agent

11% of pts with mutations in actionable genes went on genotype-matched trials
Lack of Enrollment **NOT** Due to Lack of Available Matched Trials

<table>
<thead>
<tr>
<th>MUTATIONS SCREENED</th>
<th>ABL1</th>
<th>CSF1R</th>
<th>FGFR2</th>
<th>IDH1</th>
<th>MLH1</th>
<th>PTPN11</th>
<th>TP53</th>
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<tbody>
<tr>
<td><strong>AKT1</strong></td>
<td>CTNNB1</td>
<td>FGFR3</td>
<td>IDH2</td>
<td>MPL</td>
<td>RB1</td>
<td>VHL</td>
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<td><strong>ALK</strong></td>
<td>EGFR</td>
<td>FLT3</td>
<td>JAK2</td>
<td>NOTCH1</td>
<td>RET</td>
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<tr>
<td><strong>APC</strong></td>
<td>ERBB2</td>
<td>GNA11</td>
<td>JAK3</td>
<td>NPM1</td>
<td>SMAD4</td>
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<td><strong>ATM</strong></td>
<td>ERBB4</td>
<td>GNAQ</td>
<td>KDR</td>
<td>NRAS</td>
<td>SMARCB1</td>
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<td></td>
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<tr>
<td><strong>BRAF</strong></td>
<td>EZH2</td>
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<td>KIT</td>
<td>PDGFRA</td>
<td>SMO</td>
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<td><strong>CDH1</strong></td>
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<td>HNF1A</td>
<td>KRAS</td>
<td>PIK3CA</td>
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<tr>
<td><strong>CDKN2A</strong></td>
<td>FGFR1</td>
<td>HRAS</td>
<td>MET</td>
<td>PTEN</td>
<td>STK11</td>
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</tbody>
</table>

Increasing number of histology-agnostic or multiple histology “basket” trials
Increase % patients with actionable alterations with larger platforms and copy number data
Mutations in Patients Enrolled in Genomically Matched Trials

- PIK3CA: 41%
- BRAF: 28%
- PTEN: 1%
- AKT1: 3%
- ALK: 1%
- EGFR: 8%
- CDKN2A: 1%
- ERBB2: 5%
- ERBB3: 1%
- KIT: 3%
- KRAS: 5%
- MET: 1%
- NRAS: 1%
- PDGFRA: 1%
- RET: 1%
- PDGFRA: 1%
Analysis Suggests Opportunities to Improve Patient Recruitment on Targeted Trials

Did Patient Return to Clinic after Testing? (n=429)
- Yes (354)
  - New regimen at MDACC?
    - No (124)
    - Yes (230)
- No (75)
  - Could an easy-to-access decision support infrastructure, coupled with a proactive alert system and accurate clinical trial tracking improve our ability to optimize patient recruitment onto genotype-selected and genotype-driven trials?
  - 69% had test results mentioned
  - 67% had genotype-matched trials discussed
  - 58% enrolled on genotype-matched trials

- Treatment Elsewhere (2)
- No Trials or Slots (4)
- Insurance Denial (1)
- Poor PS (4)
- Non-Investigational Treatment (17)
- Not Eligible (11)
- Non-Genotype Matched Trial (5)
- Genotype Relevant drug Off-Protocol (1)
Needs Identified for Utilization of NGS “Big Data” at MD Anderson

1. Resource that provides physicians with a clear understanding of which genomic alterations are actionable at a gene and variant level

2. Resource that matches clinically available therapies with specific genotypes

3. Resource that provides concise representation of the level of evidence associated with each therapy within the patient’s genomic context

4. Resource for identifying genotype-relevant clinical trials

5. Simplified reporting scheme that incorporates all this information in a patient-specific report

6. Timely proactive notification of actionable genomic alterations identified and potential courses of action

The overarching goal of the Precision Oncology Decision Support System (PODSS) is to meet these needs and improve clinical utilization of molecular testing at MD Anderson
From Circles on Lists to Decision Support
• Basic annotations communicated without assessment of ‘actionability’

  • **Actionable** = Variant is likely driving tumorigenesis and there is an available therapeutic option to inhibit it.

  • Requires knowledge of the function of the gene (ex: BRAF)

  • Requires searching and reading through published articles within PubMed and conference abstracts for any known effects of the variant of interest (ex: BRAF V600E).

  • Requires scouring drug databases and the published literature for drugs that may target the variant; Identifying clinical trials that utilize those agents

~14,000 Patients; ~6,300 Variants
Not All Mutations Are Equally ‘Actionable’

- **Phase II Imatinib in KIT-Mutant/Amplified melanoma**
- **Common in mucosal and acral melanoma**

<table>
<thead>
<tr>
<th>Subtype</th>
<th>Mutation</th>
<th>Amplification (Ratio)</th>
<th>Amplified Pattern</th>
<th>Mutant: Wild-Type Ratio</th>
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</thead>
<tbody>
<tr>
<td>Acral</td>
<td>Ex 17 D820Y</td>
<td>Yes (5-10)</td>
<td>Uniform</td>
<td>1:1</td>
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<tr>
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<td>NA</td>
<td>1:1</td>
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<td>1:1</td>
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<tr>
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<td>Ex 11 L576P</td>
<td>Yes (5-10)</td>
<td>Mixed</td>
<td>1:1</td>
</tr>
<tr>
<td>Mucosal</td>
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<tr>
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<td>Uniform</td>
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<tr>
<td>Acral</td>
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<td>No</td>
<td>Yes (&gt;10)</td>
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<td>Yes (&gt;2.5)</td>
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<td>Mixed</td>
<td>4:1&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

- **Selection critical**
- **Recurrent Mutations (K642E, L576P)**
  - 40% RR
- **Non Recurrent Mutations**
  - 0%

Carvajal, R. D. et al. JAMA 2011;305:2327-2334
Elements of Actionability

**Alterations**
- **Retrieve literature, aggregate data** (including unpublished internal data)
- **Manually annotate** the *functional significance* of the alterations

**Drugs**
- Annotate drug targets, development status (FDA approved or clinical development) and therapeutic implications (if any)

**Clinical Trials**
- **Manually annotate** the trials’ genotype/biomarker-specific selection criteria
- Annotate for other inclusion criteria, including tumor type, bring in NLP
Website: 33 genes fully annotated
>1,025 functionally significant SNVs
>15,000 SNVs reviewed

Single Patient Annotation Effort: 3200 Single patients annotated

Drug Curation Effort: 1504 drugs annotated

Clinical Trial Curation Effort: 3240 cancer clinical trials annotated
# Decision Support in Real Time

![MD Anderson Clinical Trials Table]

**MD ANDERSON CLINICAL TRIALS**

The PODS team has identified the following clinical trials that may be relevant to your patient’s alterations. Please note the following: although this list has been filtered by its relevance to your patient’s gene and disease type, further consultation regarding enrollment eligibility and availability of clinical trial slots should be discussed with respective PI and/or clinical trial coordinator.

### Biomarker-Relevant Trials

<table>
<thead>
<tr>
<th>Relevant Biomarker(s)*</th>
<th>Drugs**</th>
<th>Title</th>
<th>NCTID</th>
<th>Protocol ID</th>
<th>Phase</th>
<th>PI</th>
<th>Dept</th>
</tr>
</thead>
<tbody>
<tr>
<td>MDM2 Any Alteration</td>
<td>DS-3032b</td>
<td>A Phase I Multiple Ascending Dose Study of DS-3032b, an Oral MDM2 Inhibitor, in Subjects With Advanced Solid Tumors or Lymphomas</td>
<td>NCT01877382</td>
<td>2013-0257</td>
<td>Phase 1</td>
<td>Hong, David S.</td>
<td>Investigational Cancer Therapeutics</td>
</tr>
</tbody>
</table>

*All relevant genotypes may not be listed. Only those relevant to the patient’s genomic profile are listed. **All drugs used within the trial are listed; however, drugs curated by IPCT to be relevant to the patient’s genomic profile are underlined.

### Biomarker-Relevant Trials Requiring Additional Biomarkers

<table>
<thead>
<tr>
<th>Relevant Biomarker(s)*</th>
<th>Additional Required Biomarker(s)</th>
<th>Drugs*</th>
<th>Title</th>
<th>NCTID</th>
<th>Protocol ID</th>
<th>Phase</th>
<th>PI</th>
<th>Dept</th>
</tr>
</thead>
<tbody>
<tr>
<td>MDM2 Any Alteration</td>
<td>ERBB2_Negative, ESR1_Positive, TP53_Wildtype</td>
<td>A Phase I Open-Label Study to Determine the Safety and Tolerability of ALRN-6924 in Patients With</td>
<td>NCT022546</td>
<td>2015-0465</td>
<td>Phase 1</td>
<td>Meric-Bernstam, Funda</td>
<td>Investigational Cancer Therapeutics</td>
<td></td>
</tr>
</tbody>
</table>

* STGA1: GNAS_T204A

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**Sheikh Khalifa Bin Zayed Institute for Personalized Cancer Therapy**

Dear Dr. Smith,

The PODS team has reviewed the molecular profile for

**Patient:** Doe, John
**MRN:** 1234567
**Tumor Type:** Sarcoma NOS

Please see your complete annotation below and don’t hesitate to contact us if you have any questions.

<table>
<thead>
<tr>
<th>Gene</th>
<th>Alteration</th>
<th>gBIO</th>
<th>COSMIC</th>
<th>CMS50</th>
<th>T204</th>
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</thead>
<tbody>
<tr>
<td>FGFR1</td>
<td>S249Y</td>
<td>0/8469 (0%)</td>
<td>0/7848 (0%)</td>
<td>0/10629 (0%)</td>
<td>0/2414</td>
</tr>
</tbody>
</table>

The PODS team routinely assesses the availability of targeted therapies within alterations that is not considered actionable at this time. We will include additional supportive evidence for if found.

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* STGA1: GNAS_T204A
Scope of the Problem:

>1 million variants without functional annotation

Are these passengers or drivers and are drivers hypomorphs, hypermorphs or neomorphs?
Construct lentiviral vector carrying wild type or mutated genes
Introduce into addicted sensor cells line Ba/F3 or MCF10A cells
Establish stable driver addicted cell lines
Sensitivity to informer targeted therapeutic library
Iterative algorithm to identify POTENTIAL DRIVER ABBERATIONS
High throughput generation of mutant ORFs
Select potential drivers
Context dependent in vivo screen for potential drivers.
Establish stable driver addicted cell lines

Data sets
MDACC
TCGA
ICGC

Drivers and Therapies

Integrative analysis for function, mechanism and therapy

Current 50 per month: Point indel fusion Readily scalable

Patients

细胞 viability assay
Annotating Function to the 95%
All patients with identified somatic variants

- 188 patients with mutation(s) only in non-actionable gene
- 196 patients with variant in actionable gene

68 known activating
- ~20% enrolled

4 inferred activating

7 inactivating
- ~20% enrolled

34 inferred inactivating

1 benign

291 variant of unknown significance
- ~7% enrolled

Approximately 25% of patients with mutations in actionable genes were enrolled on clinical trials using matched therapies (~12% can be potentially enrolled - still awaiting progression)

Decision Support in Real Time Improves ‘Matching’ to ‘Right’ Drug
The most common “phenotype”: variable responses

Responses vary significantly even when appropriately matched

Sosman J et al. NEJM 2012
It’s Not About Big Data, It’s About Informatics and Designing the Right Trials (to collect the Right Data)

The cancer genome is a highly inter-connected and redundant network of aberrations… we need to treat it (and design trials and support testing strategies) as if we KNOW it.
Acknowledgements

Khalifa Institute for Personalized Cancer Therapy-
MD Anderson Cancer Center