Disclosures

**Funding:** NCI/NIDDK, Prostate Cancer Foundation, Early Detection Research Network, Starr Cancer Foundation, Bresnan Foundation, DOD, Ventana Roche, Millennium and Sanofi Aventis

**Patents:** Michigan and Harvard have a U.S. Patent covering prostate cancer gene fusion for diagnostics and therapeutics. Dr. Rubin is listed as a co-inventor. WCMC has pending patents for NMYC and AURKA and SPOP mutations in prostate cancer.
Toward Precision Medicine
Building a Knowledge Network for Biomedical Research and a New Taxonomy of Disease

Committee on A Framework for Developing a New Taxonomy of Disease
Board on Life Sciences
Division on Earth and Life Studies

NATIONAL RESEARCH COUNCIL
OF THE NATIONAL ACADEMIES

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SU2C Prostate Dream Team Leaders and Principals
The SU2C-PCF “CRPC 500” Clinical Trial Schema

- **ABIRATERONE NAIVE**
  - LEAD SITE: UMICH
  - Trial 1: Abiraterone Standard Care
  - AIM 4: Abiraterone
  - AIM 6a: Abiraterone +/- ABT888

- **POST-ABIRATERONE**
  - Trial 2: DFCI
  - AIM 5b: Abiraterone + ARN509
  - Trial 3: MSKCC
  - AIM 5a: ARN509 +/- Everolimus
  - Trial 4: ICR
  - AIM 6b: OLAPARIB

**AIM 2: Precision Medicine Tumor Boards:** Actionable Targets

At time of disease progression

Enrollment/Eligibility for Targeted Therapies
SU2C-PCF Precision Trials Work Flow

**Pathology Data Coordination Center (WCMC)**
- Image archive
- Pathology review
- Integrated Database
- Pathology CDEs

**SU2C-PCF Precision Trials Web Portal**
- Portal (Oncomine, IGV, cBIO)
- Browse and analyze data by investigators
- Download of integrated datasets for trials

**Precision Tumor Boards**
- Path images
- DNA/RNA quality

**Sequencing and Analysis Sites**
- Frozen Sectioning
- RNA/DNA Isolation
- Integrative Sequencing
- Computational Analysis
- Mutation Calls

**Clinical Sites**
- Enroll patients to cohort study
- Data collection
- Biopsy, Sample transport
- Clinical trials

**Clinical Data Elements**
- Clinical site coordination
- Clinical CDEs
- Integrated clinical data

**Tumor Biopsies**

**University of Michigan**

**The Broad Institute**

**DFCI/BIDMC**

**UM**

**MSKCC**

**UW**

**ICR/RMH**
Computational Analysis Pipeline

Next-Generation Sequencing Pipeline

Picard pipeline
Broad’s Sequencing Platform

Calibrate quality scores
Align to genome (MAQ, BWA)
Mark duplicate reads

dbGAP
BAM file
Visualization (IGV)

QC

Mutations
Indels
Purity ploidy
Copy-number
Rearrangements
Fusion-genes
Pathogens

Annotation + Reports
muTect
Indelocator ABSOLUTE
SegSeq
dRanger
PathSeq

dbGAP

FIREHOSE
Cancer Genome Analysis

Broad’s Cancer Genome Analysis Group
Areas of implementation for Cancer

Routine Cancer Care
   CLIA Test development underway

Clinical trials
   Established for prostate cancer (e.g., Millennium NEPC)
   General cancer trials pending IRB

Pharmacogenomics (Resistance)
   technology that analyses how genetic makeup affects an individual's response to drugs.
Research For Precision Medicine
IRB Protocol # 1305013903

Mark A. Rubin, MD
Director of the Institute for Precision Medicine
New York Presbyterian- Weill Cornell Medical College

Clinical Protocol Principal Investigator: Himisha Beltran, MD
Protocol Rationale

Understanding molecular alterations driving cancer will aid in the design of more effective targeting strategies.

Advances in cancer genome sequencing have provided critical insights into the molecular classification of several cancers.

Targeted therapies are clinically effective:

- Her2/neu gene amplification - herceptin (breast cancer)
- BCR-ABL gene fusion - imatinib (chronic myelogenous leukemia)
- EGFR point mutation – erlotinib (lung cancer)
- EML4-ALK gene fusion - crizotinib (lung cancer)
- BRAF point mutation - vemurafenib (melanoma)
Protocol (IRB#1305013903) is not a therapeutic study; rather it is focused on tissue collection and tumor sequencing for research purposes.
Clinical Pathway to Treatment

Patient/Doctor → Biopsy → Report → Medical record → Treatment plan

- MRN 007
- PTB Consult
- MRN 007 History
- Radiology
- PTB consult
- Diagnosis

Tumor and normal
Genome/exome Seq
Genotyping (SNP arrays)
copy number alterations
point mutations
rearrangements
indels

RNA-seq
Gene expression
Gene fusions

Precision Medicine
Tumor Board (consultation)

Caring doctor
consults with PM
team
Discussion with care givers and PM team members to develop consultation report
Risks

- Biopsy and Phlebotomy
- Confidentiality
- Genetic Risks
- Access to Biospecimens and Data for Research

*Described in detail in Informed Consent*
Where are we as of Oct 17, 2013
71 yo M presents with back pain, PSA 3325 ng/ml
PM1: Blastic Bone Metastasis
PM6

- 75 M with RP in 1991, intermittent ADT
- 2011 metastases to LN and bone, PSA 0.9 ng/ml
- 2012 Abiraterone
- 2013 Progression, no change in bone lesions, PSA 0.6 ng/ml, serum chromogranin 1439 ng/ml (normal <95)
PM6

- 75 M with metastatic NEPC
- Millenium trial patient

Diagnosis: Metastatic carcinoma consistent with prostatic origin
PM6 Copy Number Alterations

PM6

Chromosome chr1

Chromosome chr2

Chromosome chr3

Chromosome chr4

Chromosome chr5

Chromosome chr6

Chromosome chr7

Chromosome chr8

Chromosome chr9

Chromosome chr10

Chromosome chr11

Chromosome chr12

Chromosome chr13

Chromosome chr14

Chromosome chr15

Chromosome chr16

Chromosome chr17

Chromosome chr18

Chromosome chr19

Chromosome chr20

Chromosome chr21

Chromosome chr22

Chromosome chrX

Chromosome chrY
## PM6 potential actionable alterations

<table>
<thead>
<tr>
<th>Alteration</th>
<th>Potential actionability</th>
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</thead>
<tbody>
<tr>
<td>IGFBP2 point mutation</td>
<td>-</td>
</tr>
<tr>
<td>CHD1 loss</td>
<td>- PARP inhibitors</td>
</tr>
<tr>
<td></td>
<td>- WGS to characterize chromothripsis</td>
</tr>
<tr>
<td>MYC gain</td>
<td>BRD4 inhibitor</td>
</tr>
<tr>
<td>PTEN loss</td>
<td>PI3K/mTOR inhibitors</td>
</tr>
<tr>
<td>AR gain</td>
<td>-</td>
</tr>
</tbody>
</table>
PM NGS Analytic Pipeline

Step 1: BWA alignment (multicore, GATK compatible), sam to sorted bam using samtools

Step 2: realign around indels using GATK

Step 3: remove clonal reads using Picard

Step 4: quality score recalibration using GATK

Step 5: quality control and sample check (# mapped reads, coverage stats, % on target, SPIA)

Step 6: SNV/indel/CNA detection using multitool strategy: SNVseeqer, Goby, Varscan, GATK, CNVseeqer

Step 7: Sensitive identification of variants from CLIA mutation master list

Step 8: Identify all somatic variants SNV/indel/CNA detection using multitool strategy: SNVseeqer, Goby, Varscan, GATK, Mutect, CNVseeqer

Step 9: Identify somatic variants from CLIA mutation master list

Step 10: Merge/Rank somatic variants using Rank Fusion algorithm

Step 11: Annotate all somatic alterations

Step 12: Report mutations from CLIA master list if present + all somatic alterations. Load data into cBIO and Tumor Book

Olivier Elemento, Fabien Campagne, Andrea Sboner, Francesca Demichelis
Development of the IPM report
Structure of the report

- Clinical information
- Genomic alterations (summary)
  - clinically relevant genes
  - cancer genes
  - remaining
- Details (divided by categories)

GENOMIC ALTERATIONS: Summary

Somatic alterations in clinically relevant genes
188 clinically relevant genes were analyzed. We found 2 alteration(s) in clinically relevant genes.

Somatic alterations in known cancer genes
503 cancer genes were scanned. We found 4 alteration(s) in cancer associated genes.

Somatic alterations of unknown significance
20305 genes were scanned with exome sequencing. Average coverage of these genes was 130. We found 19 alterations (listed below).
Clinical information

**Institute for Precision Medicine Report**

<table>
<thead>
<tr>
<th>Patient ID:</th>
<th>PMtest</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diagnosis:</td>
<td>Prostatic adenocarcinoma</td>
</tr>
<tr>
<td>Report Date:</td>
<td>Sep. 17, 2013</td>
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**CLINICAL INFORMATION**

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<thead>
<tr>
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<th>PMtest-T01</th>
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</thead>
<tbody>
<tr>
<td>Physician:</td>
<td>IPM</td>
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<tr>
<td>Specimen ID:</td>
<td>PMtest-T01</td>
</tr>
<tr>
<td>Sample type:</td>
<td>Biopsy</td>
</tr>
<tr>
<td>Diagnosis:</td>
<td>Prostatic adenocarcinoma</td>
</tr>
<tr>
<td>Date Received - Processed:</td>
<td>01/01/2013 - 09/13/2013</td>
</tr>
<tr>
<td>Neoplastic content:</td>
<td>95 %</td>
</tr>
</tbody>
</table>

Site: Prostate

**GENOMIC ALTERATIONS:**

...
## GENOMIC ALTERATIONS: Summary

### Somatic alterations in clinically relevant genes

188 clinically relevant genes were analyzed. We found 2 alteration(s) in clinically relevant genes.

### Somatic alterations in known cancer genes

508 cancer genes were scanned. We found 4 alteration(s) in cancer associated genes.

### Somatic alterations of unknown significance

20305 genes were scanned with exome sequencing. Average coverage of these genes was 130. We found 19 alterations (listed below).
### Clinically relevant genomic alterations

<table>
<thead>
<tr>
<th>Gene</th>
<th>FDA approved drugs with indication</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>EGFR p.L858R</td>
<td>NSCLC: Erlotinib, Gefitinib</td>
<td>In NSCLC, the p.L858R mutation is associated with sensitivity to the Erlotinib and Gefitinib RTK inhibitors.</td>
</tr>
<tr>
<td>KRAS p.G12V</td>
<td>mCRC: Resistance to cetuximab and panitumumab</td>
<td>KRAS mutations are associated with resistance to cetuximab and panitumumab in metastatic colorectal cancer. G12A, G12C, G12D, G12R, G12S, G12V, A146T, G13D are the most prevalent mutations however other activating mutations have been found.</td>
</tr>
</tbody>
</table>

### Genomic alterations in cancer genes

<table>
<thead>
<tr>
<th>Hugo Symbol</th>
<th>Classification</th>
<th>Type</th>
<th>Ref Allele</th>
<th>Tumor Allele 1</th>
<th>Tumor Allele 2</th>
<th>AA change</th>
<th>Normal tissue depth</th>
<th>Normal VAF</th>
<th>Tumor tissue depth</th>
<th>Tumor VAF</th>
</tr>
</thead>
<tbody>
<tr>
<td>BCOR</td>
<td>Nonsense_Mutation</td>
<td>SNP</td>
<td>G</td>
<td>G</td>
<td>A</td>
<td>p.R1183*</td>
<td>75</td>
<td>0.0%</td>
<td>75</td>
<td>28.0%</td>
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<tr>
<td>TP53</td>
<td>Missense_Mutation</td>
<td>SNP</td>
<td>T</td>
<td>T</td>
<td>C</td>
<td>p.Y220C</td>
<td>54</td>
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<td>55</td>
<td>34.5%</td>
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<td>MAML2</td>
<td>In_Frame_Del</td>
<td>DEL</td>
<td>TGCTGCTGC</td>
<td>-</td>
<td>-</td>
<td>p.Q604_nofs</td>
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<td>0.0%</td>
<td>89</td>
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</tr>
<tr>
<td>Hugo Symbol</td>
<td>Classification</td>
<td>Type</td>
<td>Ref Allele</td>
<td>Tumor Allele 1</td>
<td>Tumor Allele 2</td>
<td>AA change</td>
<td>Normal tissue depth</td>
<td>Normal VAF</td>
<td>Tumor tissue depth</td>
<td>Tumor VAF</td>
</tr>
<tr>
<td>------------</td>
<td>----------------</td>
<td>------</td>
<td>------------</td>
<td>----------------</td>
<td>----------------</td>
<td>-----------</td>
<td>----------------------</td>
<td>------------</td>
<td>-------------------</td>
<td>----------</td>
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<tr>
<td>OTOP2</td>
<td>Frame_Shift_Del</td>
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<td>C</td>
<td>0</td>
<td>0</td>
<td>p._fs</td>
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<td>DEL</td>
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<td>0</td>
<td>p._nofs</td>
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<td>ZNF526</td>
<td>Missense_Mutation</td>
<td>SNP</td>
<td>C</td>
<td>C</td>
<td>T</td>
<td>p.R395C</td>
<td>72</td>
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<td>69</td>
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<td>HSD11B1L</td>
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<td>SNP</td>
<td>T</td>
<td>T</td>
<td>G</td>
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<td>Missense_Mutation</td>
<td>SNP</td>
<td>C</td>
<td>C</td>
<td>T</td>
<td>p.G351R</td>
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<td>LMOD1</td>
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<td>SNP</td>
<td>C</td>
<td>C</td>
<td>T</td>
<td>p.G193E</td>
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<td>0.0%</td>
<td>79</td>
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<td>C</td>
<td>T</td>
<td>p.V1048M</td>
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<td>G</td>
<td>A</td>
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<td>C</td>
<td>C</td>
<td>T</td>
<td>p.P196L</td>
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<td>0.0%</td>
<td>79</td>
<td>32.9%</td>
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<td>CADM2</td>
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<td>SNP</td>
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<td>C</td>
<td>T</td>
<td>p.S236L</td>
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<td>CNBD1</td>
<td>Missense_Mutation</td>
<td>SNP</td>
<td>C</td>
<td>C</td>
<td>T</td>
<td>p.T181I</td>
<td>59</td>
<td>0.0%</td>
<td>56</td>
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<td>60</td>
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<td>C</td>
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<td>T</td>
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<td>T</td>
<td>C</td>
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<td>C</td>
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<td>p.R353C</td>
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<td>65</td>
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<tr>
<td>FAM193B</td>
<td>Frame_Shift_Ins</td>
<td>INS</td>
<td>-</td>
<td>+CGCGCGGC</td>
<td>+CGCGCGGC</td>
<td>p.C20_fs</td>
<td>20</td>
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<td>20</td>
<td>60.0%</td>
</tr>
</tbody>
</table>
### Case images (optional)

**Institute for Precision Medicine Report**

**Patient ID:** PMtest  
**Diagnosis:** Prostatic adenocarcinoma  
**Report Date:** Sep. 17, 2013

#### CLINICAL INFORMATION

<table>
<thead>
<tr>
<th>Patient ID:</th>
<th>PMtest</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physician:</td>
<td>IPM</td>
</tr>
<tr>
<td>Diagnosis:</td>
<td>Prostatic adenocarcinoma</td>
</tr>
<tr>
<td>Site:</td>
<td>Prostate</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Specimen ID:</th>
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</thead>
<tbody>
<tr>
<td>Sample type:</td>
<td>Biopsy</td>
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<tr>
<td>Date Received - Processed:</td>
<td>01/01/2013 - 09/13/2013</td>
</tr>
<tr>
<td>Neoplastic content:</td>
<td>95 %</td>
</tr>
</tbody>
</table>

#### CASE IMAGES

![Image 1](image1.png)  
![Image 2](image2.png)  
![Image 3](image3.png)
Exome Capture Seq

one microgram of DNA
22,794 genes+
Agilent Haloplex Exome Target Enrichment System
Why Use Haloplex Exome?

- Low DNA input (225ng)
- High coverage (all coding content in the genome)
  37MB; 21,522 genes; 357,999 targeted exons
- Uniform amplification (RE digestion)
- Sensitive variant detection (recovered mutation easily)
- High specificity and efficiency
- FFPE compatibility designs
- Amount of Seq.(total) 4GB (PE100x2)
- Fast (overall Workflow 2 days)
Haloplex Sequencing Data Analysis
- continue
  • Total number of bases mapped: 7,647,036,325 bases
  • Number of reads in targeted regions: 53,874,990 reads
  • Percentage reads in targeted regions: 63.51%
  • Percentage reads in regions +/- 100bp: 91.64%

Percentage of targeted bases covered by...
  ...at least 1 read: 99.08%
  ...at least 5 reads: 98.03%
  ...at least 10 reads: 96.78%
  ...at least 20 reads: 93.78%
  ...at least 30 reads: 90.00%
  ...at least 40 reads: 85.59%
  ...at least 50 reads: 80.70%
  ...at least 100 reads: 53.42%
Haloplex Workflow – Restriction Enzyme Digestion

RE Buffer + BSA

72 µl per well

RE Master Mix Strip

Restriction Digestion Reaction Plate

A B C D E F G H
1 2 3 4 5 6 7 8 9 10 11 12

RE Master Mix Strip

Enzyme Strip 1

9 µl to corresponding well

5 µl per well

gDNA Samples 1-7 (5 ng/µL)
Validation of Restriction Digestion
PCR Amplicon Yield Ratio

1. Calculate the yield ratio for the 105-bp amplicon according to the following formula:
   \[ 105\text{-bp ratio} = \frac{105\text{-bp yield FFPE DNA}}{105\text{-bp yield reference DNA}} \]

2. Calculate the yield ratio for the 236-bp amplicon according to the following formula:
   \[ 236\text{-bp ratio} = \frac{236\text{-bp yield FFPE DNA}}{236\text{-bp yield reference DNA}} \]

3. Calculate the Average Yield Ratio by averaging the yield ratio values calculated for the 105-bp (from step 1) and 236-bp (from step 2) amplicons.

<table>
<thead>
<tr>
<th>Sample Integrity Category</th>
<th>Average Yield Ratio</th>
<th>Recommended DNA Input (ng) in HaloPlex protocol</th>
<th>Recommended additional sequencing</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>&gt;0.2 (&gt;20%)</td>
<td>200–500</td>
<td>1×–5×</td>
</tr>
<tr>
<td>B</td>
<td>0.05 to 0.2 (5% to 20%)</td>
<td>500–1000</td>
<td>5×–10×</td>
</tr>
<tr>
<td>C</td>
<td>&lt;0.05 (&lt;5%)</td>
<td>1000–2000</td>
<td>10×–100×</td>
</tr>
</tbody>
</table>

Intact DNA samples are enriched using the HaloPlex protocol at 200 ng of input DNA per reaction.
CLIA validation sequencing update

- **BRAF V600E**: Analyzed and mutation detected
- **KRAS V12D**: Analysis in progress
- **FLT3 ITD**: Analyzed and mutation detected
- **JAK2 V617F**: Analyzed and mutation detected
- **EGFR exon 19**: Analyzed and mutation detected
- **HER2 gain**: Analysis in progress
- **PTEN loss**: Analysis in progress

Legend:
- Green: Analyzed and mutation detected
- Orange: Analysis in progress
Three Patients with Metastatic Prostate Cancer

- **PM3**: Hormone naïve metastatic prostate cancer (bone met)

- **PM9**: Rapid progression on first line ADT (CRPC TURP)

- **PM12**: Atypical prostate cancer, relapse after platinum chemotherapy (Brain Met)
PM3

- 78 M presents to ER with urinary obstruction, PSA 4965 ng/ml, CTC count 173

Diagnosis: Metastatic prostatic adenocarcinoma
ERG rearranged (translocation) and PTEN wt by FISH

3 mo= PSA 769 ng/ml
# PM3 statistics

<table>
<thead>
<tr>
<th>Sample</th>
<th>Platform</th>
<th>Sample type</th>
<th># mapped reads</th>
<th>% on target</th>
<th>Average coverage</th>
<th>Coverage &gt;= 10X</th>
</tr>
</thead>
<tbody>
<tr>
<td>PM3_Z1_2_case-HALO</td>
<td>Haloplex</td>
<td>Fresh-frozen</td>
<td>59M</td>
<td>86.17 %</td>
<td>84X</td>
<td>96 %</td>
</tr>
<tr>
<td>PM3_D14_Ctrl-HALO</td>
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**CLIA panel statistics:**

[Image of CLIA panel statistics]
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<th>Cov tumor</th>
<th>% tumor</th>
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GENOMIC ALTERATIONS: Summary

Somatic alterations in clinically relevant genes

A set of 6 highly relevant genes was successfully tested. In addition, another set of 187 clinically relevant genes were also tested.

Somatic alterations in known cancer genes

A set of 507 cancer genes was also analyzed. We found 32 genes that were altered.

Somatic alterations of unknown significance

Exome sequencing was tested for alterations in 21,522 genes.

Method

Sequencing was performed using Illumina Hiseq 2500 PE 2x75bp. A total of 21,522 genes were analyzed with an average coverage of 84x. 61,527,806 and 69,533,450 short reads were aligned to hg19 reference using BWA [1] for case and control, respectively. PCR duplicates were removed using Picard [2]. 3.99% and 11.53% duplicates were removed, respectively. The capture efficiency was 86.17% and 86.09% for case and control, respectively.

PM9

- 63 M with metastatic CRPC rapid progression on first line ADT(<6 mo)

Diagnosis: Prostatic adenocarcinoma, treated AURKA and MYCN amplification

Pt subsequently developed liver mets with PSA <1 ng/ml
## PM9 statistics

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<th>Platform</th>
<th>Sample type</th>
<th># mapped reads</th>
<th>% on target</th>
<th>Average coverage</th>
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### CLIA panel statistics

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PM9 point mutations and indels

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<tr>
<th>Gene</th>
<th>Type</th>
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<th>AA Mut</th>
<th>Cov normal</th>
<th>% normal</th>
<th>Cov tumor</th>
<th>% tumor</th>
</tr>
</thead>
<tbody>
<tr>
<td>GRIN2B</td>
<td>SNP</td>
<td>G &gt; C</td>
<td>p.D1103E</td>
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**Activity**
Antineoplastic agent, a potent and selective inhibitor of VEGFR-1, -2 and -3 tyrosine kinases, blocking angiogenesis [DS:H00037 H00049 H00050 H00051 H00052 H00053]

**Remark**
Therapeutic category: 4291
ATC code: L01XE11

**Target**
- PDGFRA tyrosine kinase inhibitor [HSA:5156] [KO:K04363];
- PDGFRB tyrosine kinase inhibitor [HSA:5159] [KO:K05089];
- VEGFR1 tyrosine kinase inhibitor [HSA:2321] [KO:K05096];
- VEGFR2 tyrosine kinase inhibitor [HSA:3791] [KO:K05098];
- VEGFR3 tyrosine kinase inhibitor [HSA:2324] [KO:K05097];
- c-KIT tyrosine kinase inhibitor [HSA:3815] [KO:K05091]

**Pathway**
- hsa04010 MAPK signaling pathway
- hsa04020 Calcium signaling pathway
- hsa04060 Cytokine-cytokine receptor interaction
- hsa05200 Pathways in cancer

**Interaction**
CYP inhibition: CYP2D6 [HSA:1565], CYP3A [KO:K07424]

**Structure map**
map07045 Antineoplastics - protein kinases inhibitors
PM9 CNA profile
### Genomic alterations with unknown significance

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<th>Type</th>
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<th>TumorAllele 2</th>
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### Genomic alterations in cancer

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<td>C</td>
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</tbody>
</table>

### Method

Sequencing was performed using Illumina HiSeq 2500 PE 2x75bp. A total average coverage of 100x, 133,351,358 and 128,321,358 short reads were generated for case and control, respectively. PCR duplicates were removed using HTS tools.
PM12

- 66 M Radical prostatectomy in 1/25/12, PSA <1 ng/ml

Diagnosis: Prostatic adenocarcinoma, Gleason 9 (5+4) with focal neuroendocrine differentiation, PTEN hemi del

- Recurrent tumor (Urethral mass) in 7/5/2012 + liver and bone
- Treated with cisplatin - docetaxel -> complete response
PM12

- Relapse 5/23/13: Solitary brain metastasis

Diagnosis: Metastatic NEPC, PTEN hemi del

Pt is currently NED
## PM12 statistics

<table>
<thead>
<tr>
<th>Sample</th>
<th>Platform</th>
<th>Sample type</th>
<th># mapped reads</th>
<th>% on target</th>
<th>Average coverage</th>
<th>Coverage &gt;= 10X</th>
</tr>
</thead>
<tbody>
<tr>
<td>PM12_Z4-1_Case (brain met)</td>
<td>Haloplex</td>
<td>Fresh-frozen</td>
<td>52M</td>
<td>83.01 %</td>
<td>74X</td>
<td>90 %</td>
</tr>
<tr>
<td>PM12_Z10_1_case (primary)</td>
<td>Haloplex</td>
<td>FFPE</td>
<td>43M</td>
<td>87.73 %</td>
<td>65X</td>
<td>86 %</td>
</tr>
<tr>
<td>PM12_EBC2-1_Ctrl</td>
<td>Haloplex</td>
<td>Fresh-frozen</td>
<td>50M</td>
<td>83.37 %</td>
<td>71X</td>
<td>90 %</td>
</tr>
</tbody>
</table>

PM12_Z4-1_Case (met)

PM12_Z10_1_case (primary)
Number of somatic point mutations in PM12 is unusually high

- **Single nucleotide mutations**
  - PM12_Z10_1_case: 1400
  - PM12_Z4-1_Case: 600

- **Dinucleotide mutations**
  - PM12_Z10_1_case: 150
  - PM12_Z4-1_Case: 50
SPIA analysis confirms that PM12 samples are from same individual

Pair-wise comparison of 4 samples on 319 SNPs

Genetic similarity
PM12 primary tumor CNA profile (FFPE)
PM12 brain met CNA profile (fresh-frozen)
PM12 summary

Lost in primary
DNADR1, MAP2K4, ARID1A, PTEN, TNFAIP3, PRDM1, ATM

Gained in primary
MDM4

Lost in brain met
DNADR1, MAP2K4, ARID1A, PTEN, TNFAIP3, PRDM1, ATM, APC, FBXW7, TSC2

Gained in brain met
REL, MYC

Brain met (MYC, REL, TSC2)

Primary (MDM4)
Precision Medicine Technology Platform*

- Enrollment
- PM Clinic
- Sequencing
- Analysis
- PM Tumor Board
- Reporting
- Clinical outcomes

- PATENTS
- PUBLICATIONS
- PHARMA PARTNERSHIPS

*Modified Langer model
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Institute for Precision Medicine

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