Genomics and precision medicine

Apply Genomics to Precision Medicine

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TRACO
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Outline

• Success and Challenges of Treating Pediatric Cancers

• Genomics

• Next-generation Sequencing

• Application of next-generation sequencing:
  • Diagnosis
  • Identification of molecular target

• Precision Therapy
Childhood cancer

Childhood cancer: The beginning of a modern medical success story
However in the past 16 years no improvement in mortality rates despite increased intensity of treatment.
Pediatric cancers

Metastatic, Recurrent, & Refractory Disease Remains Incurable

Neuroblastoma

Ewing’s Sarcoma

Stage 4

Metastatic (Spread) Rhabdomyosarcoma

Osteosarcoma - Stage 4
Gene expression

The dramatic consequences of gene expression in biology

Same genome
Different expression pattern
Different proteome
Different tissues
Different physiology

Anise swallowtail, *Papilio zelicaon*
Gene expression

...but the complexity and diversity

Same genome or DNA →
- Different expression pattern
- Different proteome
- Different tissues
- Different physiology
Gene expression

Biology is driven by the simultaneous expression of large numbers of genes acting in concert.

80% of the Genome is Functional

- 3,000,000,000 DNA
- ~1000 miRNA
- >10,000 ncRNA
- ~25-30,000 Genes
- >150,000 Alt Splice
- >500,000 Protein

Proteomics

Phenotype
Cancer Diagnosis & Response to Treatment

Genomics

Translation
Transcription
Gene measurement

Challenge: how to measure/detect genes and their products in a massively parallel way?

- High-throughput technologies
- Computational power
Human genome

Nature

Science
Microarrays

1st generation genomic tool: microarrays

- Mechanical
- Electronic Piezo

Printing microarrays

Lithographic masks and de-protection through illumination

In-situ synthesis microarrays

Digital micromirror device (DMD)
Technologies of hybridization

Microarrays – technologies of hybridization

1) Targets are isolated and labeled
Healthy  Cancerous

2) Labeled targets are combined with array

3) Array is washed after hybridization*

4) Hybridized array is scanned
Clinical vignette

MRI: 9 x 8 x 9 cm mass in upper pole left kidney, tumor in left renal vein and inferior vena cava

Wilm’s tumor?
Cancer diagnosis

Diagnosis of cancers using gene expression profiles derived from DNA microarrays

Wilm’s tumor

Neuroblastoma
Next-generation sequencing

Next-Generation Sequencing

- Fragmentation
- Size Selection
- Adaptors Ligation
- Amplification and Sequencing

Genomic DNA or RNA
Fragment
DNA Fragments of Similar Sizes
Genomic DNA Library
Align (Map) Reads to Ref. Genome
Genome Sequence
Massively Parallel Sequencing

- Each spot = one Sanger sequencing
- Hundred of millions spot in a flow cell
Genomic Alterations

Genomic alterations detected by DNA sequencing

Reference sequence
 Chr 1
 A

Copy number alterations
  Point mutation
  Indel
  Homozygous deletion
  Hemizygous deletion
  Gain
  Translocation breakpoint
  Pathogen

Non-human sequence

Matthew Meyerson, Stacey Gabriel and Gad Getz
NATURE REVIEWS | GENETICS VOLUME 11 | OCTOBER 2010
Genomic Alterations Detected by RNA Transcriptome Sequencing

- Digital Gene Expression
- Expressed Mutations
- Alternative Splicing Events
- Expressed Fusion Transcripts
- RNA editing
- Novel Transcripts
- Non-coding RNAs
Properties

Properties of the next-generation sequencing technologies

- No need to prepare clones for DNA fragments
- No need of prior knowledge for probe design
- Able to detect balanced genome structure changes
- Parallel sequencing at basepair resolution—massive-throughput (up to 100s Gb/run)
- Cheaper (per nucleotide) and faster per genome
Next Generation Sequencing Allows for Comprehensive Analysis of Cancer Genomes on the Same Platform

**DNA**
- Whole Genome
- Genome Partition (e.g. Whole Exome)
- Methylation (e.g. MBD)
- ChIP-seq

**RNA**
- Messenger RNA
- Non-coding RNA (microRNA)
- Other

**Next Generation Sequencing**
- Copy Number
- Gene Rearrangement
- Entire/Novel Methylome
- Damaging Mutations
- Gene Expression
- Chimeric Genes
- Splice Variants
- Novel Transcripts
- Damaging Mutations

**Biomarkers: Diagnostic Prognostic**
**Biology: Drivers**
**Therapeutic Targets: Mutations**
Pediatric cancer mutations

Pediatric Cancers Have A Low Number of Somatic and Actionable Mutations At Initial Diagnosis

Can genomics help clinical care for cancer patients?

2014, Cancer Discovery, Sherm, J. F. et al., Comprehensive Genomic Analysis of Rhabdomyosarcoma
2013, Nature, Lawrence, M. S. et al., Mutational heterogeneity in cancer
ClinOmics Program

ClinOmics Program – Multidimensional Integrated Clinical Omics Platform for all patients at CCR

Personalized Medicine and Imaging

MultiDimensional ClinOmics for Precision Therapy of Children and Adolescent Young Adults with Relapsed and Refractory Cancer: A Report from the Center for Cancer Research

Wendy Chang1,2,3, Andrew S. Brohl1,4, Rajesh Patidar1, Sivasish Sindiri1, Jack F. Shern1,2, Jun S. Wei1, Young K. Song1, Marielle E. Yohe1,2, Berkley Gryder1, Shile Zhang1, Kathleen A. Calzone5, Nityashree Shivaprasad1, Xinyu Wen1, Thomas C. Badgett1,6, Markku Miettinen7, Kip R. Hartman8,9, James C. League-Pascual2,8, Toby N. Trahair10, Brigitte C. Widemann2, Melinda S. Merchant2, Rosanda N. Kaplan2, Jimmy C. Lin3, and Javed Khan1

Clin Cancer Res. 2016 Aug 1;22(15):3810-20
Study Design

- Pilot study to determine the utility and feasibility of performing comprehensive genomic analyses to identify clinically actionable mutations in pediatric and young adult patients with metastatic, refractory or relapsed solid tumors
- 59 patients enrolled to Omics protocol (10-C-0086) at the Pediatric Oncology Branch, Center for Cancer Research (CCR), NCI (2010-2014)
- Age 7 months-25 years
- 20 diagnostic categories (non-CNS, solid tumors)
- Comprehensive multi-omics exome germline & tumor, RNAseq tumor & Illumina Omni SNP arrays of tumor
**Definitions: Actionable**

- **Actionable germline mutation:** loss of function mutation or known hotspot activating mutation of a cancer consensus gene or pathogenic or likely pathogenic mutation of an American College of Medical Genetics (ACMG) Gene

- **Actionable somatic mutation:** genomic alterations that changes the patient’s diagnosis, or may be targeted with FDA approved drugs or in the context of existing clinical trials according to the NCI-adult MATCH-Criteria
Integrated landscape

Multi-Omics
Integrated Landscape

RNAseq
Diagnostic, Driver, Actionable

DNAseq and RNAseq
Somatic: Driver, Actionable

DNA copy number & RNAseq
Somatic: Driver, Actionable

DNAseq
Germ line: Disease causing, Actionable
Fusion genes

Presence or absence of fusion genes and/or expression profiles confirms diagnosis or leads to revision of diagnosis

[Diagram showing sample ID, clinical diagnosis, age at enrollment, sex, prior chemotherapy, and fusion genes with data points indicating presence or absence.]

* [Note symbol indicating a specific condition or result.]
Pediatric germline mutations

~10% of Pediatric and Adolescent Young Adults with Cancers have Actionable Germline Mutations

<table>
<thead>
<tr>
<th>Sample</th>
<th>Diagnosis</th>
<th>Gene</th>
<th>Mutation</th>
<th>Disease</th>
<th>Hotspot</th>
<th>Notes</th>
<th>Reportable by Strict ACMG Criteria</th>
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<tbody>
<tr>
<td>NCI10072</td>
<td>MM</td>
<td>ATN</td>
<td>p.Y350fs</td>
<td>Ataxia-Telangiectasia and cancer predisposition syndrome</td>
<td>No</td>
<td>Frameshift insertion of tumor suppressor gene</td>
<td>Yes</td>
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<tr>
<td>NCI10010</td>
<td>NB</td>
<td>BRCA1</td>
<td>p.R1313X</td>
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<td>Pathogenic, reportable</td>
<td>Yes</td>
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<td>NCI10010</td>
<td>NB</td>
<td>PMS2</td>
<td>p.K356fs</td>
<td>Lynch syndrome and mismatch repair cancer syndrome</td>
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<td>No</td>
<td>Yes</td>
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<td>NCINET2</td>
<td>NET</td>
<td>PTEN</td>
<td>p.R14fs</td>
<td>PTEN Hamartoma tumor syndrome</td>
<td>No</td>
<td>Frameshift deletion of tumor suppressor gene</td>
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<td>NCI01228</td>
<td>MTC</td>
<td>RET</td>
<td>M918T</td>
<td>Multiple endocrine neoplasia 2B</td>
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<td>No</td>
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<td>NCI0152</td>
<td>SS → US</td>
<td>TPS3</td>
<td>R175H</td>
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<td>Pathogenic, reportable</td>
<td>Yes</td>
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<td>NCI0226</td>
<td>ACC</td>
<td>TPS3</td>
<td>A1159K</td>
<td>Li-Fraumeni syndrome</td>
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<td>Patient tumor has LOH of wild-type tp53 on other allele</td>
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<td>NCI0211</td>
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<td>TSC1</td>
<td>p.S828R</td>
<td>Tuberous sclerosis type 1, lymphangioleiomyomatosis, focal cortical dysplasia, and everolimus sensitivity</td>
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<td>Nonsynonymous SNV, autosomal dominant, patient also has a germline TSC2 mutation</td>
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<td>p.T246A</td>
<td>Tuberous sclerosis type 2, and lymphangioleiomyomatosis</td>
<td>Yes</td>
<td>Nonsynonymous SNV, autosomal dominant, patient also has a germline TSC1 mutation</td>
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</table>

NOTE: Mutations were confirmed by direct visualization on an IGV viewer, and by Sanger sequencing.
Abbreviations: ACC, adrenocortical carcinoma; MM, malignant melanoma; MTC, medullary thyroid carcinoma; NET, neuroendocrine tumor; RMS, rhabdomyosarcoma; SS, synovial sarcoma; US, undifferentiated sarcoma; horizontal arrow indicates change in diagnosis.

Actionable somatic mutations

Approximately 50% (30/59) of Pediatric and Adolescent Young Adults with Cancers Have Actionable Somatic Mutations

<table>
<thead>
<tr>
<th>Sample</th>
<th>Diagnostics</th>
<th>Gene</th>
<th>Stage</th>
<th>Mutality</th>
<th>Mutation</th>
<th>AA Change</th>
<th>Level</th>
<th>Drug</th>
<th>Clinical trial: pediatric</th>
<th>FDA Approval in adults</th>
<th>Exact mutation</th>
<th>Reference practical data for level 3</th>
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<td>BRAF</td>
<td>Relapsed</td>
<td>WES/WTS</td>
<td>NS SNV</td>
<td>p.V600E</td>
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<td>Verroafenib</td>
<td>Yes</td>
<td>Yes</td>
<td>Exact</td>
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<td>MM</td>
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<td>NS SNV</td>
<td>p.V600E</td>
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<td>JAK1</td>
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<td>p.R1019C</td>
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<td>IMD8363 inhibitor</td>
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<td>CDK4/6 inhibitor</td>
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<td>Everolimus</td>
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</table>

Abbreviations: EWS, Ewing sarcoma; PI, epithelioid inflammatory myofibroblastic tumor; MM, malignant melanoma; MRT, malignant rhabdoid tumor; MTC, medullary thyroid carcinoma; NB, neuroblastoma; NET, neuroendocrine tumor; OS, osteosarcoma; RMS, rhabdomyosarcoma; WT, Wilms tumor.

Summary

- Demonstrated the importance and feasibility of performing multi-dimensional ClinOmics in the clinical setting in real time.

- ~50% of children with pediatric or AYA patients with relapsed or refractory cancers have actionable somatic mutations.

- ~10% have actionable germline mutations. Importance of performing parallel germline sequencing; some therapeutically actionable (e.g. DNA repair, PTEN, TSC1, TSC2, HRAS, RET, ALK).
Precision medicine

Genomics Enables Precision Medicine

- Metastatic Disease
- Genomics-Biomarkers
  - Good Signature
    - FGFR4
  - Poor Signature
    - ALK
    - BRAF

Standard Therapy
Targeted Individualized Combinational Therapy
ClinOmics Program

CCR ClinOmics Program

Patient referred to CCR → Patient enrolled in Clinical Protocols

Pathology QC & nucleic acid extraction

NGS Experimental & Analysis Workflow

Tissue Procurement

Pls order NGS Test

Precision Therapy

4 Weeks Turnaround

Research Data → Germline Data

ClinOmics BRTIS Databases

Genetics Board

Tumor Board

Clinical EMR (CRIS)
Sequencing equipment

Sequencing Equipment

- Two NextSeq500s for speed and lower throughput
  - 65 Gb/run
  - 14 hours/run
- One HiSeq2500: for high throughput
  - 1000 Gb/run
  - 32 exomes or transcriptomes
  - 14 days/run
Patient diagnoses

396 Patients of 93 diagnoses

ACC
Anaplastic Astrocytoma
Anaplastic PXA
Bladder cancer
Cholangiocarcinoma
Dermatofibrosarcoma protuberans
diffuse intestinal pseudo-glioma
Epidermoid
GI stromal tumor
Giant cell osteosarcoma
Grade 3 Diffuse astrocytoma
Invasive well differentiated squamous cell carcinoma
Lymphoma
Malignant
Malignant peripheral nerve sheath tumor
Meningioma
Multiple myeloma
Neurofibrosarcoma
Osteosarcoma
Papillary tumor of the pineal region
Pituitary tumor (long vs. short)
Renal cell carcinoma
Small cell cancer of the rectum
Temporal high grade glioma
Uveal melanoma
Acute lymphoblastic leukemia
Anaplastic Ependymoma
Aneurysmal fibrous histiocytoma
Brain cancer
Chordoma
dermatofibrosarcoma protuberans
Endothelial cancer
Ewing’s sarcoma
Gliomatosis
Hepatocellular carcinoma
Keratoacanthoma
Melanoma
Merkel cell carcinoma
Mesothelioma Tenke Vignolle
MPNST
Myxopapillary ependymoma
Neuroblastoma
Osteosarcoma
Osteosarcoma of the pineal region
Poorly differentiated carcinoma (long vs. short)
Renal cell carcinoma
Small cell cancer of the rectum
temporal high grade glioma
Uveal melanoma
Acute myeloid leukemia
Anaplastic meningioma
Astrocytoma
Carcinoid, BRAC3 positive
Clear cell carcinoma
Desmoplastic small round cell tumor
Endothelial sarcoma
Endometrial stromal sarcoma
Extraosseous Ewing’s sarcoma
Glioblastoma
Hepatocellular carcinoma
Left Ventricular sarcoma
Medullary thyroid cancer metastatic
Mesothelioma
Metastatic Adenocarcinoma
Multinodular and Vascularizing Neuroepithelial Tumor
Neuroendocrine carcinoma
Neuroendocrine tumor of the pineal gland
Osteosarcoma
Pancreatic cancer
Pheochromocytoma
Primary meningioma
Recurrent glioblastoma
SCLC
Small cell endometrioid
Thyroid
Thymoma
Undifferentiated sarcoma
Ampullary cancer
Acute lymphoblastic leukemia
Anaplastic oligodendroglioma
Atypical central neuroepithelial tumor
Carcinosarcoma of the pelvis
cancer
Carcinosarcoma of the pelvis
Cancer
Carcinosarcoma of the pelvis
Carcinosarcoma of the pelvis
Cancer
Carcinosarcoma
Data portal

ClinOmics Data Portal
https://clinomics.ncifcrf.gov/production/public/
Patient summary
QC report

QC Report:
Sequencing Statistics & Genotyping

Run Statistics

Genotyping
Coverage

QC Report: Coverage

Circos

Tumor Content

RNA Coverage

Hotspot Coverage
Mutations

Germline and Somatic Mutations
EGFR mutations
Tumor copy number

Tumor Copy Number

CN gain
CN neutral
CN Loss
Mutation signatures

Mutation Signatures for Tumor

NCI0263: Melanoma

Signature 7: UV signature

COSMIC (https://cancer.sanger.ac.uk/cosmic/signatures)
Mutation burden

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<th>Diagnosis</th>
<th>Sample Name</th>
<th>Experiment Type</th>
<th>Caller</th>
<th>Burden</th>
<th>Total bases</th>
<th>Burden Per MB</th>
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Showing 1 to 2 of 2 entries (filtered from 6 total entries)
Fusion gene detection

Fusion Gene Detection from RNA-seq experiments

EWS-WT1 fusion t(11;22)(p13;q12) in desmoplastic small round cell tumors (DSRCT)
Genomic information

Other Useful Genomic Information

- HLA typing (Tissue typing)
- Neoantigen prediction
- Gene expression
- Gene Set Enrichment Analysis (GSEA)
- Survival analysis if outcome data is available
Conclusions

- Next generation sequencing (including whole genome, exome, and transcriptome) determines the complete genomic and epigenetic portrait of cancers at the base pair level.

- Integrated analyses of the cancer can identify biologically relevant diagnostic, prognostic biomarkers and novel targets for precision medicine.
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