

Genomics and precision medicine

Apply Genomics to Precision Medicine

Jun S. Wei, Ph.D.
Oncogenomics Section
Genetics Branch
Center for Cancer Research
National Cancer Institute

TRACO
November 5, 2018



Outline

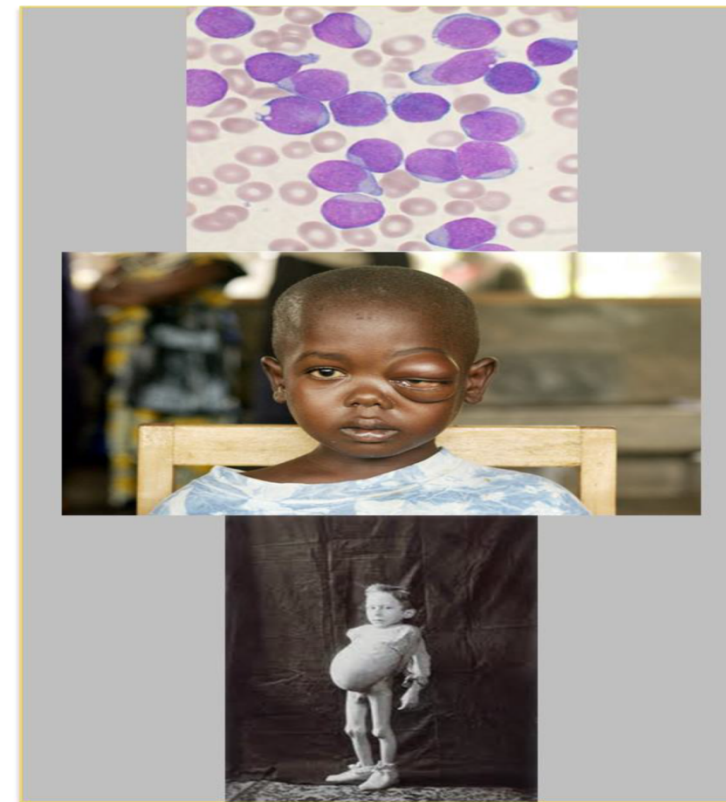
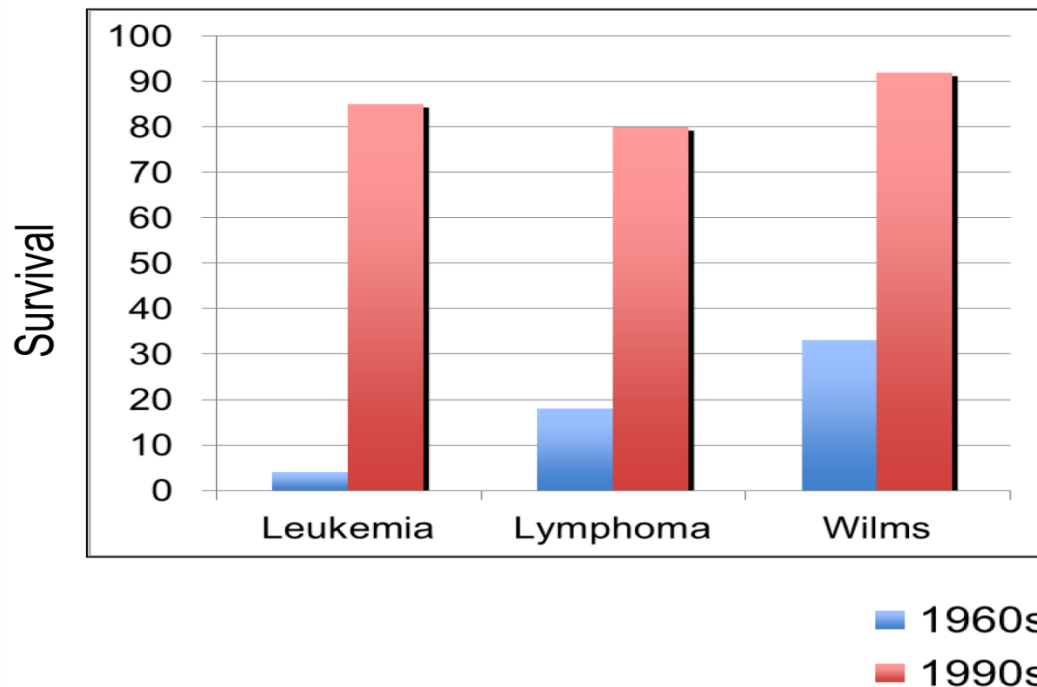
Outline

- **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

National Cancer Institute

Childhood cancer: The beginning of a modern medical success story

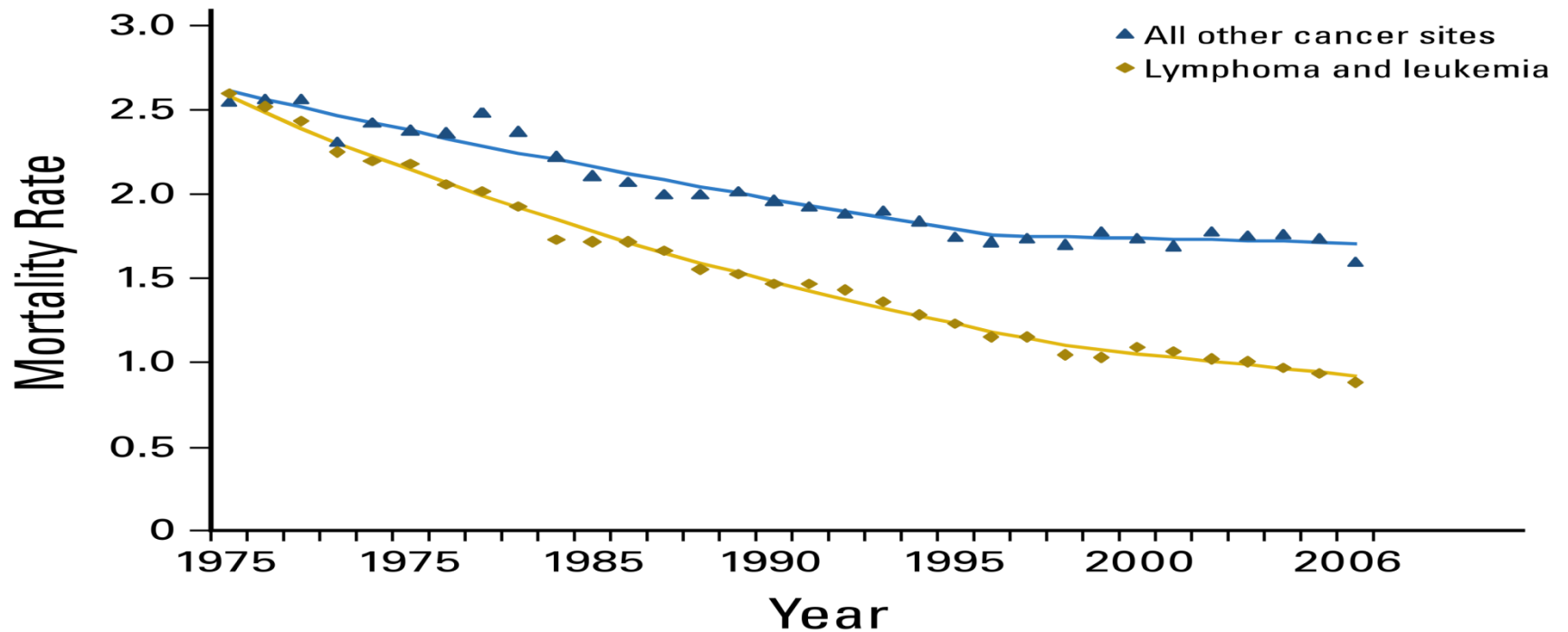


Courtesy: John Maris

Mortality rates

National Cancer Institute

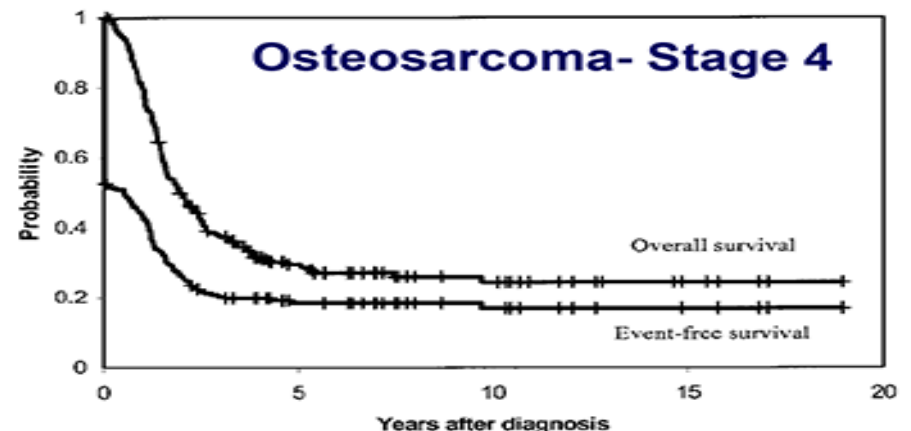
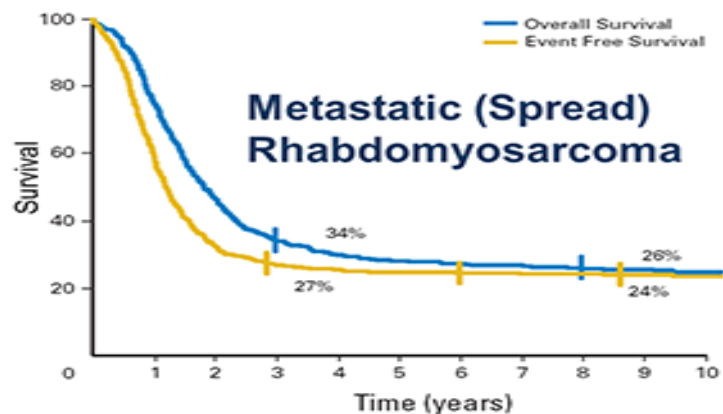
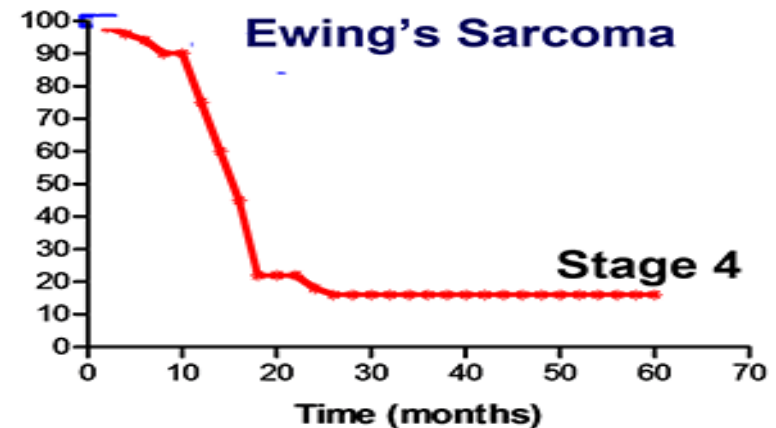
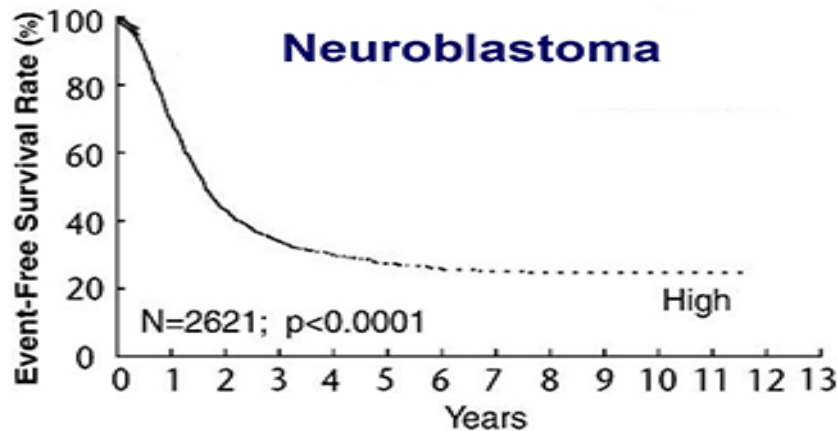
However in the past 16 years no improvement in mortality rates despite increased intensity of treatment



Courtesy: Malcolm Smith

Pediatric cancers

Metastatic, Recurrent, & Refractory Disease Remains Incurable



Gene expression

The dramatic consequences of gene expression in biology



Anise swallowtail, *Papilio zelicaon*

Same genome →
Different expression pattern
Different proteome
Different tissues
Different physiology

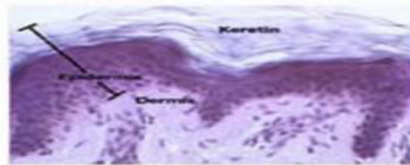


Gene expression

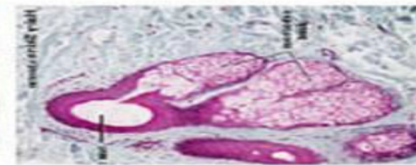
...but the complexity and diversity

Same genome or DNA →

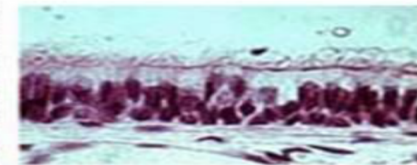
- Different expression pattern
- Different proteome
- Different tissues
- Different physiology



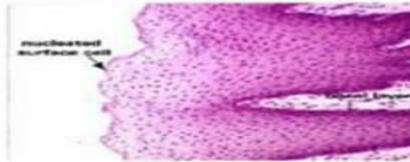
skin



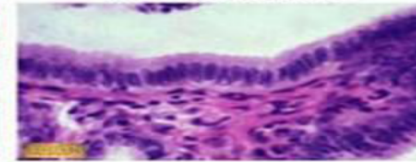
sebaceous gland



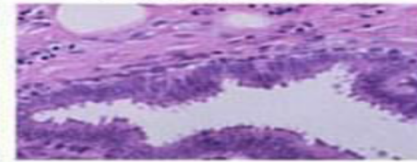
airway epithelium



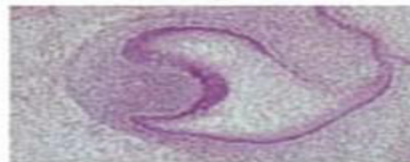
tongue



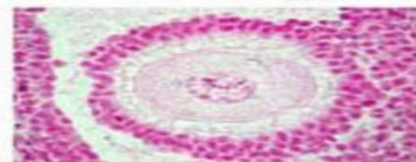
intestinal crypt



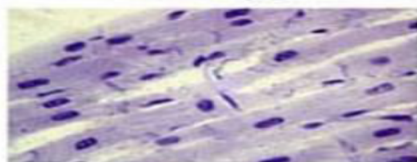
mammary gland



developing tooth



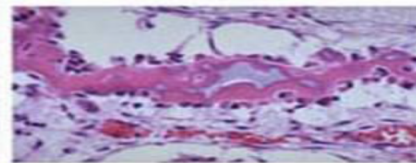
follicle



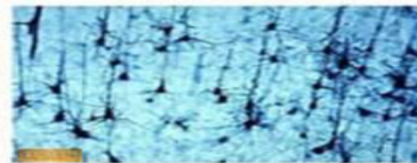
skeletal muscle



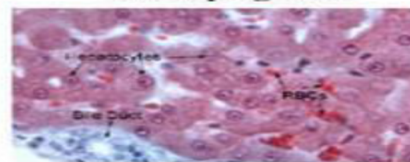
developing bone



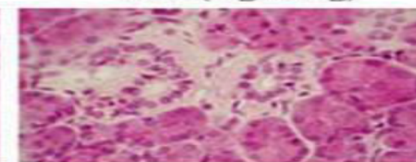
bone (high mag)



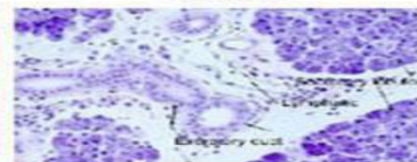
neuron



liver



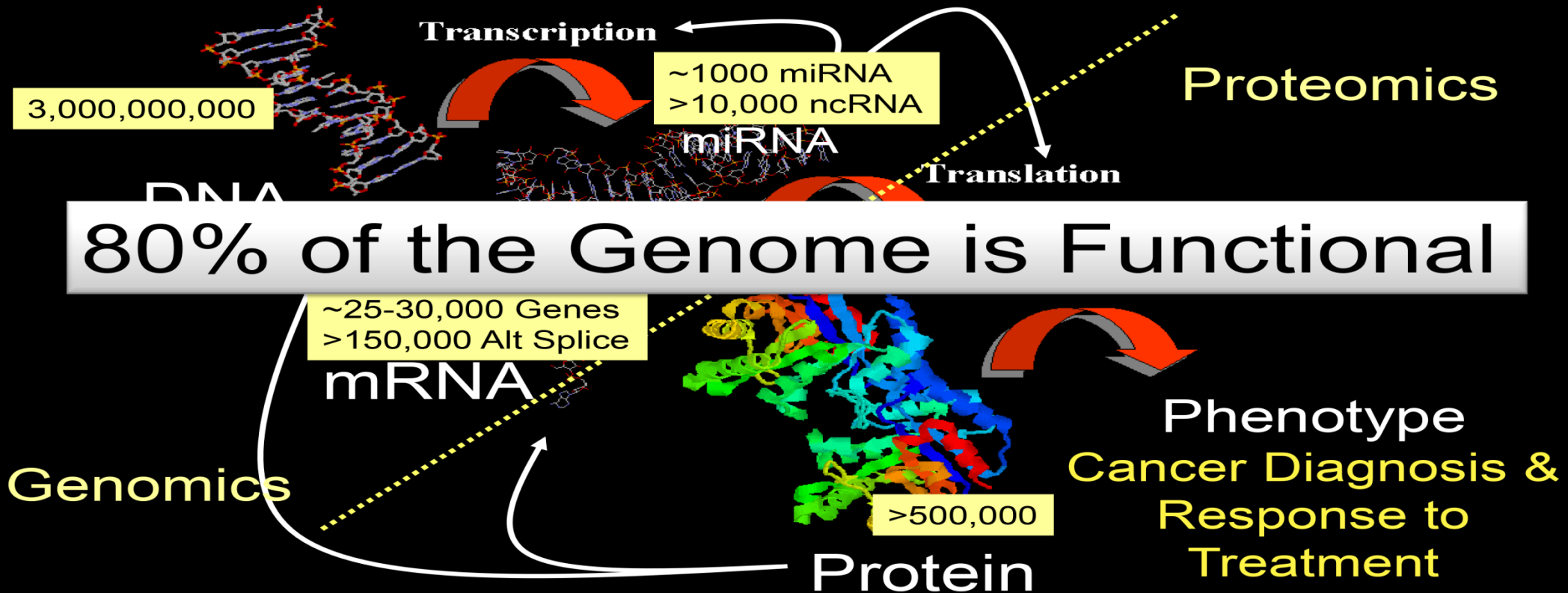
pancreas



parathyroid gland

Gene expression

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



Gene measurement

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

- **High-throughput technologies**
- **Computational power**

Human genome



First generation tools

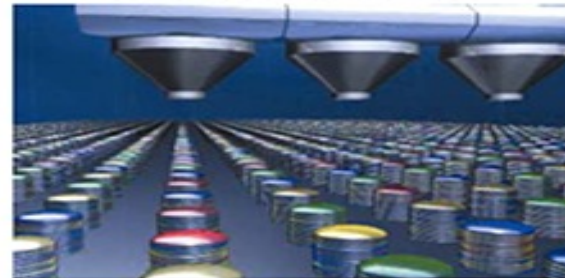
1st generation genomic tool: microarrays

Printing microarrays

Mechanical

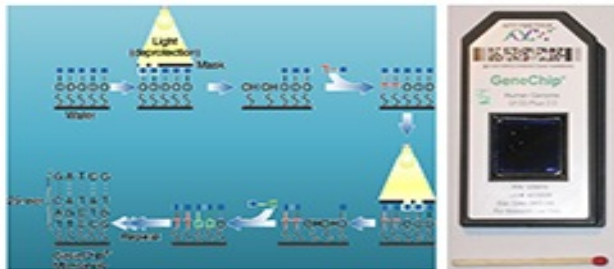


Electronic Piezo

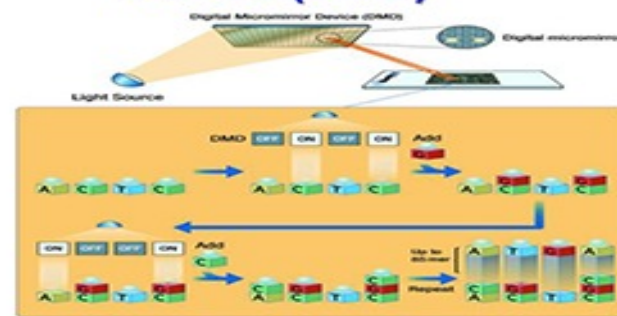


In-situ synthesis microarrays

Lithographic masks
and de-protection
through illumination



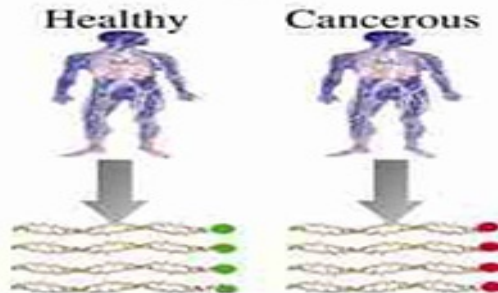
Digital micromirror device (DMD)



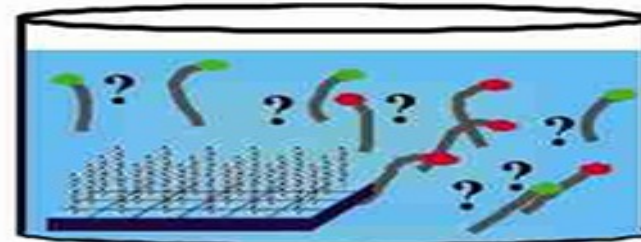
Microarrays

Microarrays – technologies of hybridization

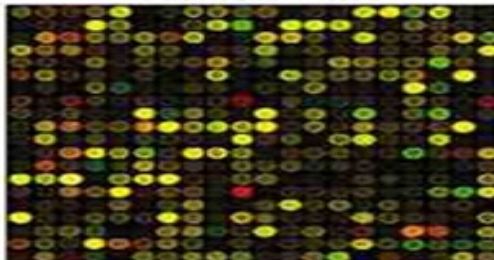
1) Targets are isolated and labeled



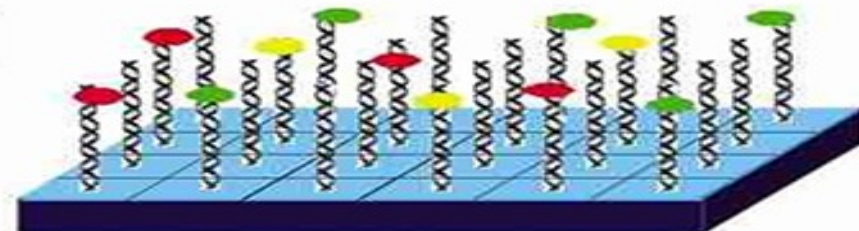
2) Labeled targets are combined with array



4) Hybridized array is scanned



3) Array is washed after hybridization*

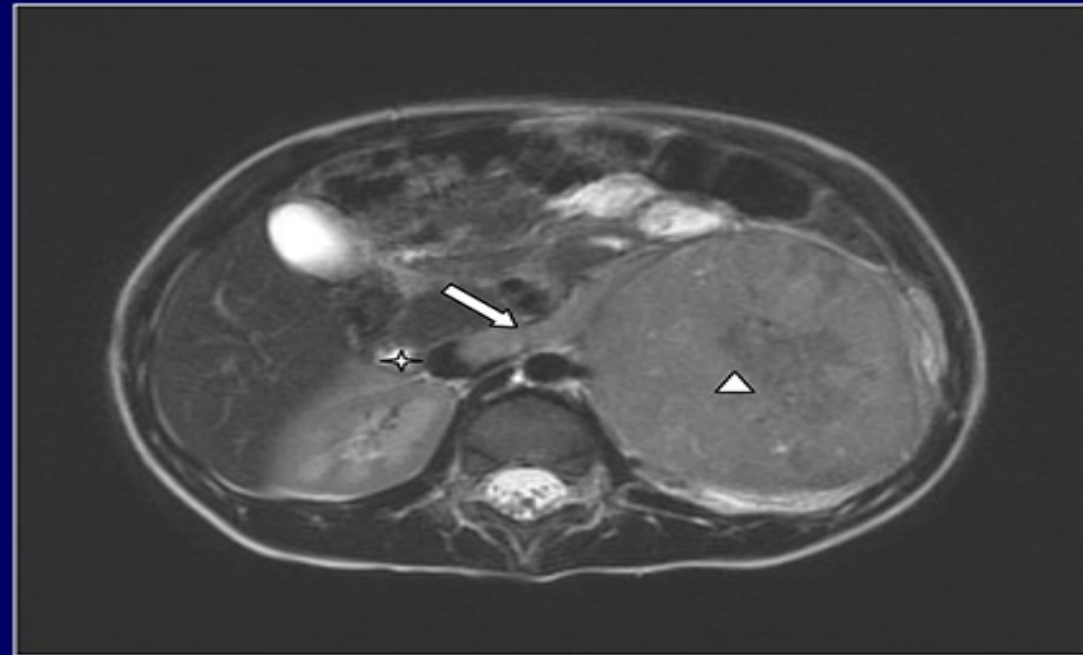


Wilms tumor

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

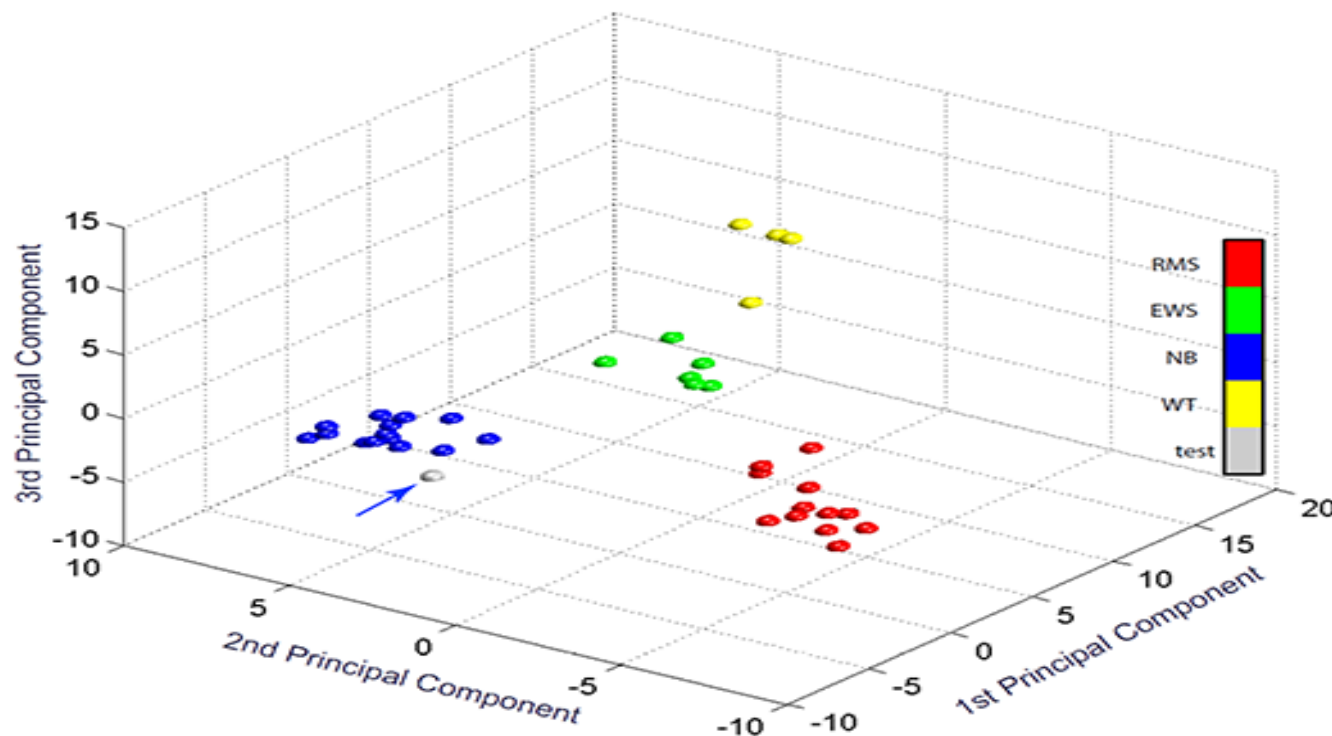


Initial diagnosis: Wilm's tumor



Cancer diagnosis

Diagnosis of cancers using gene expression profiles



Wilm's tumor

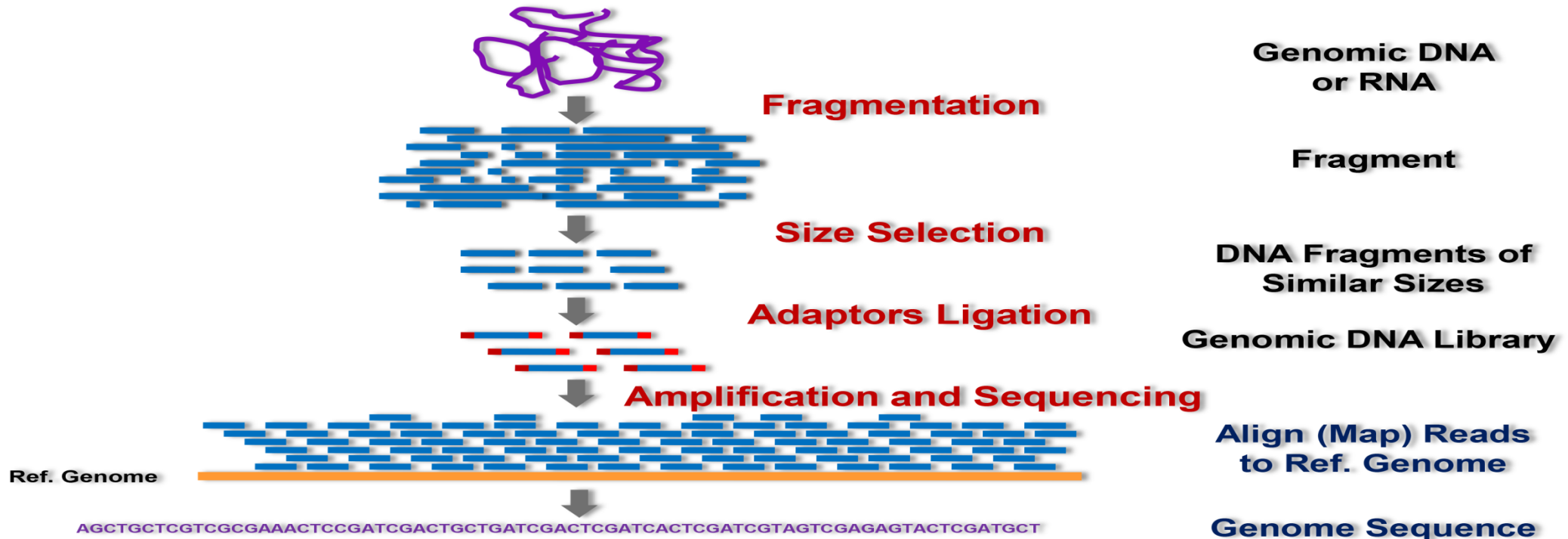


Neuroblastoma

- Patient was switched to high risk neuroblastoma treatment included stem cell transplant
- Doing well 1 yr after diagnosis

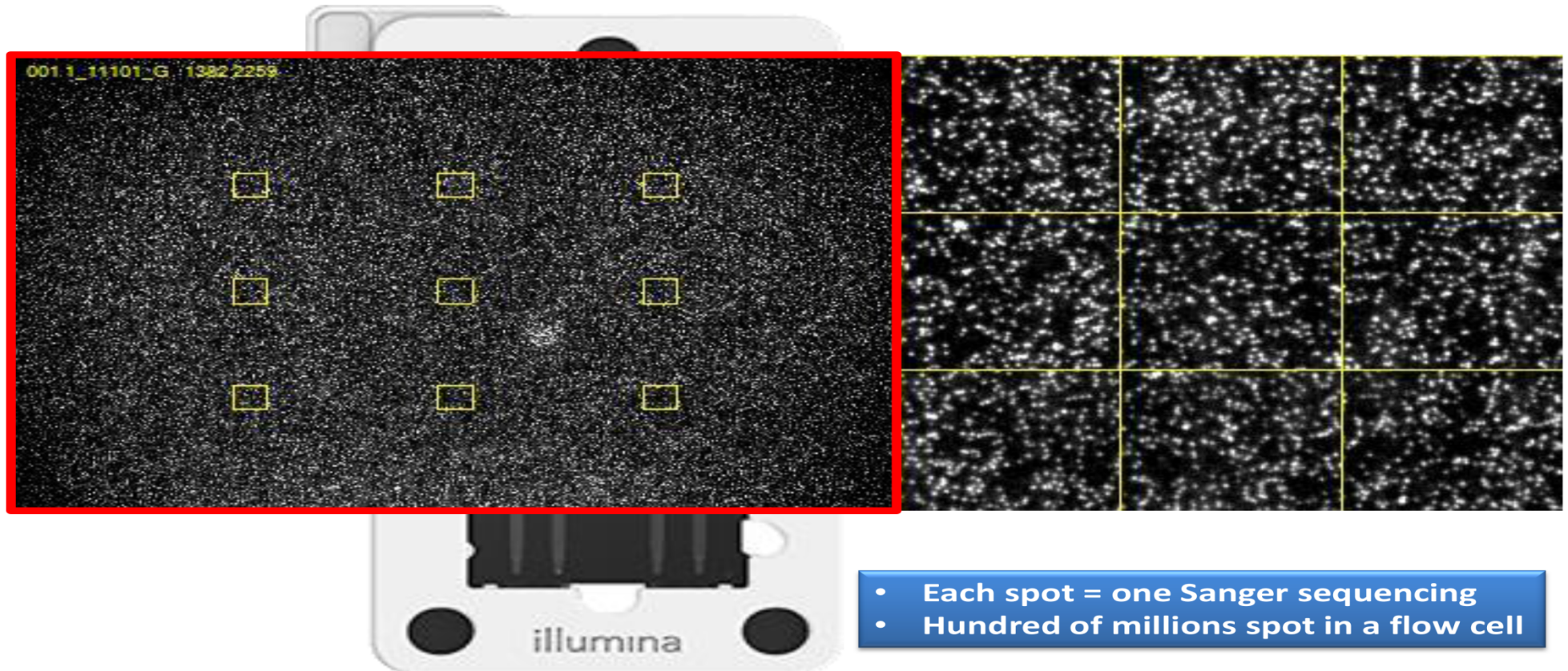
Next-generation sequencing

Next-Generation Sequencing



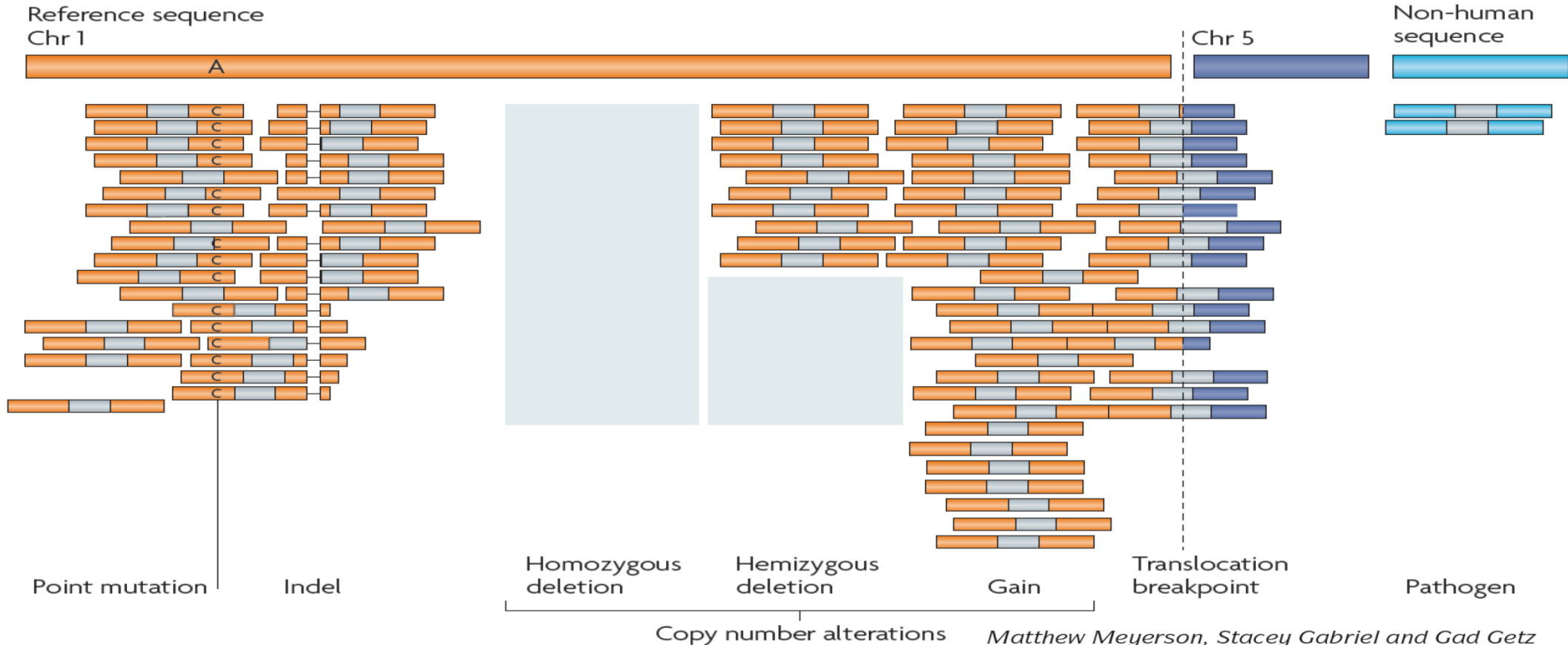
Massively Parallel Sequencing

Massively Parallel Sequencing



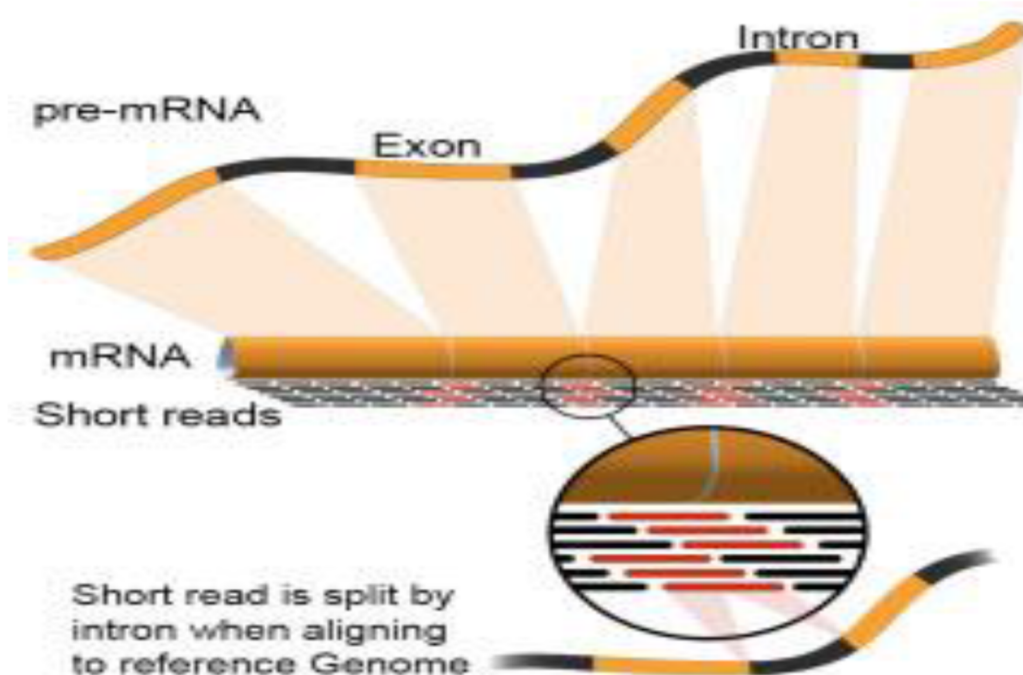
Genomic Alterations

Genomic alterations detected by DNA sequencing



Genomic Alterations

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

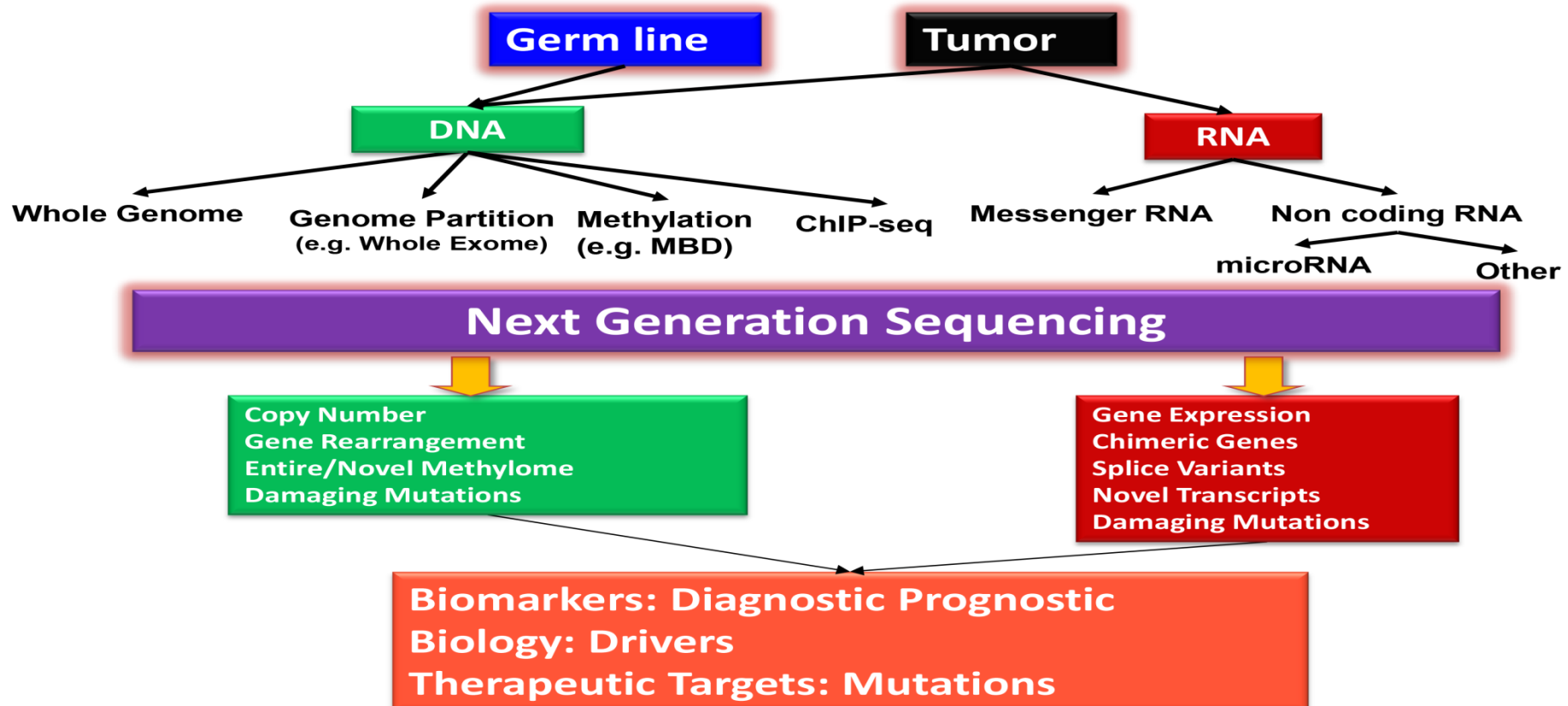
Properties

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

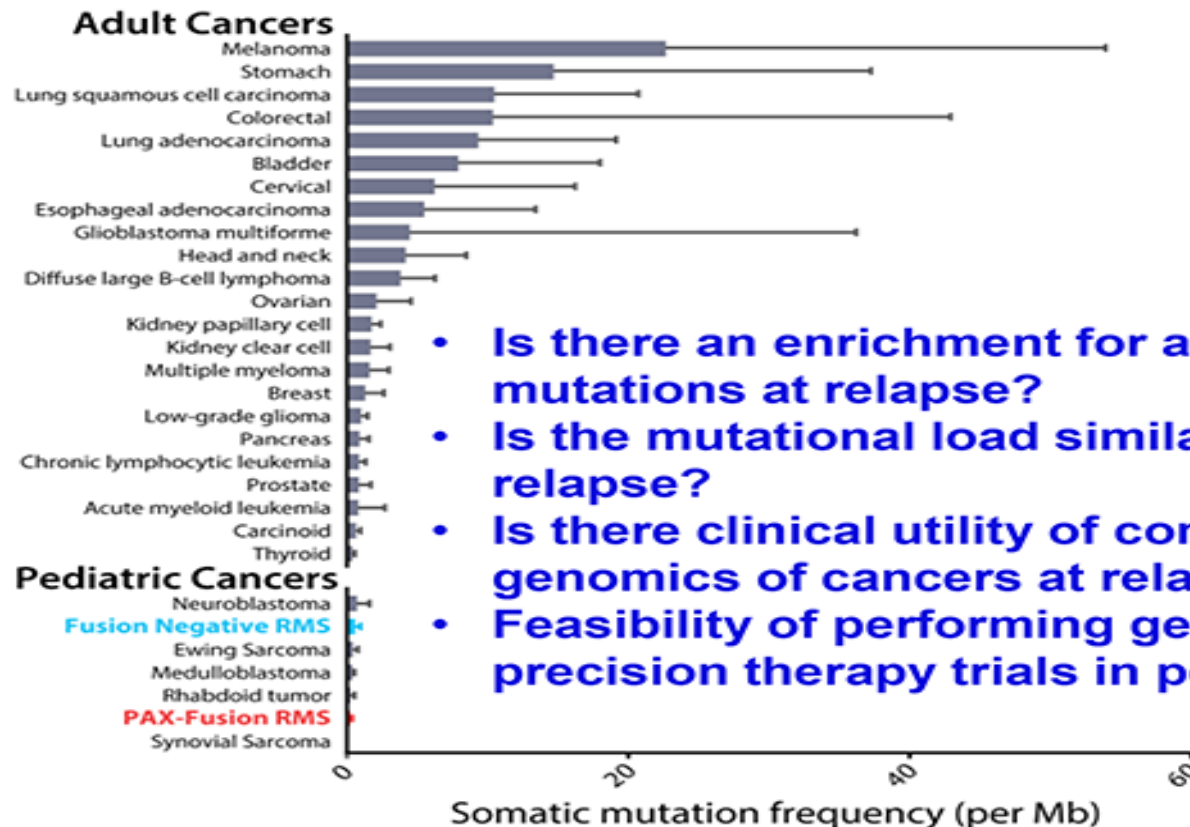
Cancer Genomes

Next Generation Sequencing Allows for Comprehensive Analysis of Cancer Genomes on the Same Platform



Pediatric cancer mutations

Pediatric cancers have a low number of somatic and actionable mutations at initial diagnosis



- Is there an enrichment for actionable mutations at relapse?
- Is the mutational load similarly low at relapse?
- Is there clinical utility of comprehensive genomics of cancers at relapse?
- Feasibility of performing genome guided precision therapy trials in pediatrics?

Clinomics for precision medicine

Personalized Medicine and Imaging

Clinical
Cancer
Research

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 Chang^{1,2,3}, Andrew S. Brohl^{1,4}, Rajesh Patidar¹, Sivasish Sindiri¹, Jack F. Shern^{1,2}, Jun S. Wei¹, Young K. Song¹, Marielle E. Yohe^{1,2}, Berkley Gryder¹, Shile Zhang¹, Kathleen A. Calzone⁵, Nityashree Shivaprasad¹, Xinyu Wen¹, Thomas C. Badgett^{1,6}, Markku Miettinen⁷, Kip R. Hartman^{8,9}, James C. League-Pascual^{2,8}, Toby N. Trahair¹⁰, Brigitte C. Widemann², Melinda S. Merchant², Rosandra N. Kaplan², Jimmy C. Lin¹, and Javed Khan¹

Clin Cancer Res. May 2016

Protocol Number: 10-C-0086

Title: “Comprehensive Omics Analysis of Pediatric Solid Tumors and Establishment of a Repository for Related Biological Studies” or Omics protocol

Study design

Study Design

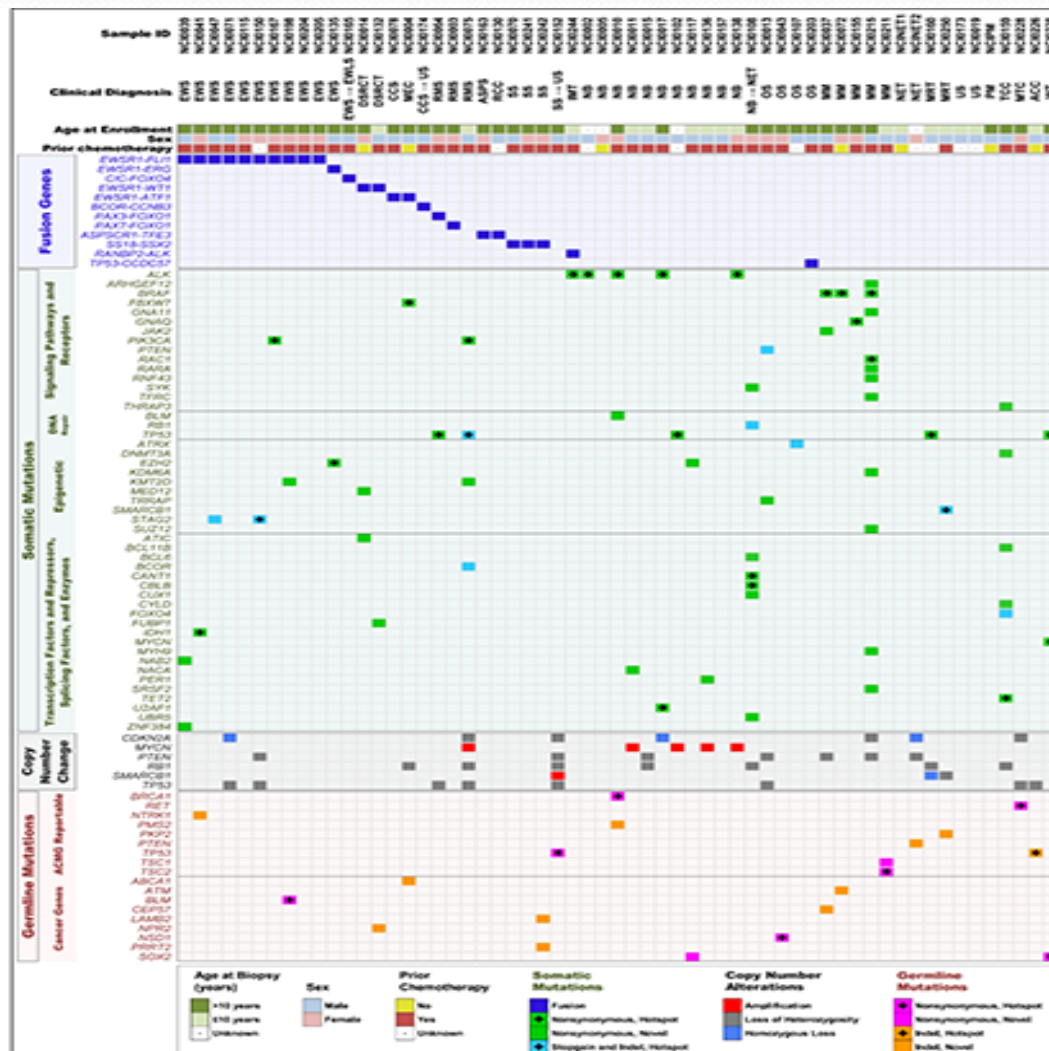
- Pilot study to determine the utility and feasibility of performing comprehensive genomic analyses to identify clinically actionable mutations in pediatric and young adult patients with metastatic, refractory or relapsed solid tumors
- 59 patients enrolled to the pediatric oncology branch, Center for 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

Mutations

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

Multi-omics integrated landscape



Multi-Omics Integrated Landscape

RNAseq
Diagnostic, Driver, Actionable

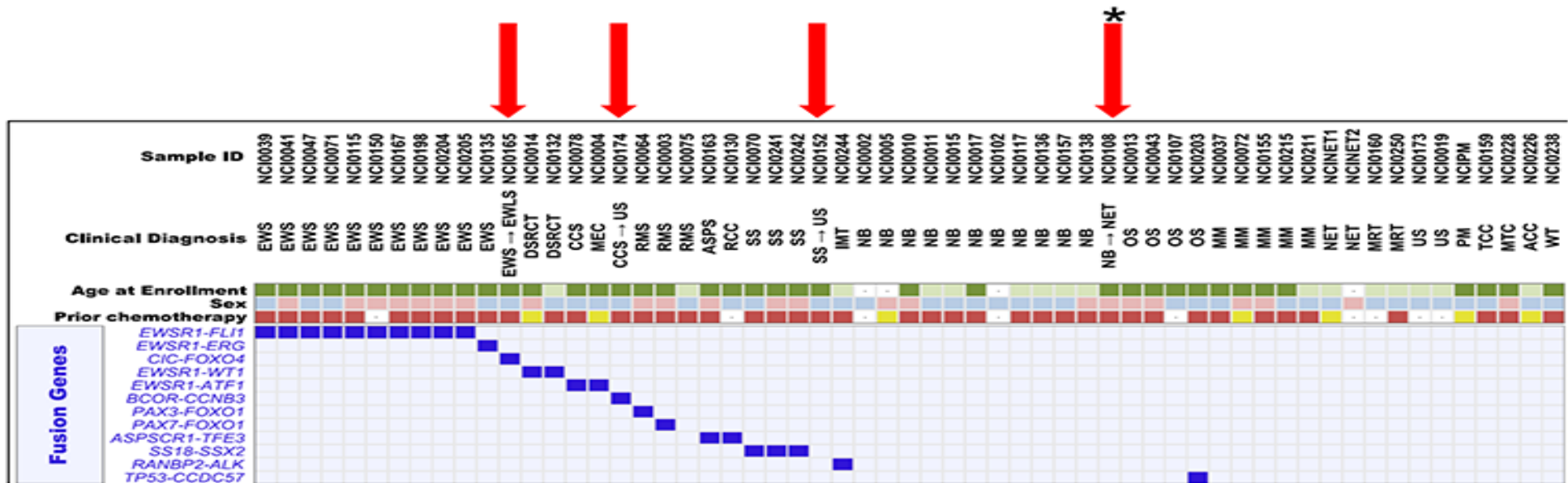
DNAseq and RNAseq
Somatic: Driver, Actionable

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



Tumor mutations

Approximately 50% of Pediatric and Adolescent Young Adults with Cancers have Actionable Tumor Mutations

Sample	Diagnosis	Gene	Stage	Modality	AA Change	Level	Drug	Clinical Trial: Pediatric	FDA Approval in Adults	Exact Mutation vs. Hotspot
NCI0041	EWS	IDH1	Relapsed	WES/WTS	p.R132C	2a	IDH1 inhibitors	No	No	Exact
NCI0167	EWS	PIK3CA	Refractory	WES/WTS	p.D1017G	2a	PI3K/AKT/mTOR inhibitors	Yes	Yes	Exact
NCI0071	EWS	CDKN2A	Relapsed	SNP Array/WTS	Homozygous loss	3	CDK4/6 inhibitor	No	No	-
NCI0047	EWS	STAG2	Relapsed	WES/WTS	p.E984X	3	PARP inhibitors	Yes	No	-
NCI0150	EWS	STAG2	-	WES/WTS	p.R216X	3	PARP inhibitors	Yes	No	Hotspot
NCI0244	IMT	ALK	Relapsed	WTS	RANSP2-ALK fusion	2a	Crizotinib	No	Yes	Exact
NCI0244	IMT	ALK	Relapsed	WES/WTS	p.I1171T	2a	Crizotinib	No	Yes	Exact
NCI0037	MM	BRAF	Relapsed	WES/WTS	p.V600E	1	Vemurafenib, Dabrafenib	Yes	Yes	Exact
NCI0072	MM	BRAF	Diagnostic	WES/WTS	p.V600E	1	Vemurafenib, Dabrafenib	Yes	Yes	Exact
NCI0215	MM	BRAF	Relapsed	WES/WTS	p.V600E	1	Vemurafenib, Dabrafenib	Yes	Yes	Exact
NCI0155	MM	GNAQ	Relapsed	WES/WTS	p.Q209L	1	Temsirolimus, Trametinib, Vorinostat	No	Yes	Exact
NCI0215	MM	GNA11	Relapsed	WES/WTS	p.S268F	2a	Trametinib	No	Yes	-
NCI0211	MM	TSC1	Relapsed	WES/WTS	p.S828R	3	Everolimus	No	Yes	-
NCI0211	MM	TSC2	Relapsed	WES/WTS	p.T246A	3	Everolimus	No	Yes	-
NCI0160	MRT	SMARCB1	-	SNP Array/WTS	Homozygous loss	3	EZH2 inhibitors	No	No	-
NCI0250	MRT	SMARCB1	Refractory	WES/WTS	p.R40X	3	EZH2 inhibitors	No	No	-
NCI0228	MTC	RET	Relapsed	WES/WTS	p.M918T	2a	Vandetanib	Yes	Yes	Exact
NCI0002	NB	ALK	-	WES/WTS	p.R1275Q	2a	Crizotinib	Yes	Yes	Exact
NCI0010	NB	ALK	Relapsed	WES/WTS	p.F1174V	2a	Crizotinib	Yes	Yes	Exact
NCI0017	NB	ALK	Relapsed	WES/WTS	p.F1174L	2a	Crizotinib	Yes	Yes	Exact
NCI0138	NB	ALK	Relapsed	WES/WTS	p.Y1278S	2a	Crizotinib	Yes	Yes	Exact
NCI0017	NB	CDKN2A	Relapsed	SNP Array/WTS	Homozygous loss	3	CDK4/6 inhibitor	No	No	-

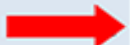
Sample	Diagnosis	Gene	Stage	Modality	AA Change	Level	Drug	Clinical Trial: Pediatric	FDA Approval in Adults	Exact Mutation vs. Hotspot
NCI0011	NB	MYCN	Relapsed	SNP Array/WTS	Amplification	3	bromodomain inhibitors	No	No	-
NCI0102	NB	MYCN	-	SNP Array/WTS	Amplification	3	bromodomain inhibitors	No	No	-
NCI0136	NB	MYCN	Relapsed	SNP Array/WTS	Amplification	3	bromodomain inhibitors	No	No	-
NCI0138	NB	MYCN	Relapsed	SNP Array/WTS	Amplification	3	bromodomain inhibitors	No	No	-
NCINET2	NET	PTEN	-	WES/WTS	p.R14fs	2a	PI3K/AKT/mTOR inhibitors	Yes	No	-
NCINET2	NET	CDKN2A	-	SNP Array/WTS	Homozygous loss	3	CDK4/6 inhibitor	No	No	-
NCI0013	OS	PTEN	Relapsed	WES/WTS	p.K80fs	2a	PI3K/AKT/mTOR inhibitors	Yes	No	-
NCI0075	RMS	PIK3CA	Relapsed	WES/WTS	p.P104Q	2a	PI3K/AKT/mTOR inhibitors	Yes	Yes	Exact
NCI0075	RMS	MYCN	Relapsed	SNP Array/WTS	Amplification	3	bromodomain inhibitors	No	No	-
NCI0238	WT	MYCN	Relapsed	WES/WTS	p.P44L	3	bromodomain inhibitors	No	No	-

NCI-Adult MATCH Criteria for Matching Mutation to Drug

Level 1	Gene variant approved for selection of an approved drug (BRAF V600E and vemurafenib). The variant will be Level 1 in all tissues open to treatment with the approved drug.
Level 2a	Gene variant is an eligibility criteria for an ongoing clinical trial for that treatment.
Level 2b	Gene variant has been identified in an N of 1 responses (TSC1 and everolimus) for that treatment.
Level 3	Preclinical inferential data (in vivo and in vitro models) that provide biological evidence sufficient to support the use of a variant for treatment selection, e.g. - Models with variants respond to treatment and models without variant do not respond to treatment - Gain of function mutations demonstrated in pre-clinical model, e.g. D769H variant of ERBB2 results in increased tyrosine kinase-specific activity and up regulates pathway signaling (does not require treatment evidence) - Loss of function genes, tumor suppressor or pathway inhibitor (e.g. NF1) any variant that produces a stop codon including frameshift or demonstrated loss of function in pre-clinical model (does not require treatment evidence)

Germline mutations

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

Sample	Diagnosis	Gene	Mutation	Disease	Hotspot	Notes	ACMG gene
NCI0072	MM	<i>ATM</i>	p.Y380fs	Ataxia-Telangiectasia and Cancer Predisposition Syndrome	No	Frameshift Insertion of Tumor Suppressor Gene	Yes
NCI0010	NB	<i>BRCA1</i>	Q1313X	Hereditary Breast and Ovarian Cancer Syndrome	Yes	Pathogenic, Reportable	Yes
NCI0010	NB	<i>PMS2</i>	p.K356fs	Lynch Syndrome and Mismatch Repair Cancer Syndrome	No	Frameshift Deletion of Tumor Suppressor Gene	Yes
	NET	<i>PTEN</i>	p.R14fs	PTEN Hamartoma Tumor Syndrome	No	Frameshift Deletion of Tumor Suppressor Gene	Yes
	MTC	<i>RET</i>	M918T	Multiple Endocrine Neoplasia 2B	Yes	Pathogenic, Reportable	Yes
NCI0152	SS → US	<i>TP53</i>	R175H	Li-Fraumeni Syndrome	Yes	Patient Tumor has LOH of Wild-Type TP53 on Other Allele	No
NCI0226	ACC	<i>TP53</i>	A159K	Li-Fraumeni Syndrome	Yes	Tumor has LOH of Wild-Type TP53 on Other Allele, Novel, 2 Base Non-Frameshift Substitution, c.358_359delGCinsTT	No
	MM	<i>TSC1</i>	p.S828R	Tuberous Sclerosis Type 1, Lymphangioleiomyomatosis, Focal Cortical Dysplasia, and Everolimus Sensitivity	No	Nonsynonymous SNV, Autosomal Dominant, Patient also has a Germline TSC2 Mutation	No
	MM	<i>TSC2</i>	p.T246A	Tuberous Sclerosis Type 2, and Lymphangioleiomyomatosis	Yes	Nonsynonymous SNV, Autosomal Dominant, Patient also has a Germline TSC1 Mutation	No

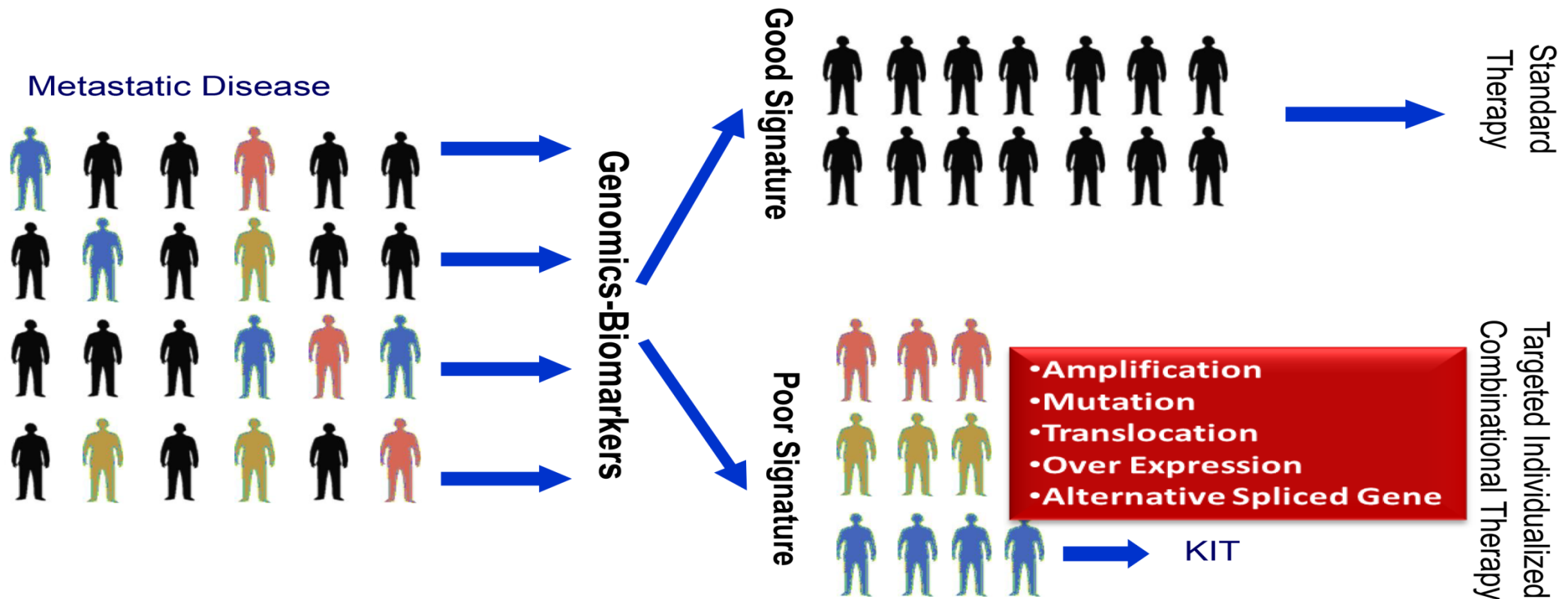
Summary

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)
- Increased tumor burden in relapsed tumors; implications for immunotherapy
- Single agent pediatric MATCH like trials are planned by COG-NCI

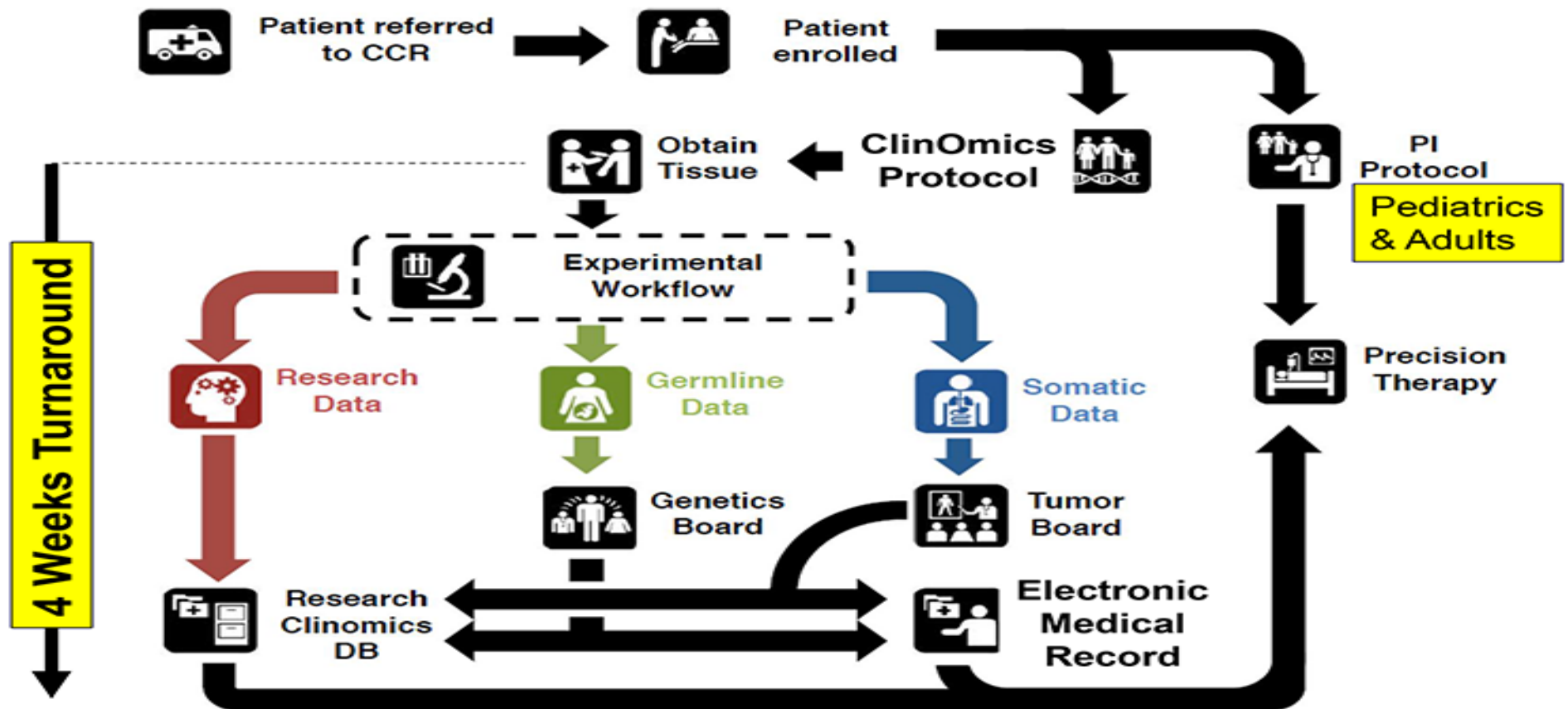
Future Trials

Genomics Enabling Precision Therapy-The Future for Pediatric Trials



ClinOmics program

CCR ClinOmics Program-CLIA



Sequencing equipment

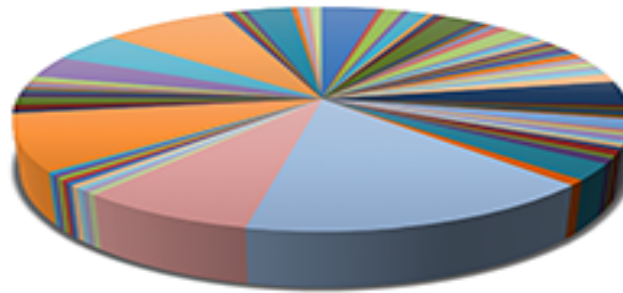
Sequencing Equipment



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

Patient diagnoses

255 Patients of 81 diagnoses

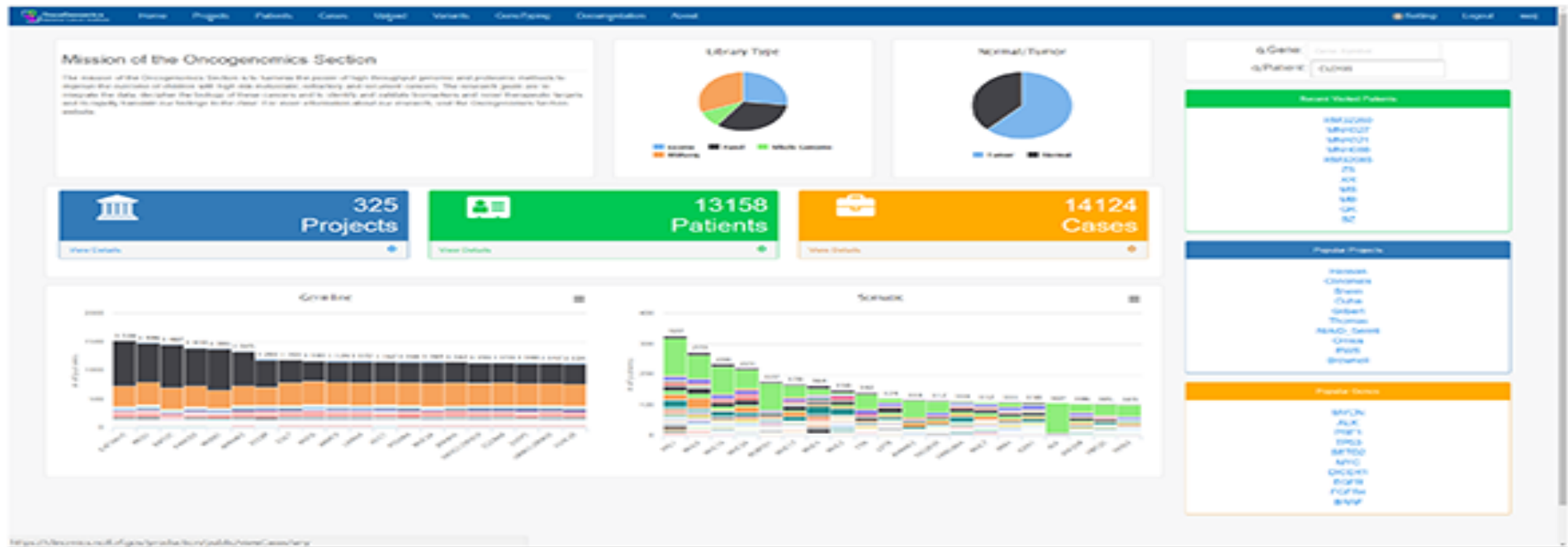


- | | | | |
|---|--|---|--|
| ■ Acute lymphoblastic leukemia | ■ Acute myeloid leukemia | ■ Adenocarcinoma | ■ Ampullary cancer |
| ■ Anaplastic Astrocytoma | ■ Anaplastic Astrocytoma/Glioblastoma IDH Mutant | ■ Anaplastic Astrocytoma/Glioblastoma IDH WT | ■ Anaplastic Ependymoma |
| ■ Anaplastic Oligodendroglioma | ■ Anaplastic PXA | ■ Aneurysmal Fibrous histiocytoma | ■ Astrocytoma |
| ■ Bladder cancer | ■ Breast cancer | ■ Cholangiocarcinoma | ■ Clear cell sarcoma |
| ■ Colon cancer | ■ Desmoid Fibromatosis | ■ Desmoplastic small round cell tumor | ■ Diffuse Astrocytoma, Grade III |
| ■ Diffuse intrinsic pontine glioma | ■ Endometrial cancer | ■ Endometrial Stromal Sarcoma | ■ Eosinophilia |
| ■ Ewing's sarcoma | ■ Extrapulmonary Small Cell Cancer | ■ Gallbladder cancer | ■ GBM |
| ■ Glioblastoma | ■ Glioblastoma IDH Mutant | ■ Glioblastoma IDH WT | ■ Glioblastoma Multiforme |
| ■ Gliosarcoma | ■ Hepatic Angiosarcoma | ■ Hepatocellular cancer | ■ Hepatocellular Carcinoma |
| ■ Hepatocellular carcinoma | ■ High grade glioma, IDH mutant | ■ Invasive well differentiated squamous cell carcinoma | ■ Keratoacanthoma |
| ■ Lung Adenocarcinoma | ■ Lung adenocarcinoma stage IA | ■ Lymphocytosis | ■ Mastocytosis |
| ■ Medullary Thyroid Cancer metastatic | ■ Melanoma | ■ Mesothelioma | ■ Mesothelioma bi compartmental |
| ■ Mesothelioma Peritoneal | ■ Mesothelioma Pleural | ■ Mesothelioma Tunica Vaginalis | ■ MNGT |
| ■ Multinodular and Vacuolating Neuronal Tumor | ■ Multiple | ■ Multiple carcinoma | ■ Myoepithelial Ependymoma |
| ■ Neuroendocrine carcinoma | ■ Neurofibromatosis 1 | ■ Neuronal tumor | ■ Non small cell lung cancer |
| ■ Neuroendocrine giant cell tumor | ■ NSGIC | ■ Osteosarcoma | ■ Pancreatic cancer |
| ■ Papillary tumor of the pineal region | ■ Pilocytic Astrocytoma | ■ Pleomorphic Xanthoastrocytoma | ■ Poorly differentiated carcinoma (lung vs. thyroid) |
| ■ Prostate cancer | ■ Renal cell carcinoma | ■ Rhabdomyosarcoma | ■ SGC |
| ■ Small cell bladder | ■ Small Cell Cancer of rectum | ■ Small Cell Carcinoma of the ovary hypercalcemic type (SGCCHT) | ■ Small cell endometrium |
| ■ Solid Tumor CAP_Survey | ■ Synovial sarcoma | ■ Teratoma | ■ Undifferentiated sarcoma |
| ■ Uveal melanoma | | | |

ClinOmics Data Portal

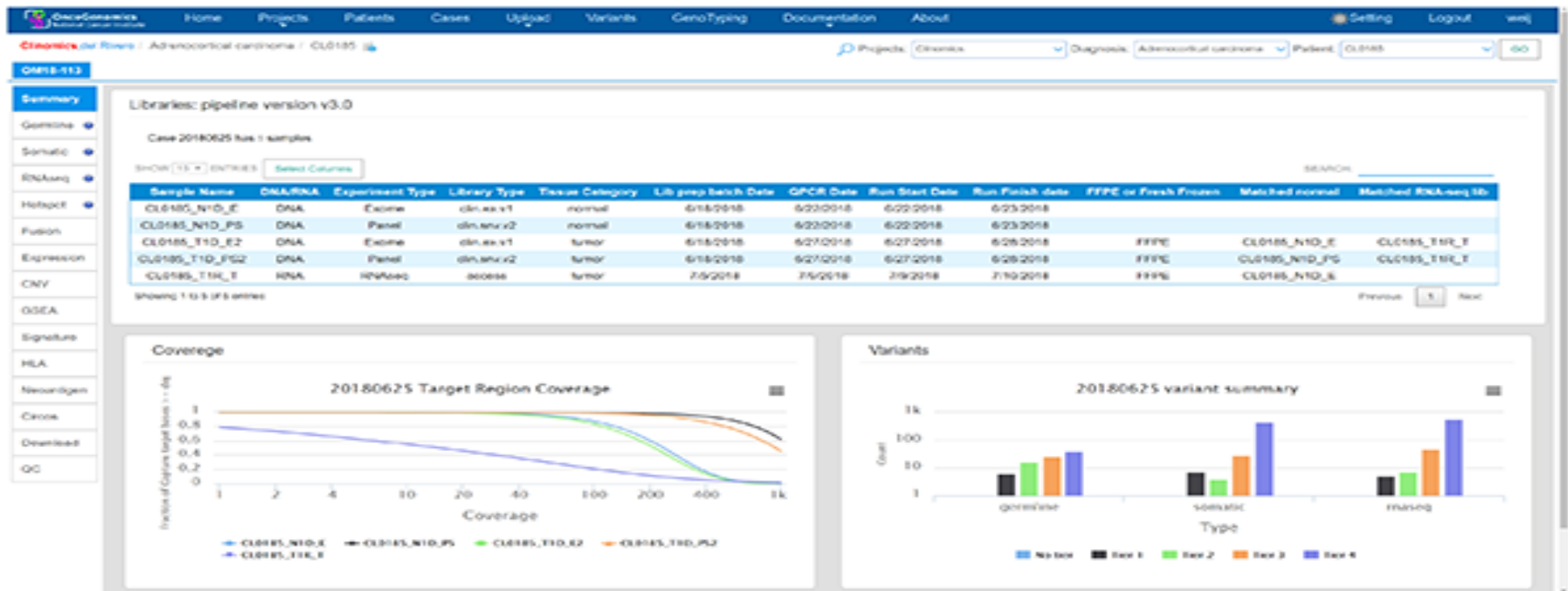
ClinOmics Data Portal

<https://clinomics.ncifcrf.gov/production/public/>



Patient Summary

Patient Summary Page



QC report

QC Report: Sequencing Statistics & Genotyping

Run Statistics

Mutations **QC**

Circos Coverage Transcript Coverage Hotspot **DNA QC** RNA QC Genotyping

Show 15 entries Select Columns Search

Sample_ID	Percent log unique onTarget	Percent log unique positions at 5x	Percent log unique positions at 10x	Percent log unique positions at 15x	Percent log unique positions at 20x	Percent log unique positions at 30x	Percent log unique positions at 50x	Percent log unique positions at 100x	Percent log unique positions at 200x	MEAN BALT COVERAGE	MEAN TARGET COVERAGE	OnTarget reads	Percent onTarget	Unique onTarget reads	Percent unique onTarget	Min mapq	Mean mapq
CL0033_T_P	98.94	97.50	97.08	96.71	96.35	95.58	93.68	87.48	75.91	709	758	33301602	44.54	25701887	77.18	0	59.23
CL0034_T_E	97.24	97.46	97.10	96.73	96.30	95.24	92.20	79.63	50.45	248	263	194065283	63.33	171540148	88.39	0	58.30
CL0034_T_P	98.92	97.30	96.73	96.20	95.64	94.33	91.19	81.83	68.37	464	496	196879910	59.58	16811999	85.39	0	59.21
CL0033_B_E	96.68	97.16	96.43	95.41	94.02	89.98	77.75	42.24	7.27	100	105	71811950	65.27	68733940	95.71	0	57.97
CL0033_B_P	98.67	96.39	95.33	94.32	92.81	89.67	81.07	58.09	19.87	137	143	5141354	58.65	4922738	95.75	0	59.04
CL0033_T3D_E	96.75	97.47	97.18	96.87	96.53	95.72	93.39	82.58	50.80	232	245	190042530	66.15	160140987	84.27	0	58.01
CL0033_T3D_P	98.69	97.38	97.08	96.83	96.62	96.22	95.43	93.21	86.68	732	763	37963486	59.30	26297292	69.27	0	59.07
CL0033_T_E	97.22	97.44	97.07	96.65	96.17	94.97	91.48	77.39	48.03	242	258	195690091	63.51	167866163	85.78	0	58.28

Showing 1 to 8 of 8 entries

Genotyping

Show 15 entries Select Columns Search

Sample	CL0033_B_E	CL0033_B_P	CL0033_T3D_E	CL0033_T3D_P	CL0033_T3E_T	CL0033_T_E	CL0033_T_P	CL0033_T_T	CL0034_T_E	CL0034_T_P	CL0034_T_T
CL0033_B_E	100%	97%	98%	93%	94%	98%	86%	94%	98%	94%	94%
CL0033_B_P	97%	100%	96%	97%	94%	96%	97%	94%	96%	98%	94%
CL0033_T3D_E	98%	96%	100%	92%	94%	98%	87%	94%	96%	94%	95%
CL0033_T3D_P	91%	97%	91%	100%	89%	90%	96%	90%	91%	97%	89%
CL0033_T3E_T	94%	94%	94%	89%	100%	94%	84%	96%	94%	90%	96%
CL0033_T_E	98%	96%	98%	90%	94%	100%	87%	94%	98%	93%	94%
CL0033_T_P	86%	97%	87%	94%	84%	87%	100%	83%	87%	97%	84%
CL0033_T_T	94%	94%	94%	96%	96%	94%	85%	100%	94%	92%	97%
CL0034_T_E	98%	96%	98%	92%	94%	98%	94%	100%	93%	94%	94%
CL0034_T_P	94%	94%	94%	97%	90%	93%	97%	92%	93%	100%	91%
CL0034_T_T	94%	94%	95%	89%	96%	94%	84%	97%	94%	91%	100%

Showing 1 to 11 of 11 entries

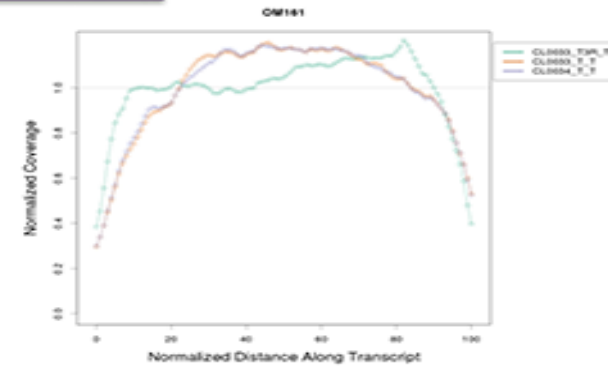
QC report

QC Report: Coverage

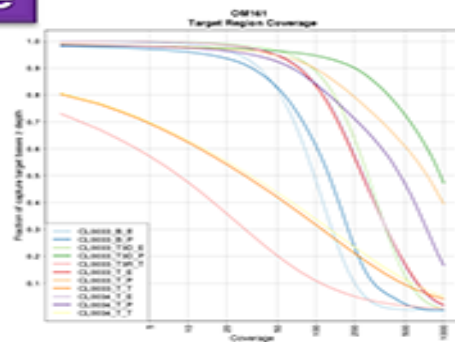
Circos



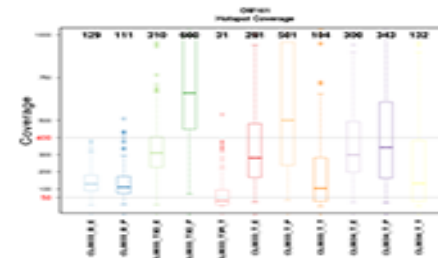
RNA Coverage



Coverage



Hotspot Coverage



Mutation view

Mutation View

Mutations

QC

Germline

Somatic

RNAseq

Gene fusion

Expression

Add filter

Clear all

Status: active

Sign out

Actionable

Mutations: 117/1892

MAF: 0.05

Min Total Cov: 10

Min VAF: 0.25

Tier 1

Tier 2

Tier 3

Tier 4

All

Show 15 entries

Select Columns

Search:

Details	IGV	Cover	Chr	Start	End	Ref	Alt	Gene	AAChange	Hotspots	Snp138	Max Public VAF	Prediction	Clinvar	Cosmic	HGMD	Reported	Germline	Germline level
		45%45%	chr1	197070697	197070707	TTT...	CTT...	ASPM	c.7674_7684TGAATACAAG										Tier 3
		45%45%	chr1	144917829	144917829	A	-	PDE4D	V552fs		rs375854543		Y						Tier 1
		18.18%	chr19	46274624	46274624	G	A	DMPK	T570M		rs146680240	0.03	Y		Y		3		Tier 3
		9.09%	chr8	37555989	37555989	G	C	ZNF703	A524P				Y						Tier 3
		9.09%	chr17	20135672	20135672	G	A	SPECC1	D769N		rs35835131	0.02	Y				1		Tier 3
		45%45%	chr8	68968166	68968171	CGA...	AGA...	PREX2	c.1195_1200AGAAAA				Y						Tier 3
		45%45%	chr1	144854597	144854598	TC	CT	PDE4D	c.6554_6555AG										Tier 3
		27.27%	chr3	159995257	159995257	C	A	DFTB0	V509F				Y						Tier 4
		9.09%	chr12	59281583	59281583	C	T	LRG3	S360N		rs201662008		Y						Tier 3
		9.09%	chr3	142281353	142281353	C	G	ATR	K297N		rs2229033	0.02	Y	Y	Y				Tier 3
		34.36%	chr22	42524310	42524310	C	A	CYP2D6	A237S		rs28371717	0.01	Y		Y				Tier 3
		9.09%	chr16	57481454	57481454	G	A	CDQ9	A13T				Y						Tier 3
		9.09%	chr16	1502857	1502864	CGG...	TGG...	CLCN7	c.1245_1252CGAGGCCA										Tier 4
		18.18%	chr21	47841933	47841941	TGA...	CGA...	PONT	c.7074_7082CGAGGCTCG										Tier 3
		18.18%	chr19	35524939	35524944	CCA...	ACA...	SCN1B	c.744_749ACAAAC										Tier 3

Showing 1 to 15 of 117 entries (filtered from 1,892 total entries)

Previous

1

2

3

4

5

...

8

Next

Khan Lab Home | Center for Cancer Research | National Cancer Institute

National Institute of Health | U.S. Department of Health & Human Services

Oncogenomics database v3.0 updated Apr 17, 2015

Please contact us for more suggestions or questions.

EGFR mutations

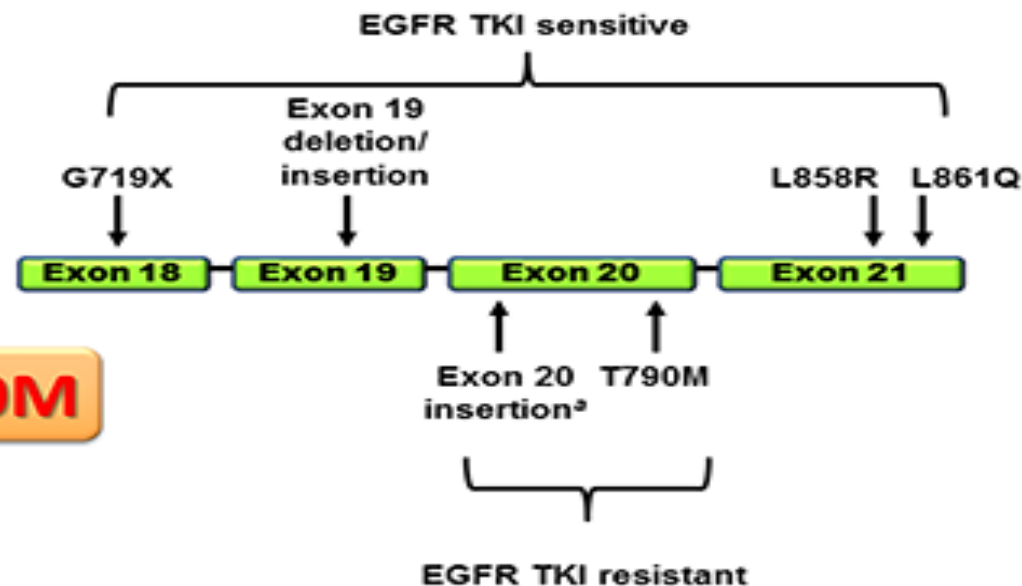
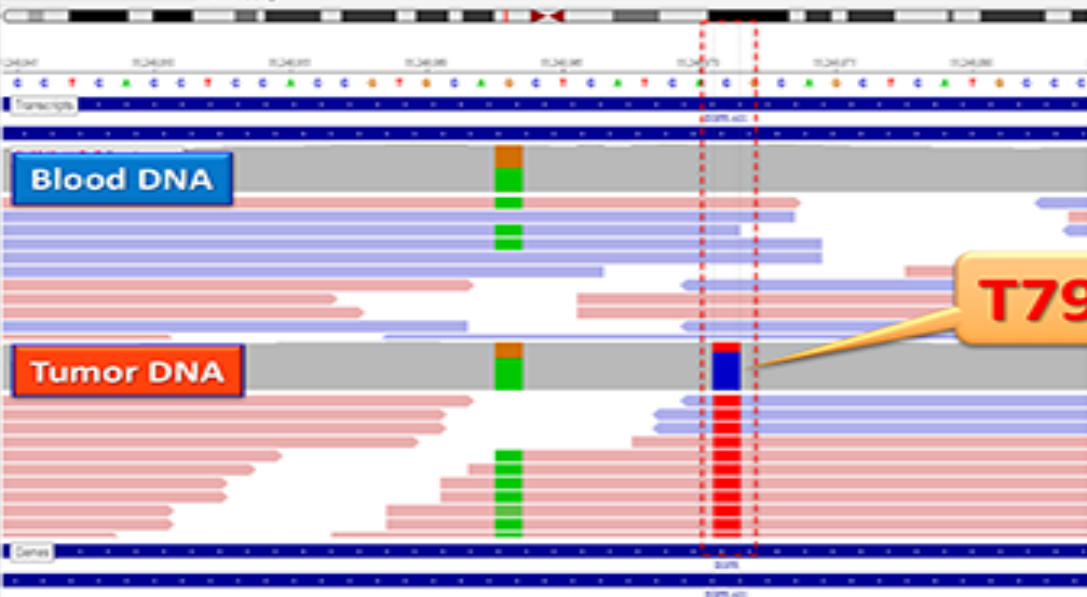
EGFR mutations in NSCLC

GV view of patient: CL0040 case: OM16-007 Total 4 sample(s)

ic: (check sample to load)

CL0040_NrD_E Exome, normal (Exome, normal) CL0040_T1D_E Exome, tumor (Exome, tumor) CL0040_NrD_P Panel, normal (Panel, normal) CL0040_T1D_P Panel, tumor (Panel, tumor)

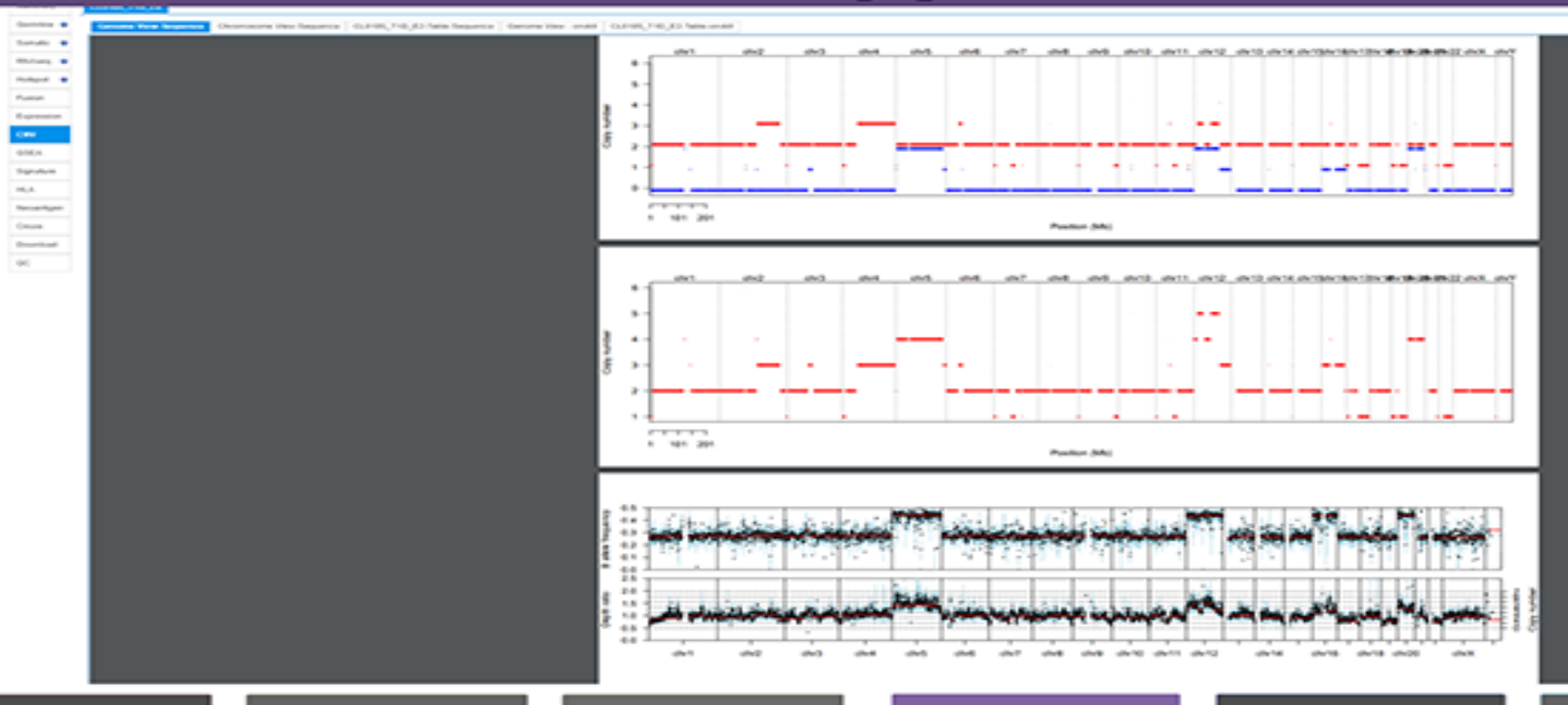
chr7:55,243,244-55,249,267 53 bp



<https://www.mycancergenome.org/content/disease/lung-cancer/egfr/>

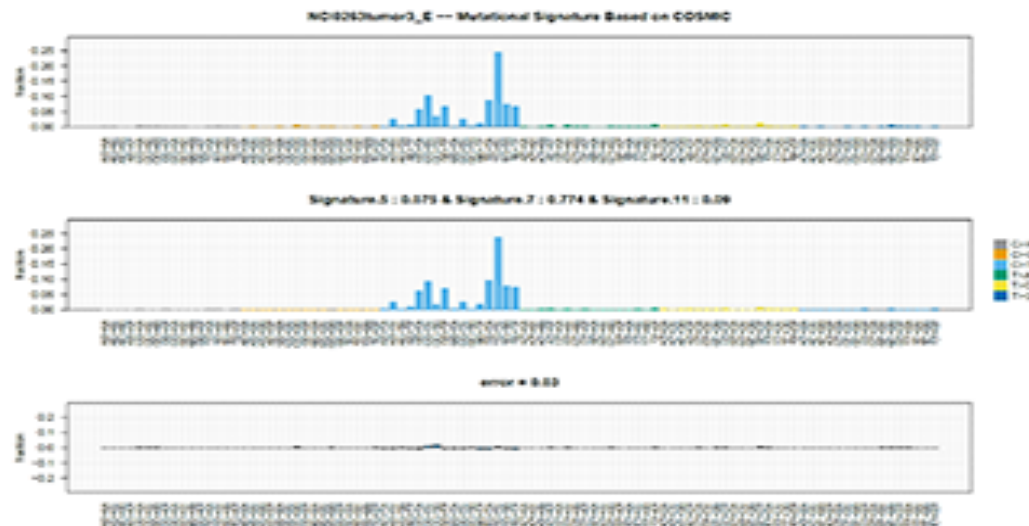
Tumor Copy Number

Tumor Copy Number



Mutation Signatures

Mutation Signatures for Tumor

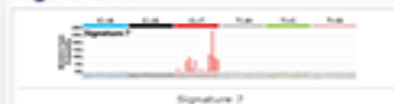


NCI0263: Melanoma



COSMIC (<https://cancer.sanger.ac.uk/cosmic/signatures>)

Signature 7



Cancer types: Signature 7 has been found predominantly in skin cancers and in cancers of the lip categorized as head and neck or oral squamous cancers.

Proposed aetiology: Based on its prevalence in ultraviolet exposed areas and the similarity of the mutational pattern to that observed in experimental systems exposed to ultraviolet light Signature 7 is likely due to ultraviolet light exposure.

Additional mutational features: Signature 7 is associated with large numbers of CC>TT dinucleotide mutations at dipyrimidines. Additionally, Signature 7 exhibits a strong transcriptional strand bias indicating that mutations occur at pyrimidines (via, e.g. formation of pyrimidine-pyrimidine photoproducts) and these mutations are being repaired by transcription-coupled nucleotide excision repair.

Cosmicdb: N/A

Signature 7: UV signature

Mutation Burden

Mutation Burden

The screenshot displays the OncoGenomics National Cancer Institute web application. The navigation bar at the top includes links for Home, Projects, Patients, Cases, Upload, Variants, GenoTyping, Documentation, and About. The search bar shows the following filters: Clinomics, Adrenocortical carcinoma, and CL0185. The 'Mutation_Burden' tab is selected in the left sidebar. The main content area shows a table of results for the 'Burden Per MB' analysis. The table has columns for Diagnosis, Sample Name, Experiment Type, Caller, Burden, Total bases, and Burden Per MB. The 'Burden Per MB' column is highlighted with a red box. The table shows two entries: Adrenocortical carcinoma, CL0185_T1D_E2, Exome, MuTect, 612, 45196537, 13.54 and Adrenocortical carcinoma, CL0185_T1D_PS2, Panel, MuTect, 36, 2465827, 14.6. The 'Burden Per MB' column is highlighted with a red box.

OncoGenomics National Cancer Institute

Home Projects Patients Cases Upload Variants GenoTyping Documentation About

Setting Logout weij

Clinomics, del Rivero / Adrenocortical carcinoma / CL0185

Projects: Clinomics Diagnosis: Adrenocortical carcinoma Patient: CL0185 GO

OM18-113

Summary Somatic-All Somatic-CL0185_T1D_PS2-Panel Somatic-CL0185_T1D_E2-Exome **Mutation_Burden**

Callers: MuTect

Select Columns

Show 15 entries

Search:

Diagnosis	Sample Name	Experiment Type	Caller	Burden	Total bases	Burden Per MB
Adrenocortical carcinoma	CL0185_T1D_E2	Exome	MuTect	612	45196537	13.54
Adrenocortical carcinoma	CL0185_T1D_PS2	Panel	MuTect	36	2465827	14.6

Showing 1 to 2 of 2 entries (filtered from 6 total entries)

Previous 1 Next

Fusion Gene Detection

Fusion Gene Detection from RNA-seq experiments



Useful 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

Conclusions

1. Integrated analysis of the cancer genome identifies biologically relevant diagnostic, prognostic biomarkers and novel targets for therapy
2. Powerful emerging tools of next generation sequencing (including whole genome, exome, and transcriptome) will determine the complete genomic portrait of pediatric cancers at the base pair level
3. This will lead to the identification of key drivers and will enable the development of future novel therapies and precision therapy

Acknowledgements

Acknowledgements

Oncogenomics Section

Javed Khan

Biologists

- Young Song
- Jack Shern
- Hongling Liao
- Dominik Bogen*
- Samuel Li*
- Susan Yeh*
- Catherine Tolman*
- Adam Cheuk*
- Laura Hurd*

Bioinformatics

- Rajesh Patidar
- Li Chen*
- Shile Zhang*
- Xinyu Wen
- Sivasish Sindiri
- Jianbin He*
- Jimmy Lin*
- Jianjun Wang*
- Qingrong Chen*
- Peter Johansson*
- Andy Brohl*

NHLBI

- James Taylor VI
- Krupa Desai
- Kushal Shah

Cell Growth Regulation Section

National Institute of Dental and
Craniofacial Research

- Silvio Gutkind,
- Jose Vaque (Chepe)

Laboratory of Molecular Pharmacology, CCR, NCI

- Jean-Claude Marshall
- Patricia Steeg

Cancer Modeling Section, Lanoratory of Molecular Pharmacology, CCR, NCI

- Yanlin Yu
- Glen Melino