

Genomics

Apply Genomics to Precision Medicine

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

TRACO
October 19, 2020

Outline

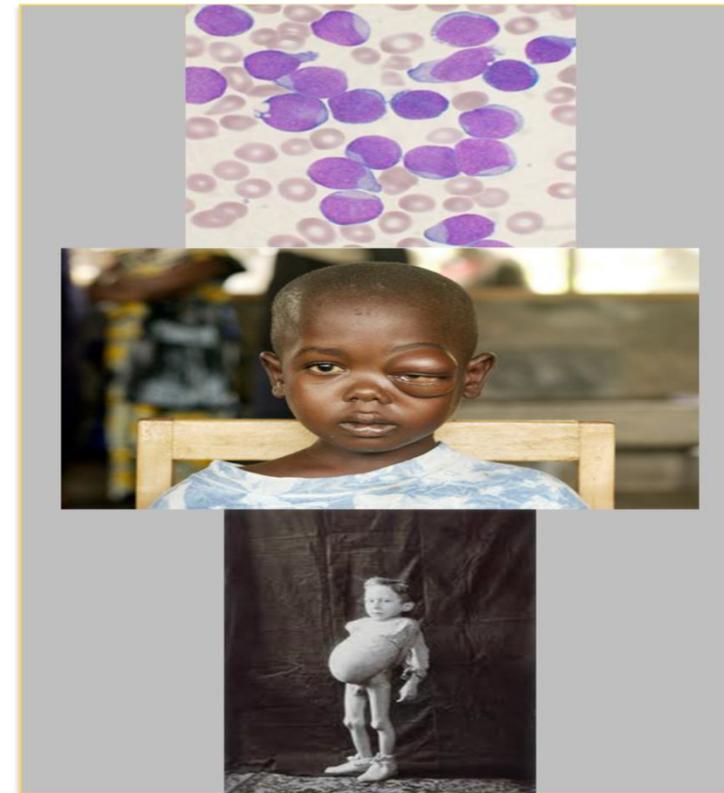
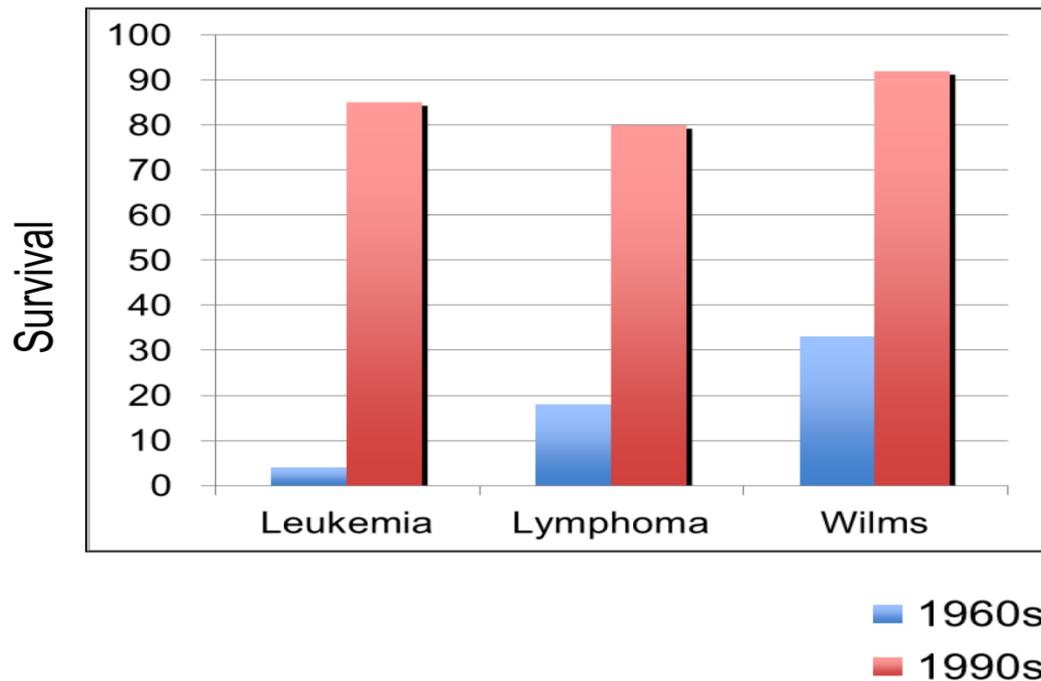
Outline

- **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

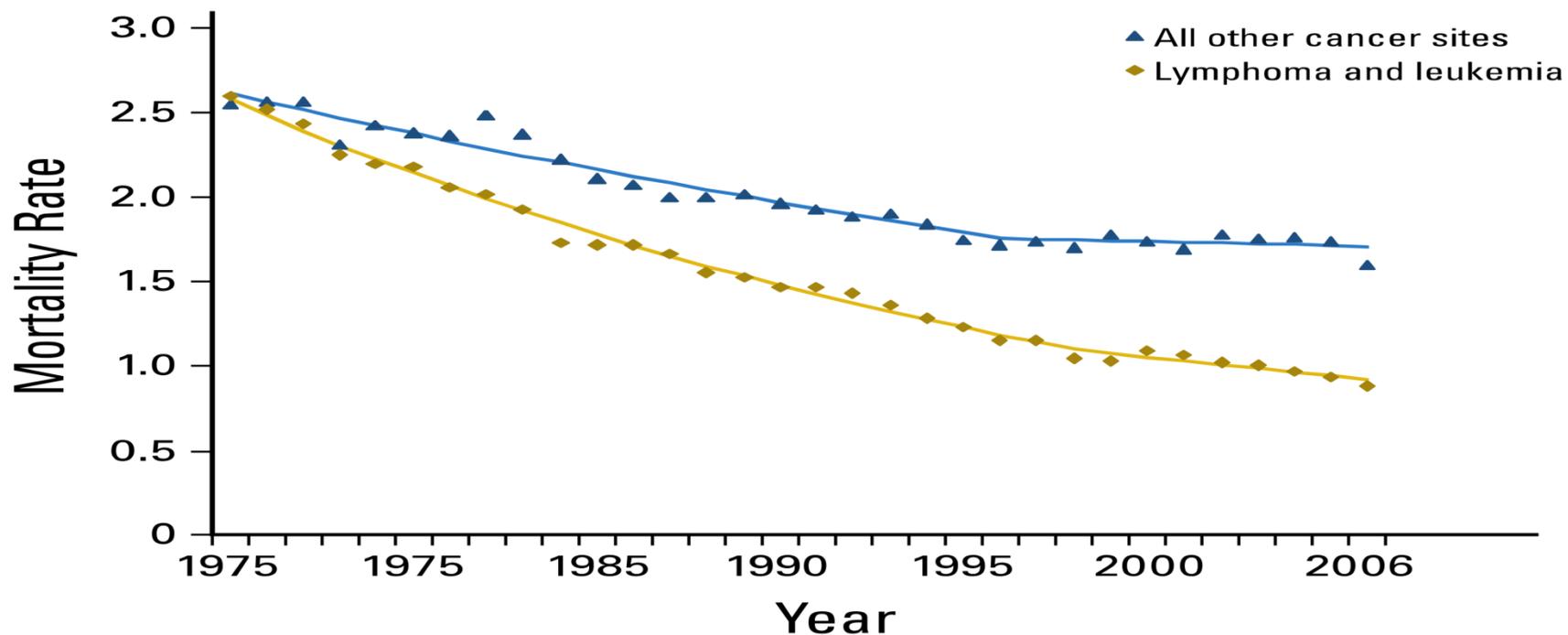


Courtesy: John Maris

Mortality rates

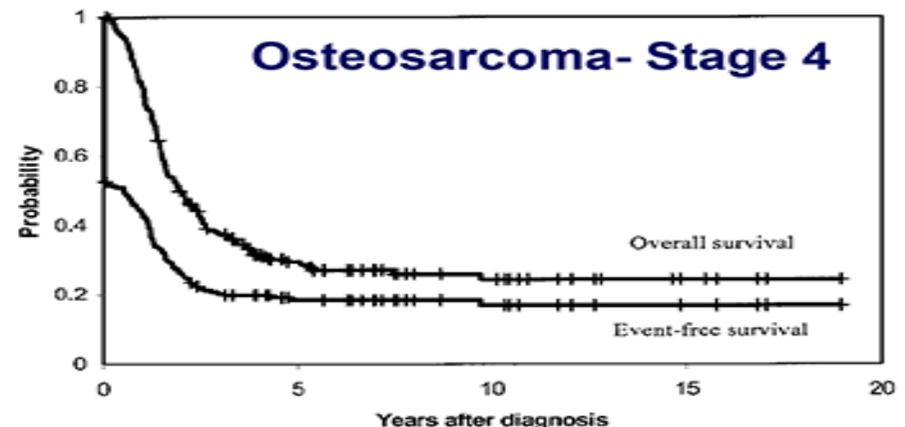
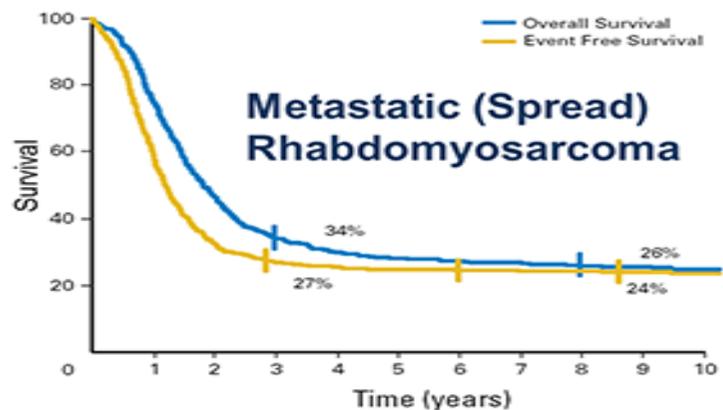
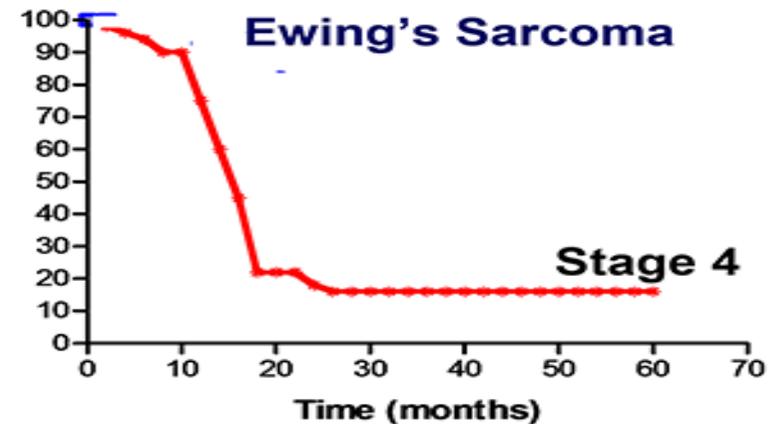
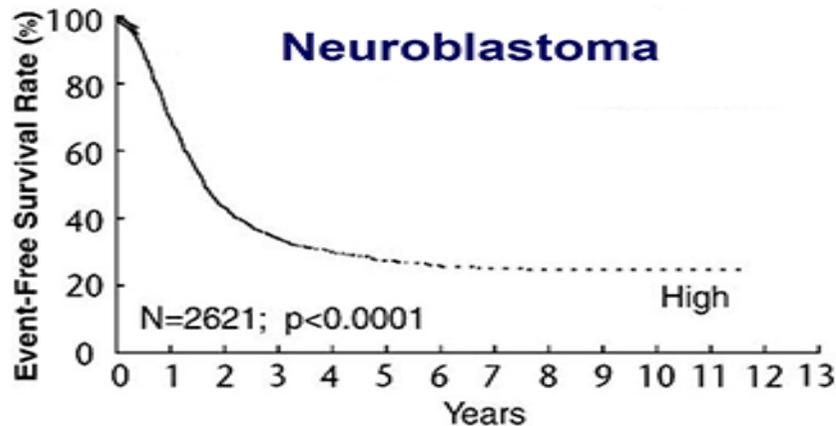
National Cancer Institute

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



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

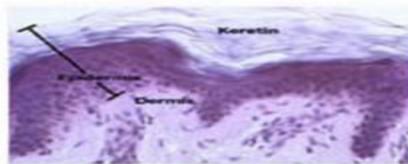


Gene expression

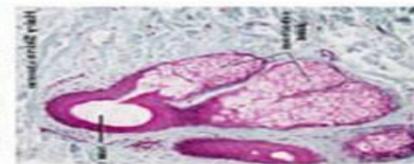
...but the complexity and diversity

Same genome or DNA →

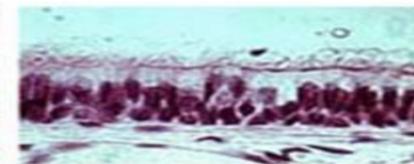
- Different expression pattern
- Different proteome
- Different tissues
- Different physiology



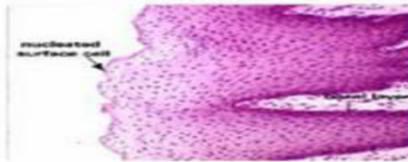
skin



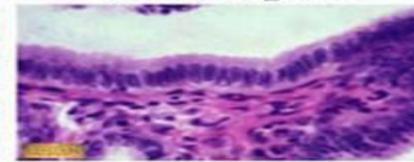
sebaceous gland



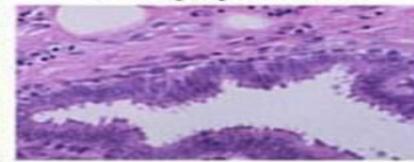
airway epithelium



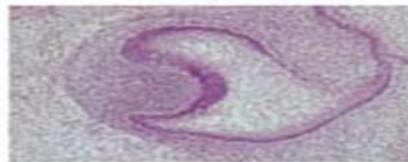
tongue



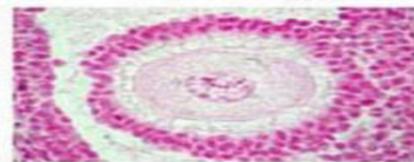
intestinal crypt



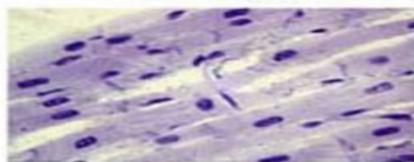
mammary gland



developing tooth



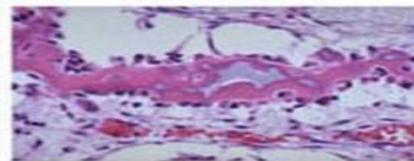
follicle



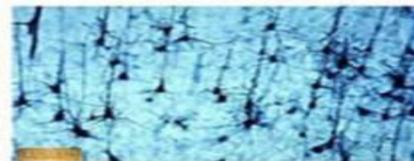
skeletal muscle



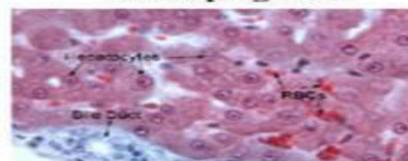
developing bone



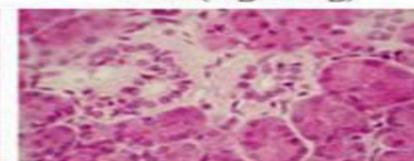
bone (high mag)



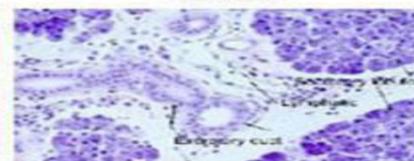
neuron



liver



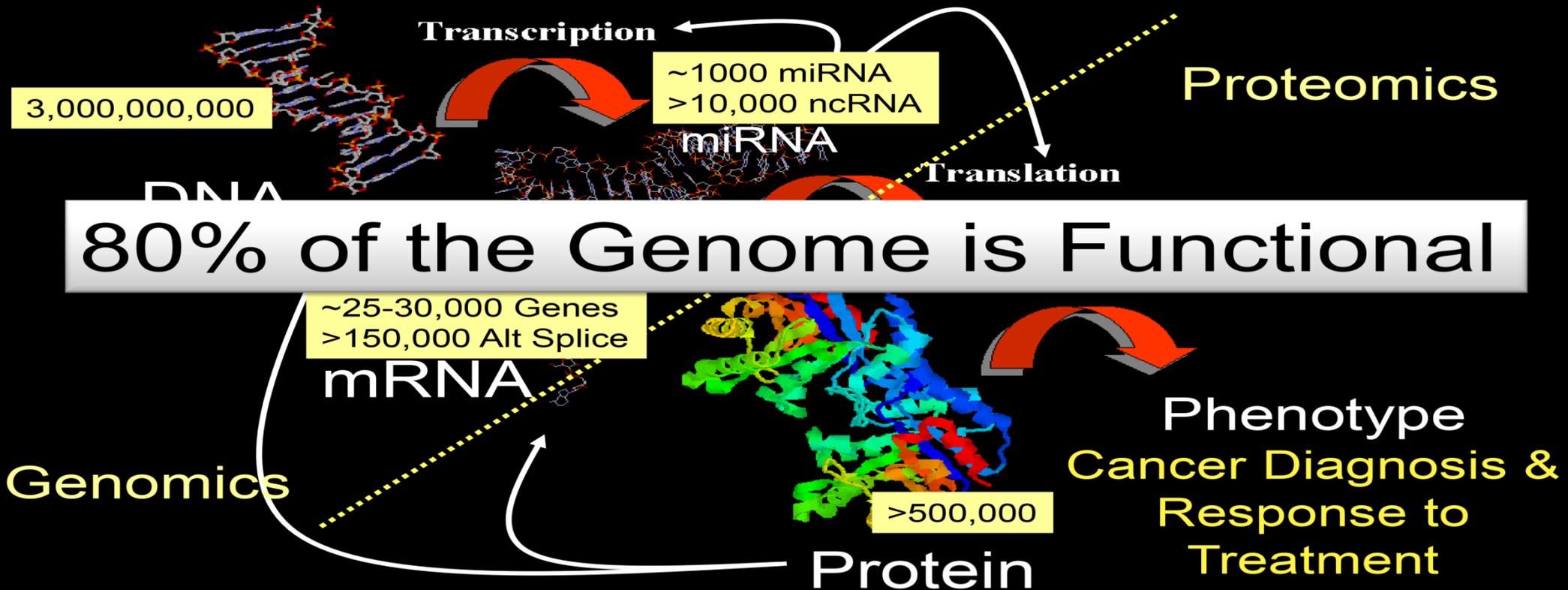
pancreas



parathyroid gland

Gene expression

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

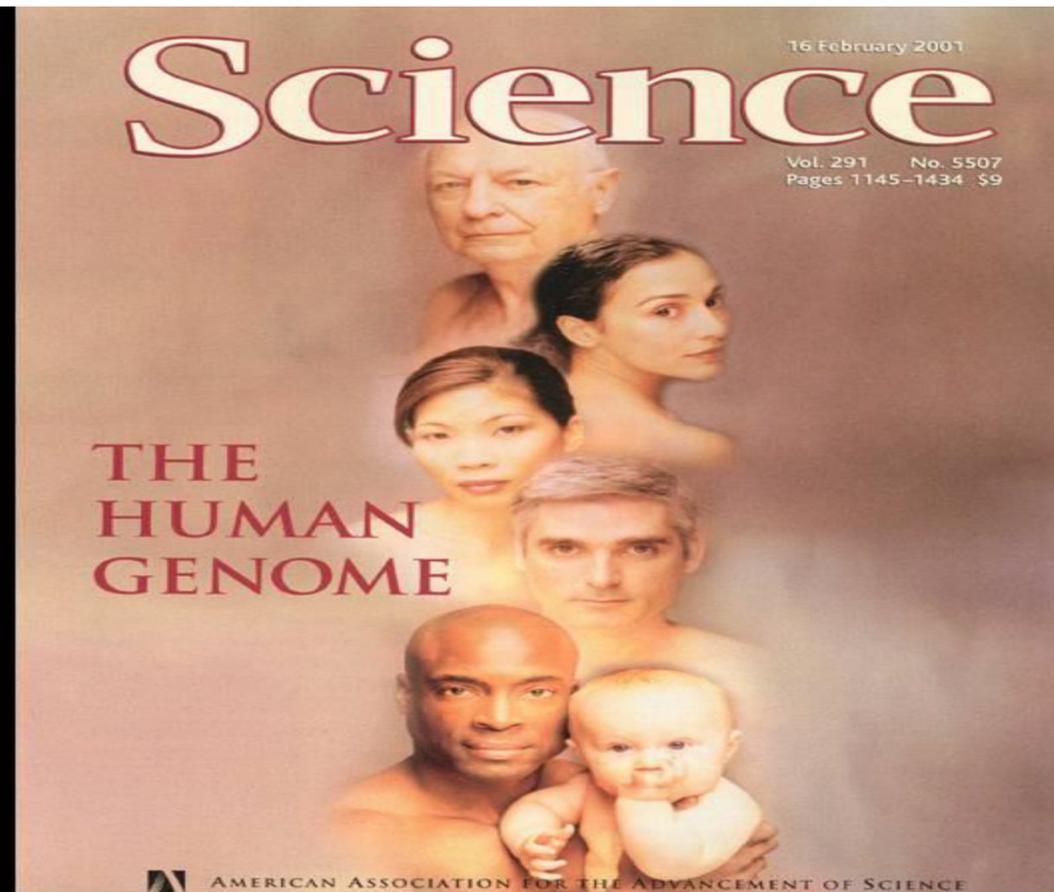


Gene measurement

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

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

Human genome



First generation tools

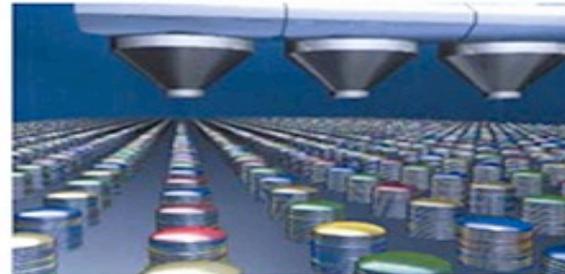
1st generation genomic tool: microarrays

Printing microarrays

Mechanical

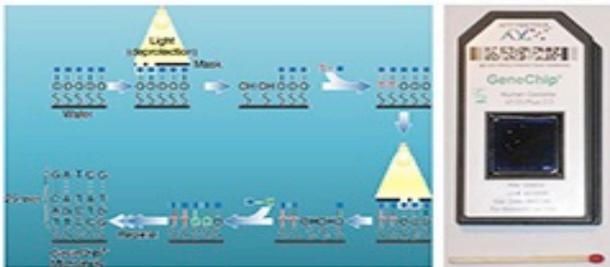


Electronic Piezo

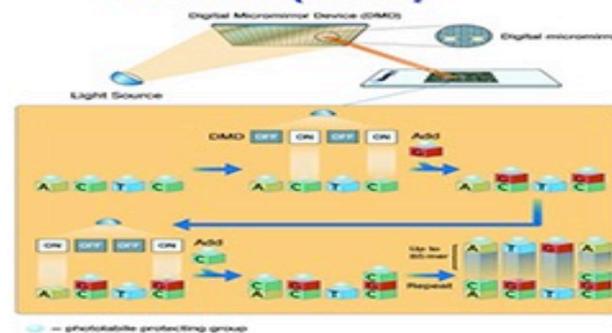


In-situ synthesis microarrays

Lithographic masks
and de-protection
through illumination

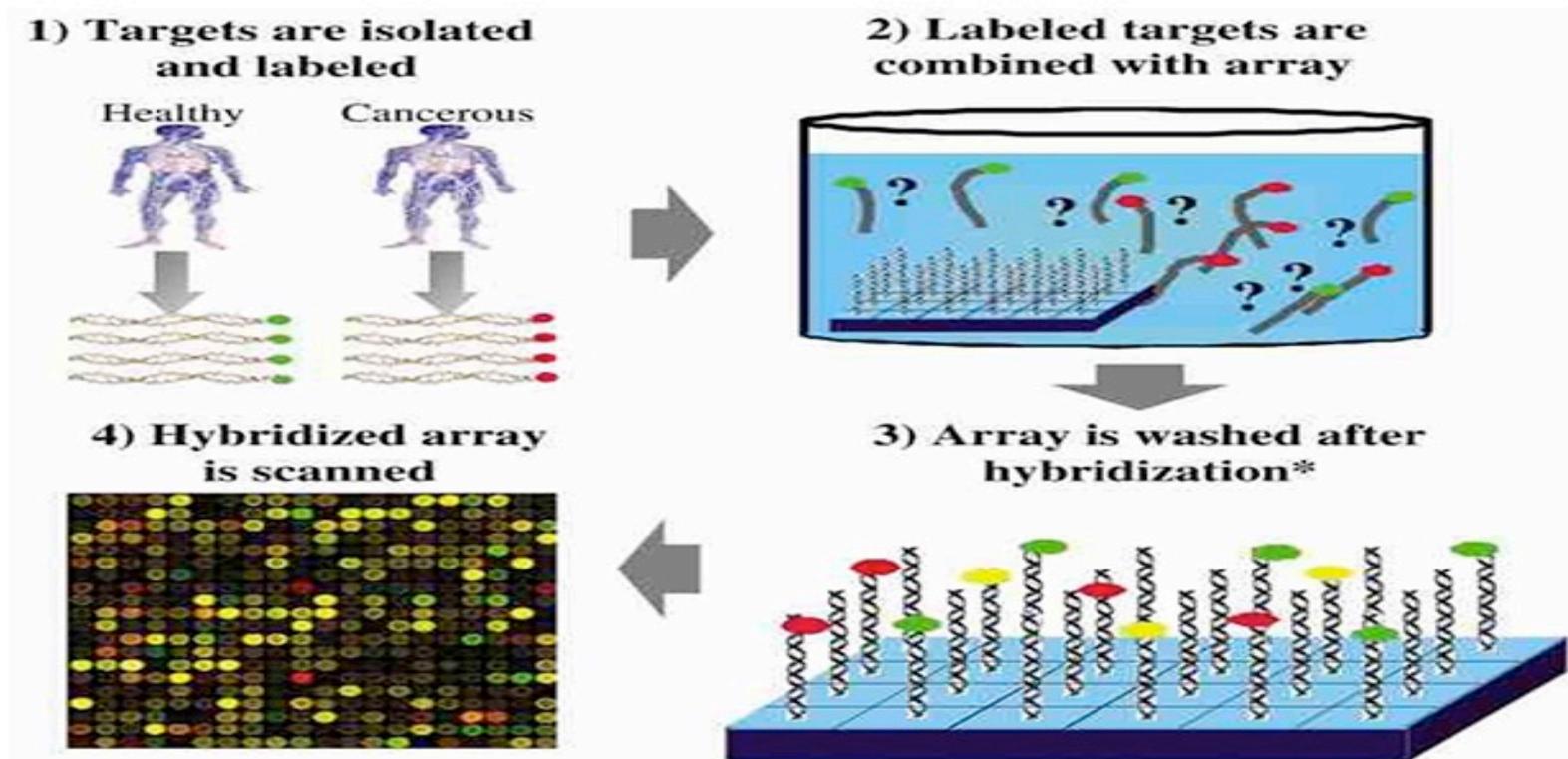


Digital micromirror
device (DMD)



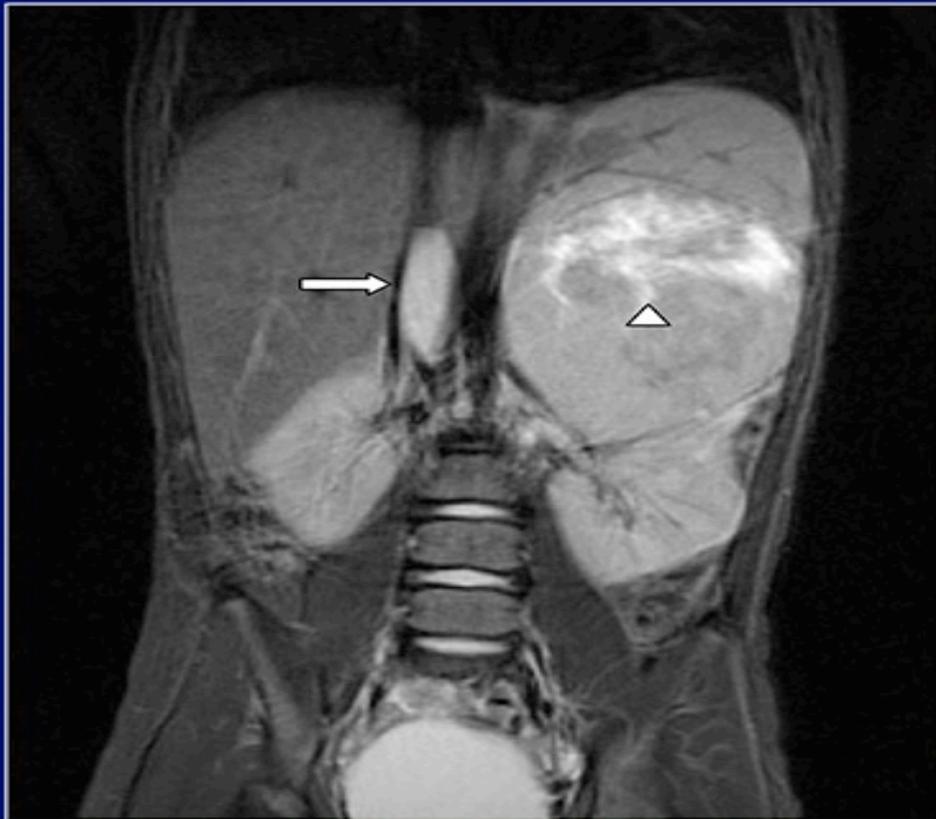
Microarrays

Microarrays – technologies of hybridization



Wilms tumor

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

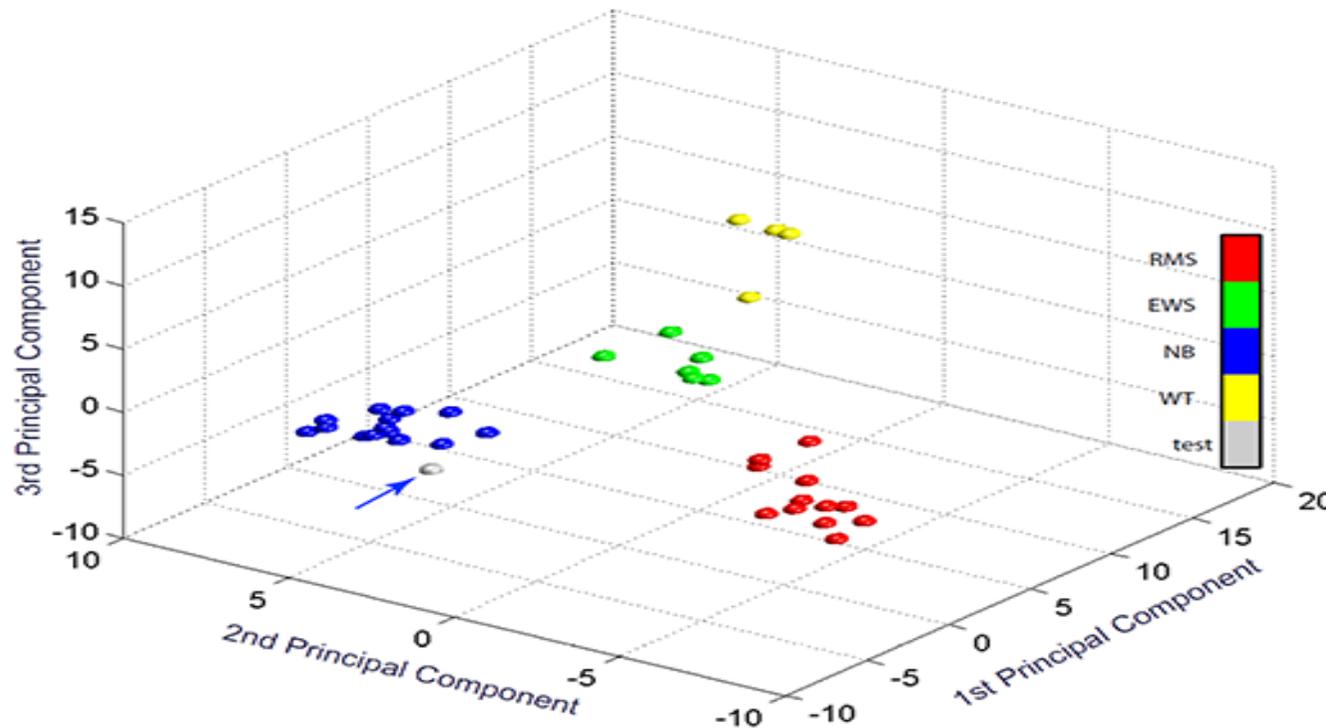


Initial diagnosis: Wilm's tumor



Cancer diagnosis

Diagnosis of cancers using gene expression profiles



Wilm's tumor

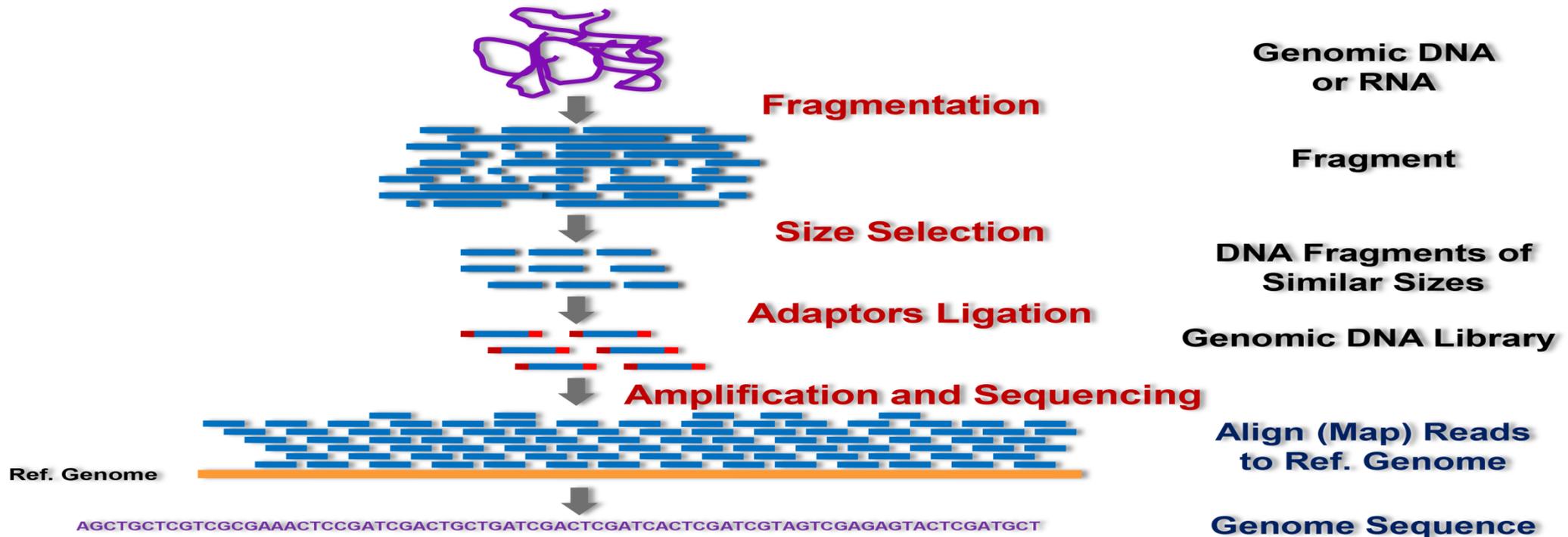


Neuroblastoma

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

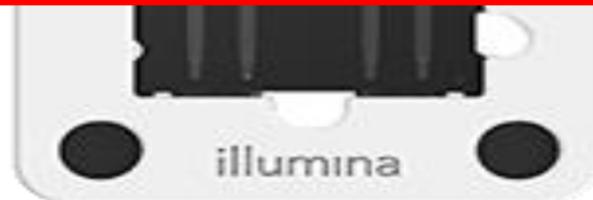
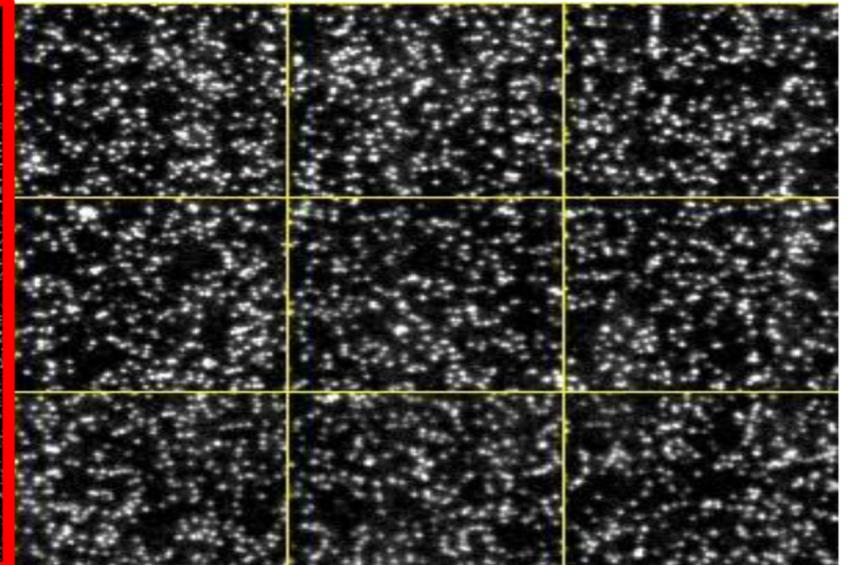
Next-generation sequencing

Next-Generation Sequencing



Massively Parallel Sequencing

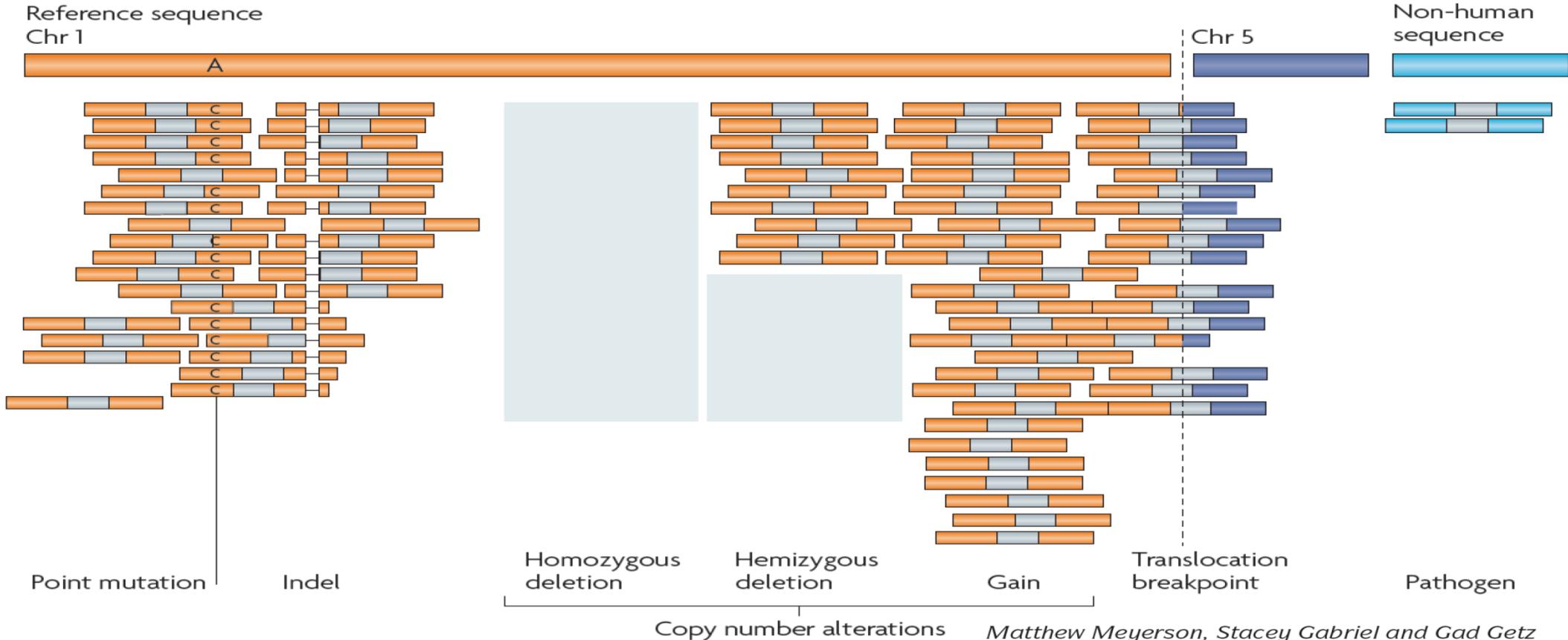
Massively Parallel Sequencing



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

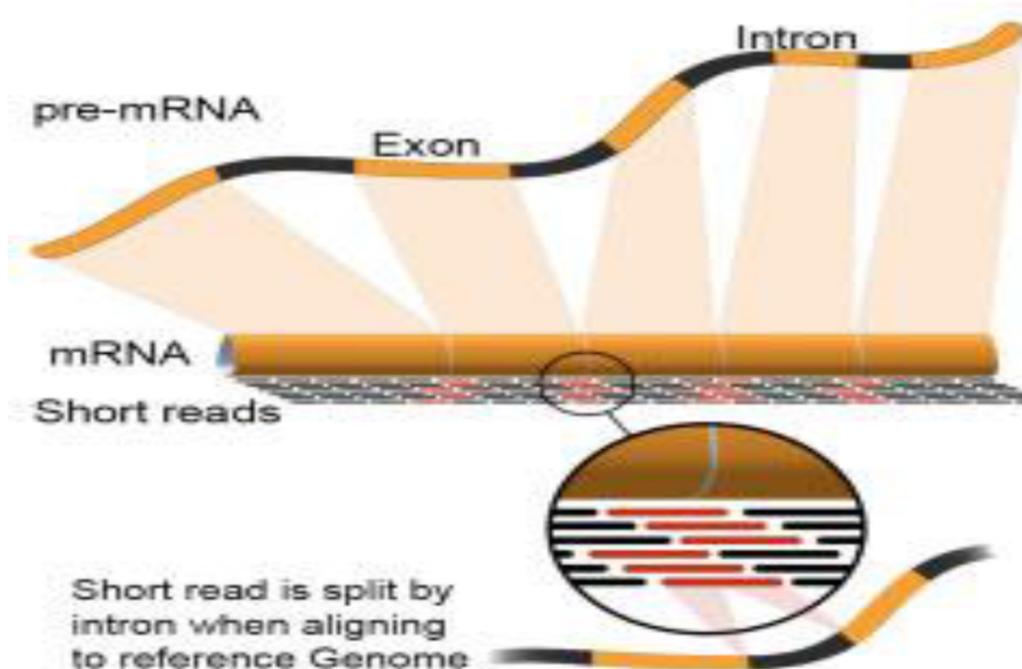
Genomic Alterations

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

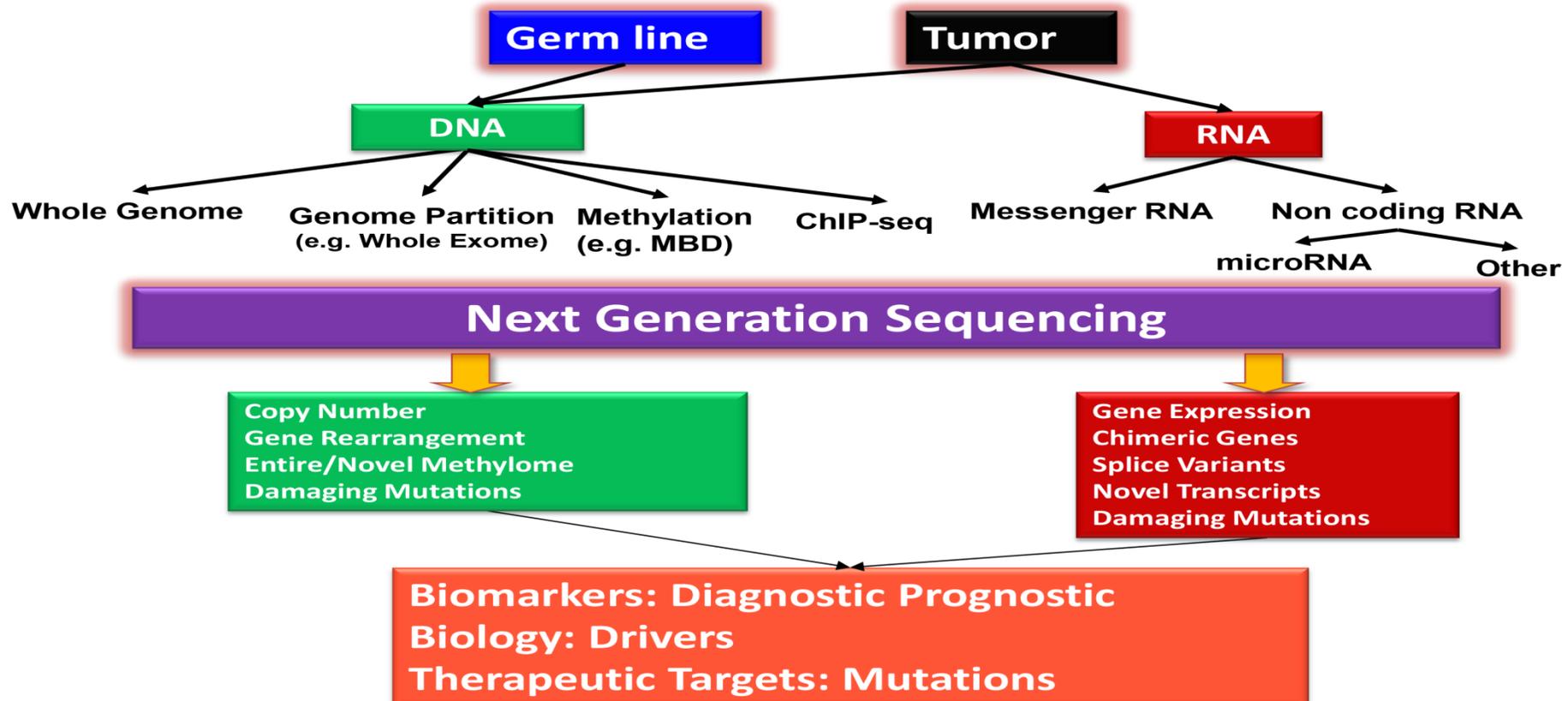
Properties

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

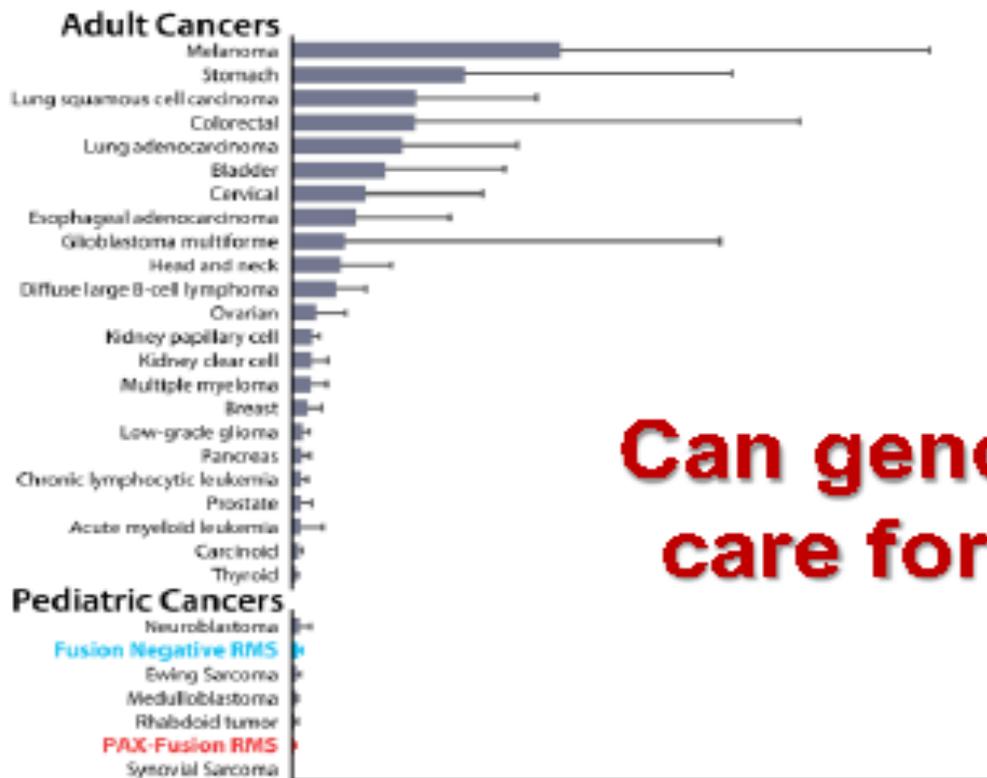
Cancer Genomes

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



Can genomics help clinical care for cancer patients?

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

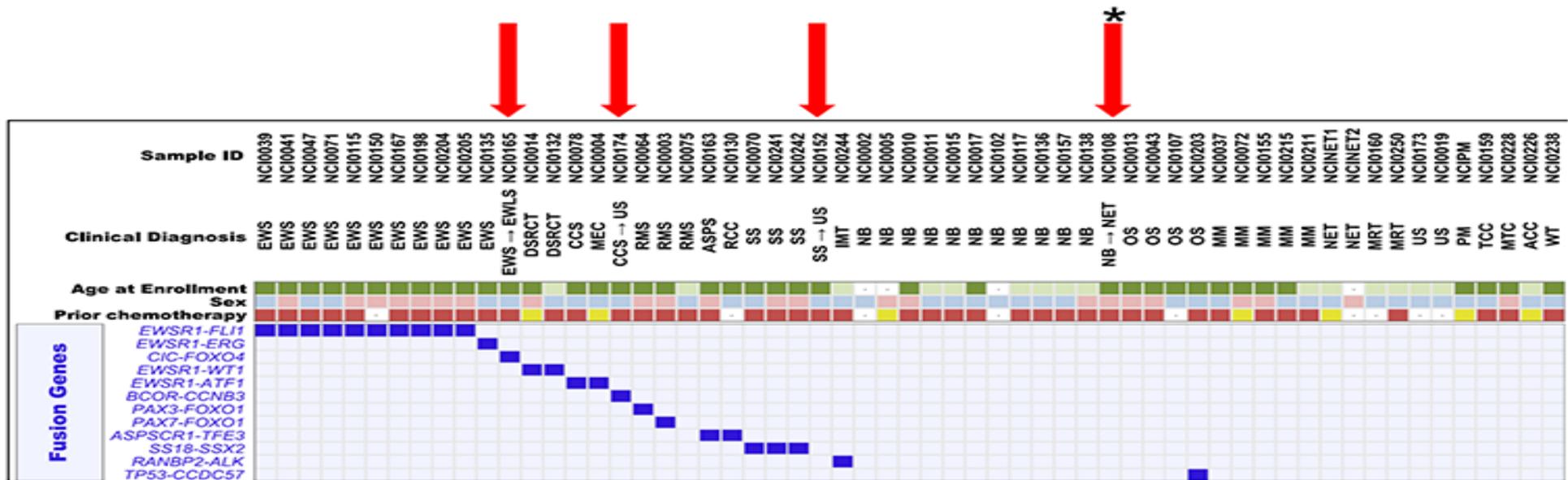
Mutations

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

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	Tamoxifen, 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	-

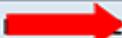
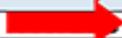
Sample	Diagnosis	Gene	Stage	Modality	AA Change	Level	Drug	Clinical Trial: Pediatric	FDA Approval in Adults	Exact Mutation vs. Hotspot
NCI0011	NB	MYCN	Relapsed	SNP Array/WTS	Amplification	3	bromodomain inhibitors	No	No	-
NCI0102	NB	MYCN	-	SNP Array/WTS	Amplification	3	bromodomain inhibitors	No	No	-
NCI0136	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 (<i>in vivo</i> and <i>in vitro</i> models) that provide biological evidence sufficient to support the use of a variant for treatment selection, e.g. <ul style="list-style-type: none"> 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

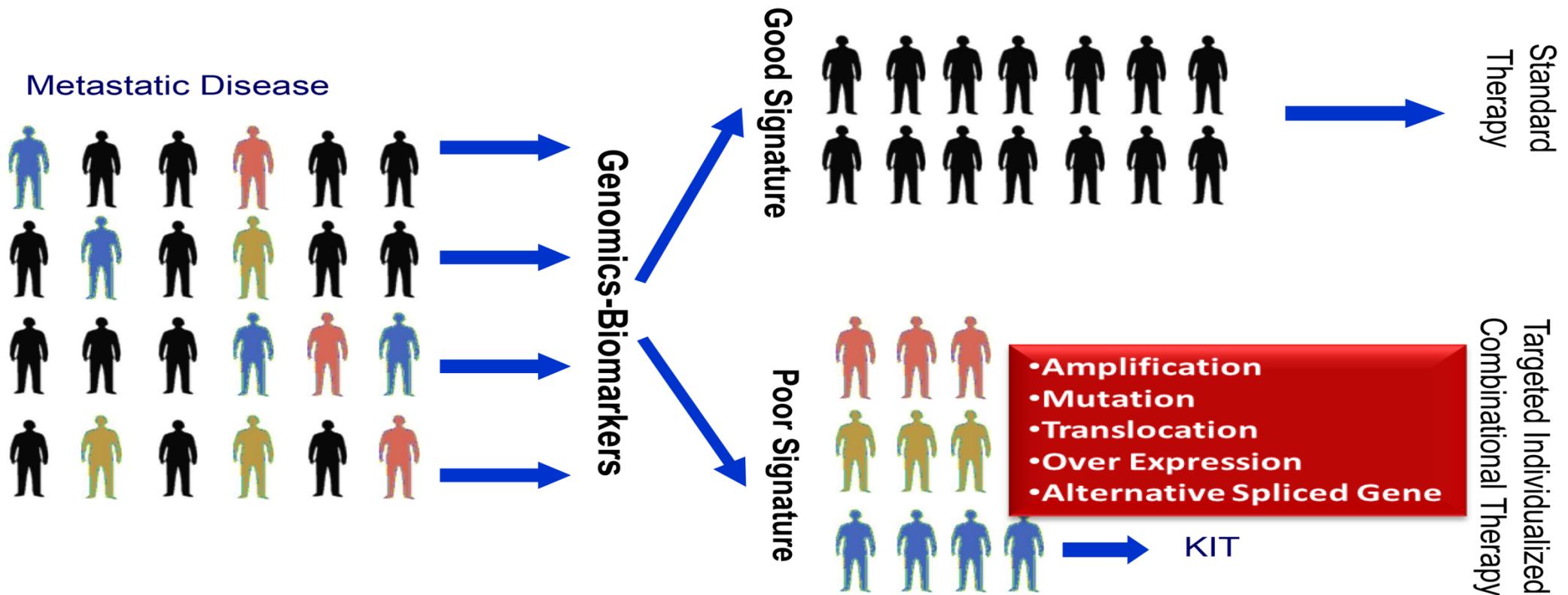
Summary

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

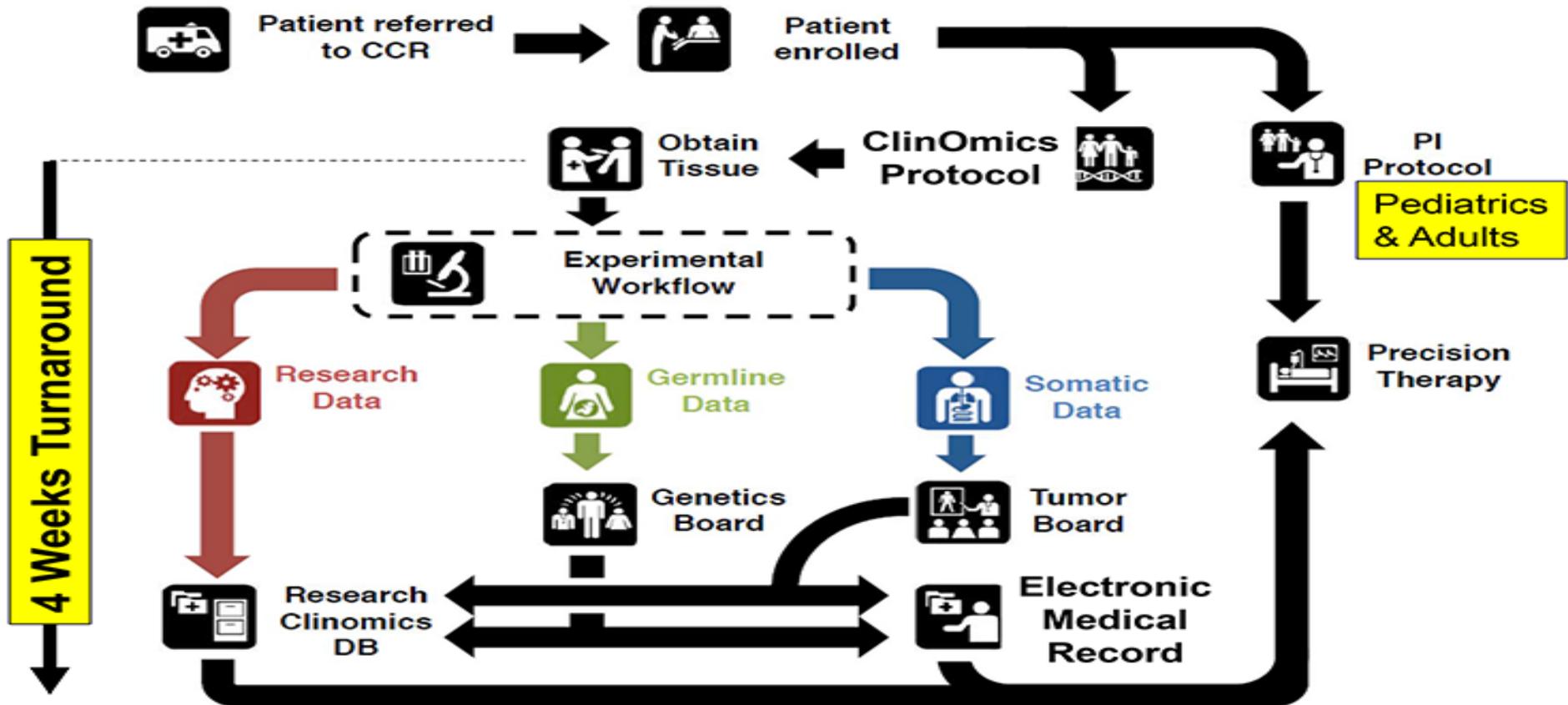
Future Trials

Genomics Enabling Precision Therapy-The Future for Pediatric Trials



ClinOmics program

CCR ClinOmics Program-CLIA



Sequencing equipment

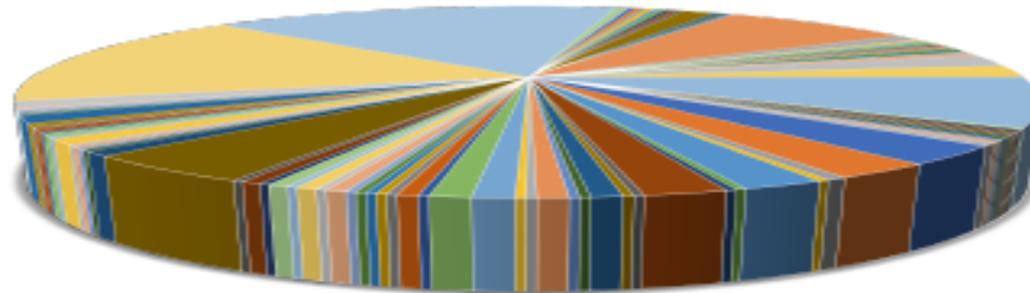
Sequencing Equipment



- 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

396 Patients of 93 diagnoses



ALLAC

- ☐ Anaplastic Astrocytoma
- ☐ Anaplastic Pilo
- ☐ Bladder cancer
- ☐ Cholangiocarcinoma
- ☐ Dermatofibrosarcoma protuberans
- ☐ Diffuse Intrinsic pontine glioma
- ☐ Ependymoma
- ☐ Glioblastoma
- ☐ Grade II Oligodendroglioma
- ☐ Grade II Oligodendroglioma
- ☐ Invasive well differentiated squamous cell carcinoma
- ☐ Lymphocytosis
- ☐ Melanoma
- ☐ Mesothelioma Pleural
- ☐ Metastatic Pancreatic Neuroendocrine Carcinoma
- ☐ Multiple Rata Tumors
- ☐ Neurofibromatosis I
- ☐ Osteosarcoma
- ☐ Papillary tumor of the pineal region
- ☐ Poorly differentiated carcinoma (lung vs. thyroid)
- ☐ Renal cell carcinoma
- ☐ Small Cell Cancer of rectum
- ☐ Temporal high grade glioma
- ☐ Uveal melanoma

- ☐ Acute lymphoblastic leukemia
- ☐ Anaplastic Ependymoma
- ☐ Anaplastic Fibrous Histiocytoma
- ☐ Breast cancer
- ☐ Chorionoma
- ☐ Desmoid Fibrosarcoma
- ☐ Endometrial cancer
- ☐ Ewing's sarcoma
- ☐ Glioblastoma
- ☐ Hepatic Angiosarcoma
- ☐ Keratoacanthoma
- ☐ Mastocytosis
- ☐ Merkel Cell-Carcinoma
- ☐ Mesothelioma Testis Vaginalis
- ☐ MPNST
- ☐ Myxopapillary Ependymoma
- ☐ Nasopharyngeal tumor
- ☐ Ovarian Serous Carcinoma
- ☐ Pleomorphic Astrocytoma
- ☐ Prostate cancer
- ☐ Pseudopapilloma
- ☐ Small Cell Carcinoma of the ovary hypercalcemic type (SCCHT)
- ☐ Teratoma

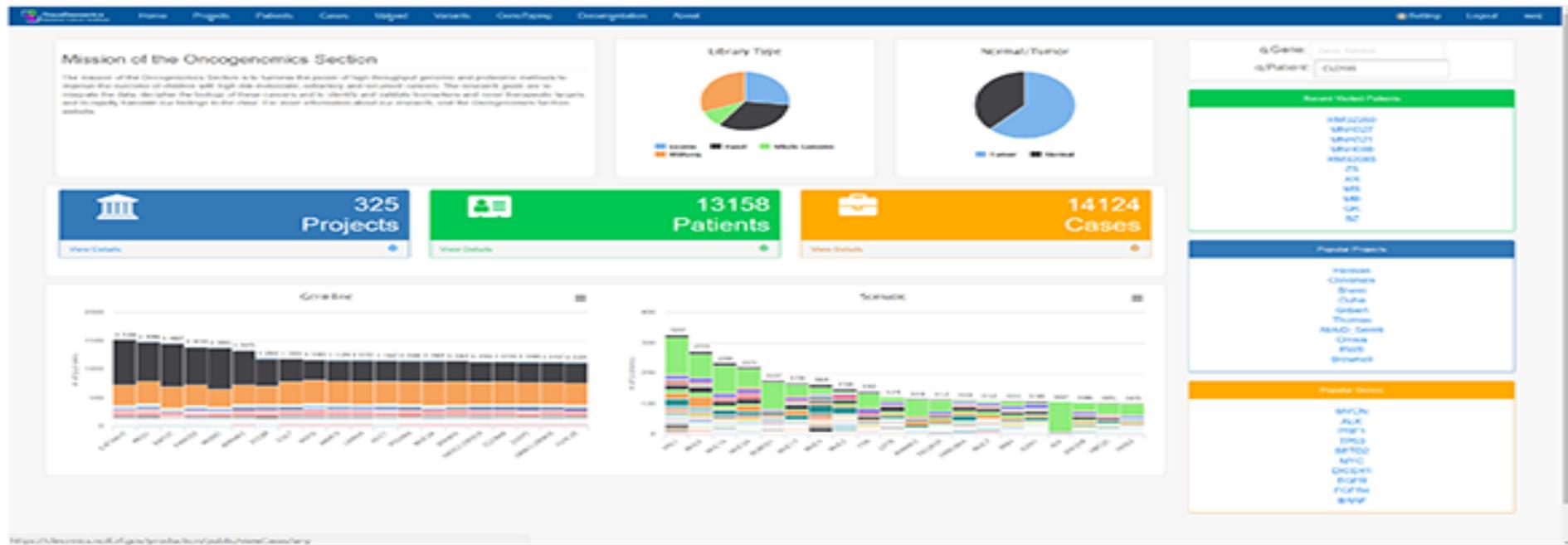
- ☐ Acute myeloid leukemia
- ☐ Anaplastic meningioma
- ☐ Astrocytoma
- ☐ Carcinoid, BRCA1 positive
- ☐ Clear cell sarcoma
- ☐ Desmoplastic small round cell tumor
- ☐ Endometrial Stromal Sarcoma
- ☐ Extracranial Small Cell Cancer
- ☐ Glioma
- ☐ Hepatocellular cancer
- ☐ Left Convoluted Sarcoma
- ☐ Medullary Thyroid Cancer metastatic
- ☐ Mesothelioma
- ☐ Metastatic Anal Carcinoma
- ☐ Multicentric and Vascularizing Neuroend Tumor
- ☐ Neuroendocrine carcinoma
- ☐ Pleomorphic Tumor of giant cell tumor
- ☐ Ovarian Teratoma
- ☐ Pleomorphic Xanthoastrocytoma
- ☐ Recurrent glioblastoma tumor
- ☐ SCLC
- ☐ Small cell endometrium
- ☐ Thyroid

- ☐ Ampullary cancer
- ☐ Anaplastic Oligodendroglioma
- ☐ Atypical Central Neurocytoma
- ☐ Carcinoma of the Pelves
- ☐ Colon cancer
- ☐ Diffuse Astrocytoma, Grade II
- ☐ Esophageal
- ☐ Gallbladder cancer
- ☐ Gliosarcoma
- ☐ Hepatocellular carcinoma
- ☐ Lung Adenocarcinoma
- ☐ Medulloblastoma
- ☐ Mesothelioma Peritoneal
- ☐ Metastatic NET
- ☐ Multiple carcinoma
- ☐ Neuroendocrine Tumor
- ☐ NSCLC
- ☐ Pancreatic cancer
- ☐ Pleomorphic xanthoastrocytoma
- ☐ Recurrent Medulloblastoma
- ☐ Small cell bladder
- ☐ Synovial sarcoma
- ☐ Undifferentiated sarcoma

ClinOmics Data Portal

ClinOmics Data Portal

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



Patient Summary

Patient Summary Page

OncoGenomics National Cancer Institute

Home Projects Patients Cases Upload Variants GenoTyping Documentation About

Settings Logout

Chronix / de Rivers / Adrenocortical carcinoma / CL0185

Projects: Chronix | Diagnosis: Adrenocortical carcinoma | Patient: CL0185

QMIS-113

Summary

Libraries: pipeline version v3.0

Case 20180625 has 1 sample

SHOW (1) ENTRIES SEARCH

Sample Name	DNA/RNA	Experiment Type	Library Type	Tissue Category	Lib prep Batch Date	GPCR Date	Run Start Date	Run Finish Date	FFPE or Fresh Frozen	Matched normal	Matched RNA-seq ID
CL0185_N1D_E	DNA	Exome	dn.ex.v1	normal	6/18/2018	6/22/2018	6/22/2018	6/23/2018			
CL0185_N1D_PS	DNA	Panel	dn.sn.v2	normal	6/18/2018	6/22/2018	6/22/2018	6/23/2018			
CL0185_T1D_E2	DNA	Exome	dn.ex.v1	tumor	6/18/2018	6/27/2018	6/27/2018	6/28/2018	FFPE	CL0185_N1D_E	CL0185_T1R_T
CL0185_T1D_PS2	DNA	Panel	dn.sn.v2	tumor	6/18/2018	6/27/2018	6/27/2018	6/28/2018	FFPE	CL0185_N1D_PS	CL0185_T1R_T
CL0185_T1R_T	RNA	RNAseq	rnaseq	tumor	7/5/2018	7/5/2018	7/9/2018	7/10/2018	FFPE	CL0185_N1D_E	

Showing 1 of 1 FFPE entries

Previous 1 Next

Coverage

20180625 Target Region Coverage

Variants

20180625 variant summary

QC report

QC Report: Sequencing Statistics & Genotyping

Run Statistics

Summary | **Clones** | Coverage | Transcript Coverage | Hotspot | Contours | Compare | **DNA QC** | RNA QC | RNA QC v2 | FASTQC | Genotyping | Versions

Genome Somatic RNAseq Hotspot Fusion Expression CNV GSEA Signature

SHOW 15 entries

Sample_ID	MEAN BAIT COVERAGE	MEAN TARGET COVERAGE	Total reads	Mapped reads	Percent mapped	On-target reads	Percent on-target	Unique on-target reads	Percent unique on-target	Hq unique on-target reads	Percent Hq unique on-target	Percent Hq unique positions at 20x	Percent Hq unique positions at 30x	Percent Hq unique positions at 50x	Percent Hq unique positions at 100x	Percent Hq unique positions at 200x	Percent Hq unique positions at 400x
CL0185_N1D_E_H2WNCBGGK7	190	210	250665548	257514346	98.55	108950930	95.06	137432906	88.81	132067057	88.95	96.41	85.53	92.74	79.74	43.42	5.53
CL0185_N1D_PS_H2WNCBGGK7	888	781	81889380	81218679	98.80	41885021	98.43	26281444	82.88	25877230	87.81	88.38	88.30	88.19	87.75	88.80	88.75
CL0185_T1D_E2_HLJY08GGK7	170	182	230619044	237366954	98.48	153908821	64.87	124328705	86.74	120344271	86.72	96.08	84.78	90.70	74.07	35.34	3.91
CL0185_T1D_PS2_HLJY08GGK7	876	833	98828876	80183182	98.88	31227008	87.84	21781308	83.88	21288182	87.78	88.33	88.25	88.04	88.88	81.71	72.70

Showing 1 to 4 of 4 entries Previous 1 Next

QC threshold

Genotyping

Summary | **Clones** | Coverage | Transcript Coverage | Hotspot | Contours | Compare | **DNA QC** | RNA QC | RNA QC v2 | FASTQC | **Genotyping** | Versions

Genome Somatic RNAseq Hotspot Fusion Expression CNV GSEA Signature

Comment...

Pass Fail

History

SHOW 15 entries

Sample	CL0185_N1D_E	CL0185_N1D_PS	CL0185_T1D_E2	CL0185_T1D_PS2	CL0185_T1N_T
CL0185_N1D_E	100%	100%	100%	98%	88%
CL0185_N1D_PS	100%	100%	100%	98%	88%
CL0185_T1D_E2	100%	100%	100%	98%	88%

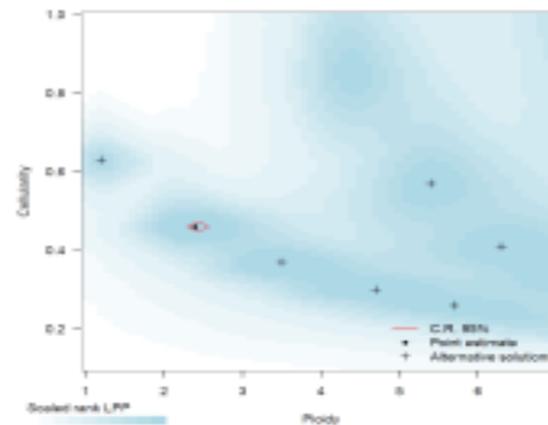
QC Report: Coverage

QC Report: Coverage

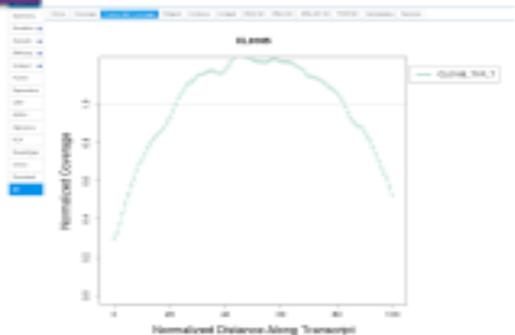
Circos



Tumor Content



RNA Coverage



Hotspot Coverage



Germline and somatic mutations

Germline and Somatic Mutations

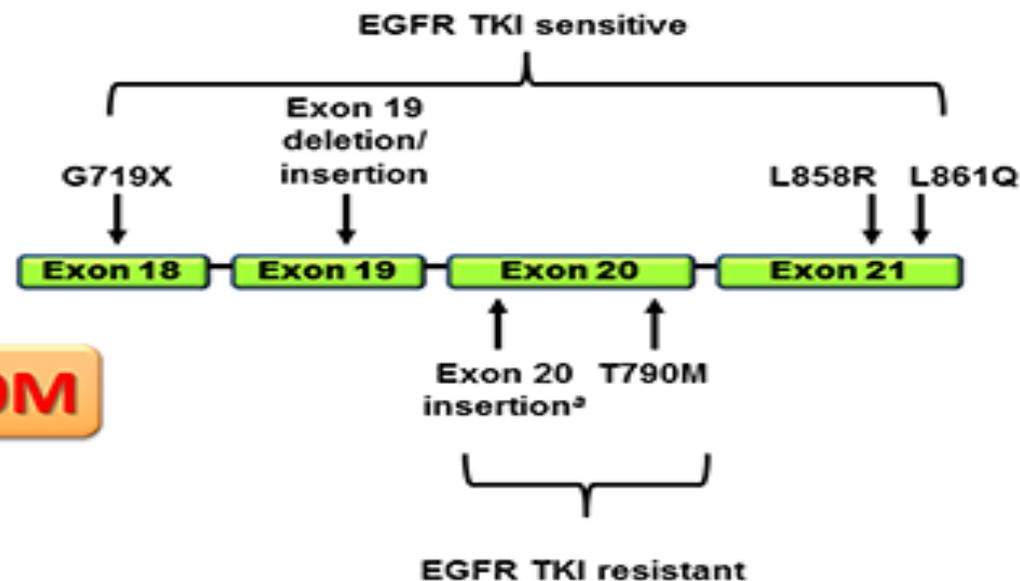
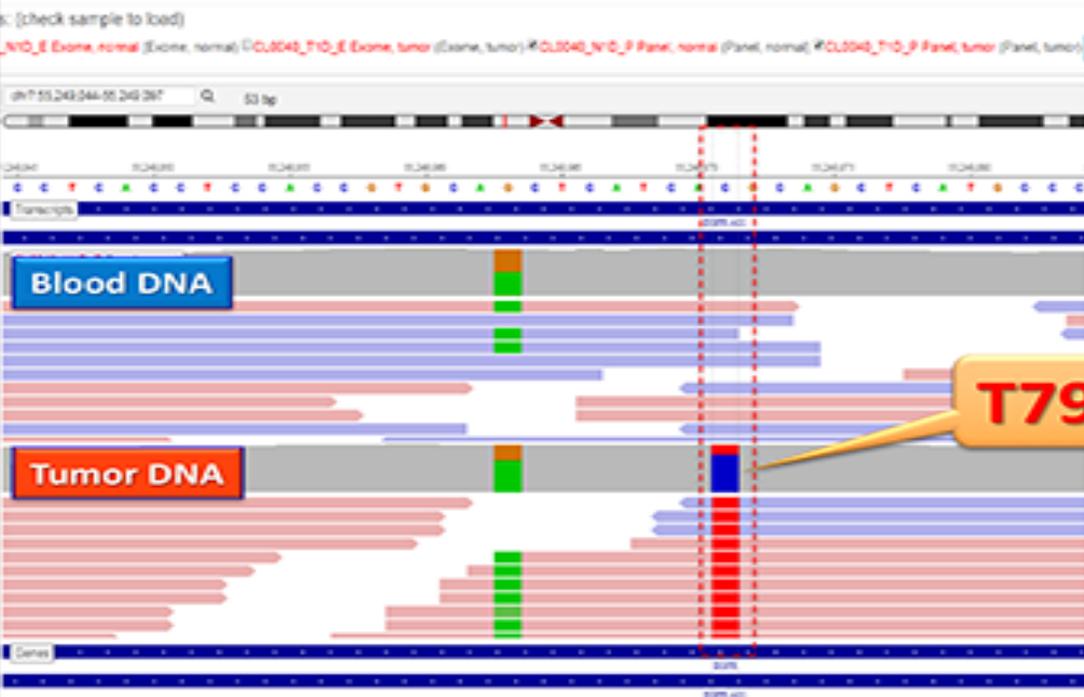
The screenshot displays a web-based genomic variant analysis interface. The main content is a table of variants. The table has the following columns: Flag, chr, pos, alt, ref, start, end, ref, alt, gene, alt_change, alt, protein, clinical, cancer, icd10, reported, alt_pos, category, alt, and somatic. The table lists various mutations across different chromosomes (chr1-22, X, Y) and genes (e.g., NR2A1, MTRR, PNH3, CH24, SPT1, SPT2, SPT3, SPT4, SPT5, SPT6, SPT7, SPT8, SPT9, SPT10, SPT11, SPT12, SPT13, SPT14, SPT15, SPT16, SPT17, SPT18, SPT19, SPT20, SPT21, SPT22, SPT23, SPT24, SPT25, SPT26, SPT27, SPT28, SPT29, SPT30, SPT31, SPT32, SPT33, SPT34, SPT35, SPT36, SPT37, SPT38, SPT39, SPT40, SPT41, SPT42, SPT43, SPT44, SPT45, SPT46, SPT47, SPT48, SPT49, SPT50, SPT51, SPT52, SPT53, SPT54, SPT55, SPT56, SPT57, SPT58, SPT59, SPT60, SPT61, SPT62, SPT63, SPT64, SPT65, SPT66, SPT67, SPT68, SPT69, SPT70, SPT71, SPT72, SPT73, SPT74, SPT75, SPT76, SPT77, SPT78, SPT79, SPT80, SPT81, SPT82, SPT83, SPT84, SPT85, SPT86, SPT87, SPT88, SPT89, SPT90, SPT91, SPT92, SPT93, SPT94, SPT95, SPT96, SPT97, SPT98, SPT99, SPT100). The table also includes a search bar and a 'Variants: 355/484' indicator.

Flag	chr	pos	alt	ref	start	end	ref	alt	gene	alt_change	alt	protein	clinical	cancer	icd10	reported	alt_pos	category	alt	somatic	
	chr1	2547044	A	G	2547044	2547044	A	G	NR2A1												
	chr1	30241	A	G	30241	30241	A	G	MTRR												
	chr4	187246	C </tr																		

EGFR mutations

EGFR mutations in NSCLC

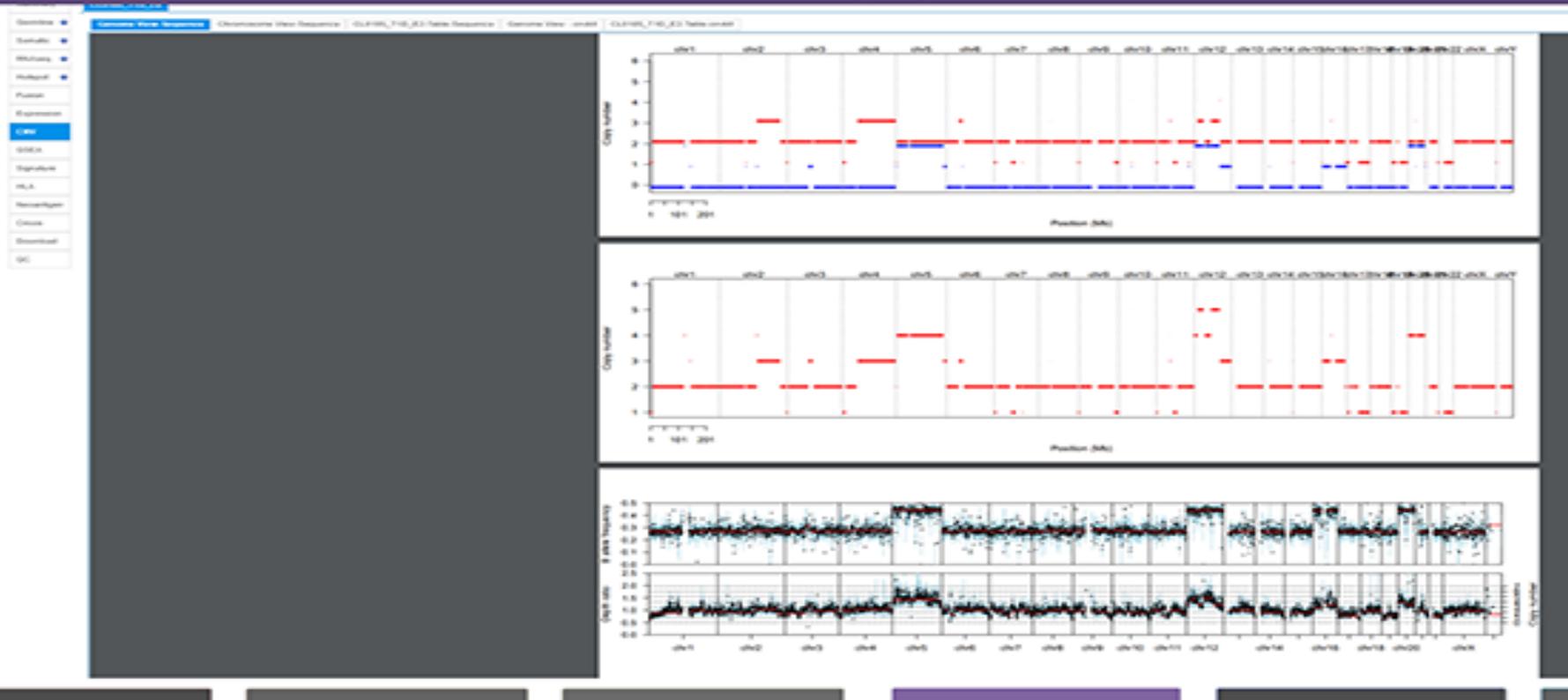
BV view of patient: CL0040 case: OM16-007 Total 4 sample(s)



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

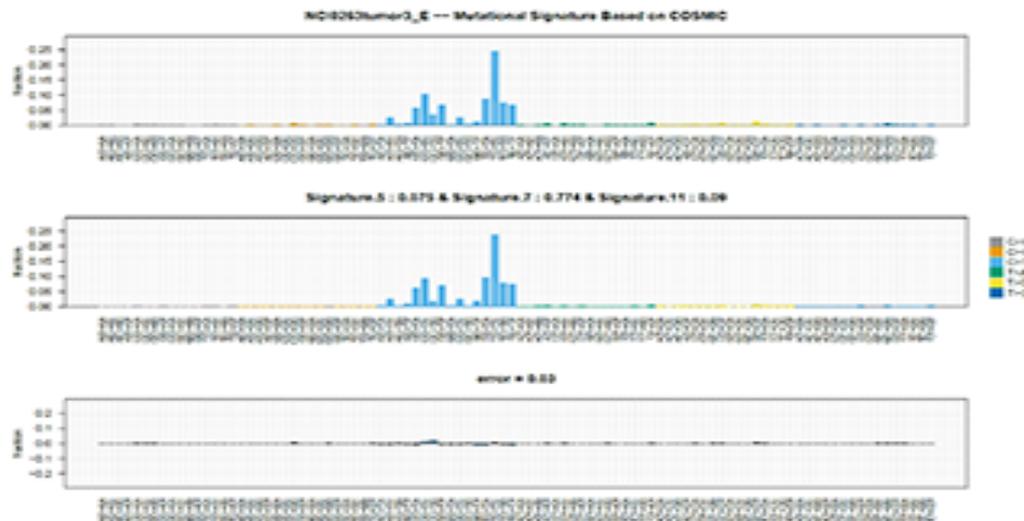
Tumor Copy Number

Tumor Copy Number

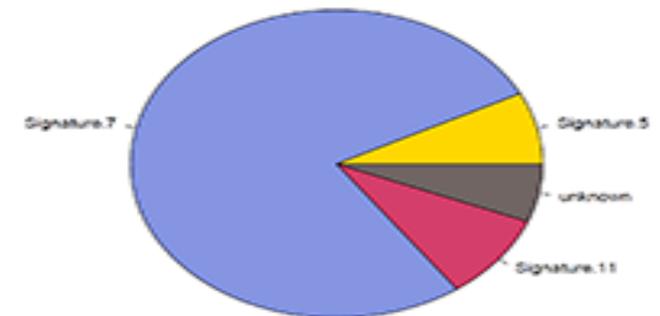


Mutation Signatures

Mutation Signatures for Tumor



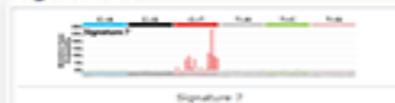
NCI0263: Melanoma



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

Signature 7: UV signature

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 (viz., by formation of pyrimidine-pyrimidine photoproducts) and these mutations are being repaired by transcription-coupled nucleotide excision repair.

Cosmetics: N/A

Mutation Burden

Mutation Burden

The screenshot displays the OncoGenomics web interface. The top navigation bar includes links for Home, Projects, Patients, Cases, Upload, Variants, GenoTyping, Documentation, and About. A user profile 'weij' is visible in the top right. The breadcrumb trail shows 'Clinomics, del Rioero / Adrenocortical carcinoma / CL0185'. Below this, filters for 'Projects: Clinomics', 'Diagnosis: Adrenocortical carcinoma', and 'Patient: CL0185' are present, along with a 'GO' button. The main content area is titled 'OM18-113' and features a sidebar with navigation options: Summary, Germline, Somatic (selected), RNAseq, Hotspot, Fusion, Expression, CNV, GSEA, Signature, and HLA. The main panel shows tabs for 'Somatic-All', 'Somatic-CL0185_T1D_PS2-Panel', 'Somatic-CL0185_T1D_E2-Exome', and 'Mutation_Burden'. The 'Mutation_Burden' tab is active, displaying a table of mutation burden data. The table has columns for Diagnosis, Sample Name, Experiment Type, Caller, Burden, Total bases, and Burden Per MB. Two entries are shown, with the 'Burden Per MB' column highlighted by a red box. The first entry is for 'Adrenocortical carcinoma' (Sample: CL0185_T1D_E2, Experiment: Exome, Caller: MuTect) with a Burden of 612 and Total bases of 45196537, resulting in a Burden Per MB of 13.54. The second entry is for 'Adrenocortical carcinoma' (Sample: CL0185_T1D_PS2, Experiment: Panel, Caller: MuTect) with a Burden of 36 and Total bases of 2465827, resulting in a Burden Per MB of 14.6. The interface also shows 'Records: 2/6', a 'Search:' field, and pagination controls for 'Previous', '1', and 'Next'.

OncoGenomics
National Cancer Institute

Home Projects Patients Cases Upload Variants GenoTyping Documentation About

Setting Logout weij

Clinomics, del Rioero / Adrenocortical carcinoma / CL0185

Projects: Clinomics Diagnosis: Adrenocortical carcinoma Patient: CL0185 GO

OM18-113

Summary Germline Somatic RNAseq Hotspot Fusion Expression CNV GSEA Signature HLA

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

Callers: MuTect

Records: 2/6

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

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:

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.

Acknowledgements

Acknowledgements

Genetics Branch

- Paul Meltzer
- Javed Khan

Wet Lab

- Young Song
- Jennifer Walling
- Chaoyu Wang
- Leslie Brents*
- Dan Edelman
- Robert L. Walker
- Marbin Pineda
- Keith Killian*
- Hongling Liao*
- Holly Stephenson*

Bioinformatics/IT

- Rajesh Patidar*
- Xinyu Wen
- Sivasish Sindiri
- Hsein-Chao Chou*
- Scott Goldweber*
- Yuelin (Jack) Zhu
- Sean Davis
- Jimmy Lin*

Laboratory of Pathology

- Ken Aldape
- Fred Barr
- Mark Raffeld
- Liqiang Xi
- Manoj Tyagi
- Vineela Gangalapudi
- Sushma Nagaraj
- Yu Jin Lee
- Tina Pham
- Trinh Pham
- Snehal Patel*
- Joseph W. Chinquee

AVIA Team

- Hue Vuong
- Uma Mudunri
- Jack Collins