TGEN FOUNDATION

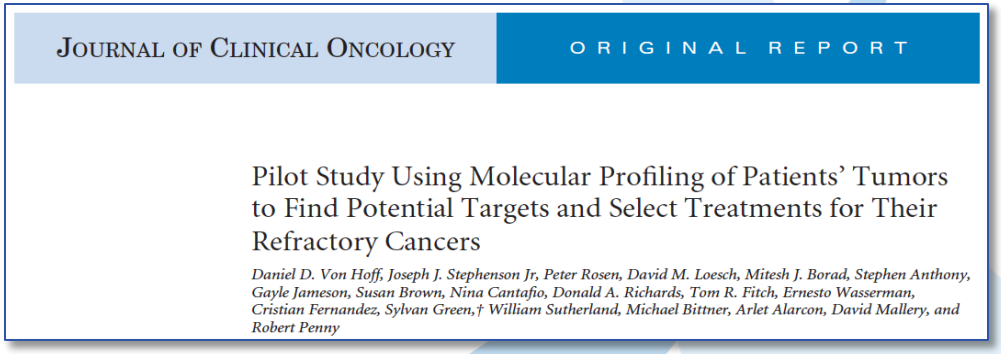
Translational Genomics Research Institute

Individualized treatment based on whole-genome sequence

Jeffrey M. Trent, Ph.D. Dan Von Hoff, M.D
David W. Craig, Ph.D. John D. Carpten

Overview

- Clinical Genomics Center
- Leadership
  - Jeffrey M. Trent, Ph.D (TGen). Dan Von Hoff, M.D (Physician)
  - David W. Craig, Ph.D. (Informatics) John D. Carpten, Ph.D. (Cancer Biology)
- Core premise - Onocology
  - Is molecular profiling using new technologies a rationale approach to increase the "options" available to oncologists for treating cancer patients, namely those who fail standard of care or those patients with otherwise chemo-resistant metastatic cancer?
- Approach
  - Integrative Analysis of whole transcriptome and genome sequencing for treatment when no other clear options are available in the context of clinical protocols
- Ongoing Studies
  - Approximately 50 patients treatments – WGS 2011
  - Triple Negative Breast Cancer (Life Foundation)
  - Rare Cancer Treatment Study (NFCR)
  - Neuroblastoma (Dell)
  - Genetics of unknown etiology
  - Several forthcoming

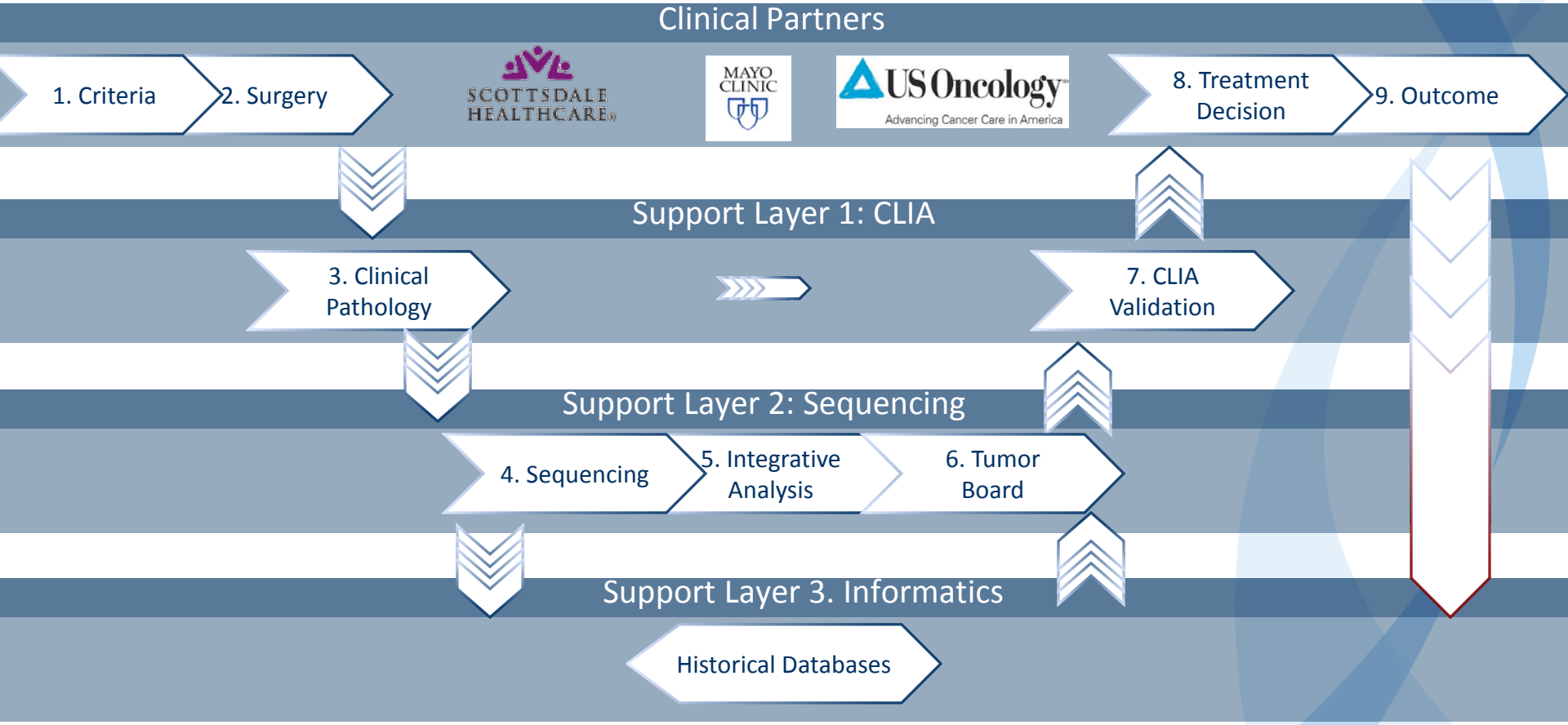

JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

Pilot Study Using Molecular Profiling of Patients' Tumors to Find Potential Targets and Select Treatments for Their Refractory Cancers

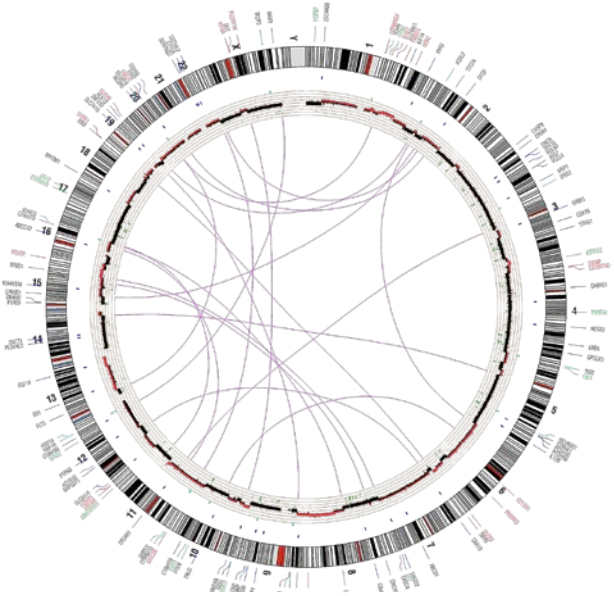
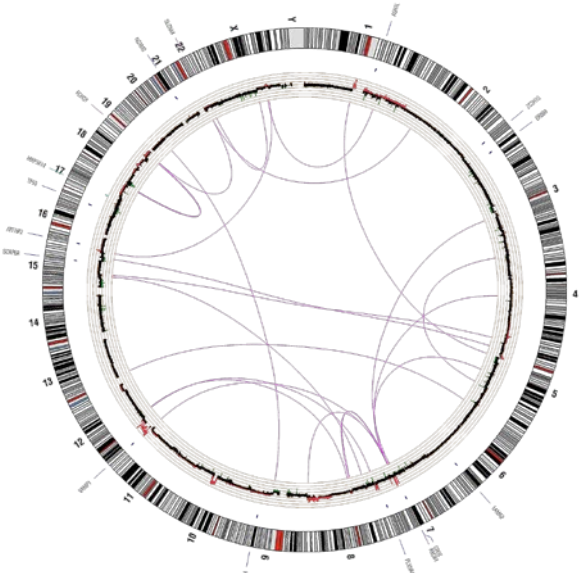
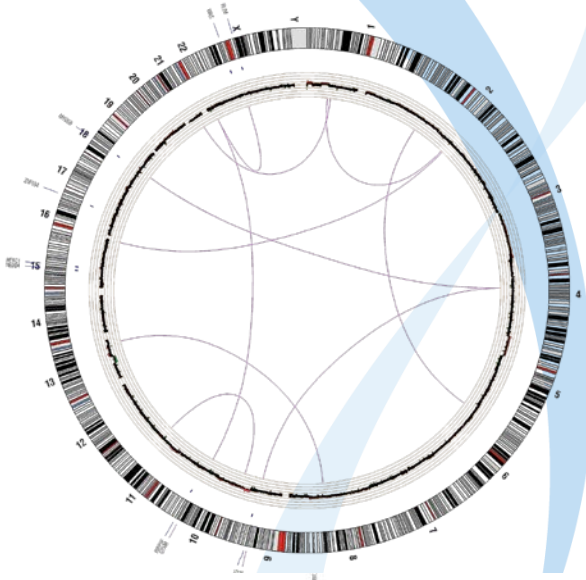
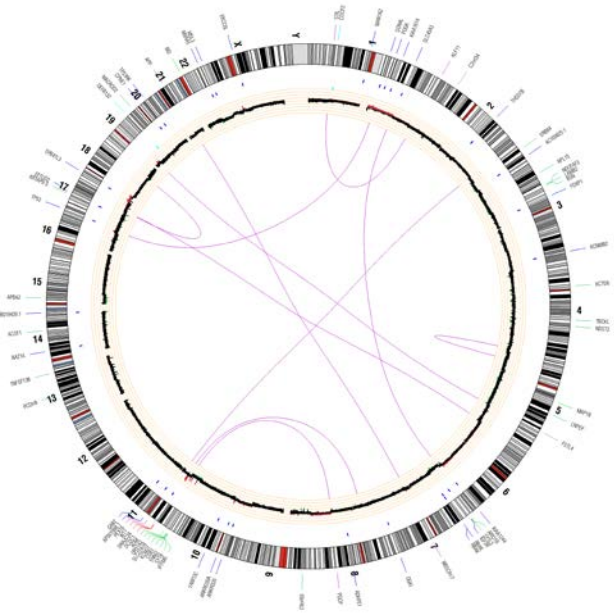
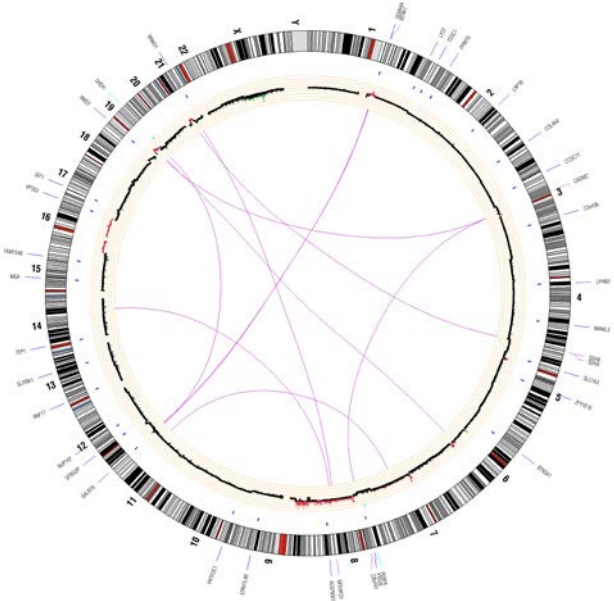
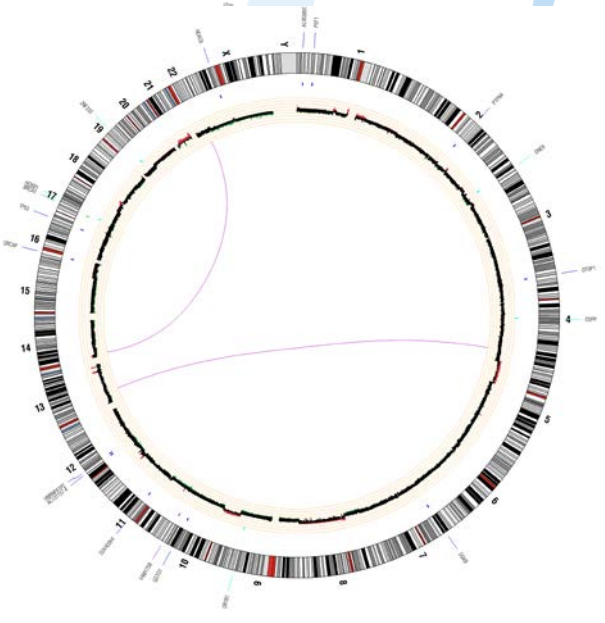
Daniel D. Von Hoff, Joseph J. Stephenson Jr, Peter Rosen, David M. Loesch, Mitesh J. Borad, Stephen Anthony, Gayle Jameson, Susan Brown, Nina Cantafio, Donald A. Richards, Tom R. Fitch, Ernesto Wasserman, Cristian Fernandez, Sylvan Green,† William Sutherland, Michael Bittner, Arlet Alarcon, David Mallery, and Robert Penny

Protocols/Trials in WGS for Oncology

Providing Support For Clinical Partners through Integrated Analysis of Whole Genome Sequencing



Goal: Each cancer genome is unique, identify events with clinical utility

Examples

Example 1: Rare Tumor – Metastatic Uterine Transitional Cell Carcinoma

- NFCR: Involved Glen Weiss, Winnie Liang, Tyler Izatt, Shripad Sinari, Alexis Christoforides, Ahmet Kurdoglu, Angela Baker, John Carpten, Dan Von Hoff, TGen/SHC (National Foundation for Cancer Research)
- Transitional cell carcinoma of the uterus is highly curable if detected early
- NFCR patient 01-08 diagnosed with Metastatic Uterine TCC
- Sequencing Design and Statistics:
  - Illumina HiSeq2000, Paired-End
  - Tumor : 46X uniquely mappable
  - Normal: 55X uniquely mappable
  - RNA-seq for tumor and normal uterus (~100 million reads)

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Rare Tumor – Metastatic Uterine Transitional Cell Carcinoma

chr	loc	geneName	refAllele	mutAllele	codonSeq	newSeqs	oldAA	codon	newAA
chr4	17190585	LAP3	A	C	GAT	GCT	D	48	A
chr7	82417498	PCLO	C	A	GAT	TAT	D	3379	Y
chr1	62013544	INADL	A	G	ACA	GCA	T	267	A
chr2	31970707	MEMO1	G	T	AGC	AGA	S	146	R
chr5	16811253	MYO10	G	A	CGG	TGG	R	608	W
chr6	26164410	HIST1H1C	T	G	AAC	CAC	N	76	H
chr7	55988458	MRPS17	G	A	GCT	ACT	A	26	T
chr16	65157404	CKLF	G	C	GAA	CAA	E	65	Q
chr4	158277128	GLRB	C	A	CCC	ACC	P	119	T
chr12	54715162	IKZF4	C	A	TCC	TAC	S	472	Y
chr1	196977997	PTPRC	C	T	CGC	TGC	R	698	C
chr11	104371742	CASP5	T	A	CAG	CTG	Q	357	L
chr2	**135413091**	**CCNT2**	**T**	**C**	**CTA**	**CCA**	**L**	**2**	**P**
chr3	113382142	SLC9A10	C	G	GAG	CAG	E	903	Q
chr17	46412171	SPAG9	T	A	TAT	TTT	Y	1116	F
chr12	46361861	RPAP3	T	A	GAA	GAT	E	333	D
chr6	147151262	C6orf103	T	A	TCT	ACT	S	399	T
chrX	**44803638**	**KDM6A**	**C**	**T**	**CGA**	**TGA**	**R**	**38**	**X**
chr7	101866560	ORAI2	G	A	CGG	CAG	R	51	Q
chr15	71422993	HCN4	C	T	CGG	CAG	R	332	Q
chr17	77267631	HGS	G	A	GAA	AAA	E	144	K
chr11	77089445	RSF1	G	T	TCA	TAA	S	826	X
chr22	37408930	TOMM22	C	G	CAA	GAA	Q	113	E
chr16	70305970	PHLPP2	C	G	TGT	TCT	C	77	S
chr19	17337551	PLVAP	C	T	TGG	TGA	W	241	X
chr11	**19213154**	**E2F8**	**A**	**G**	**ATC**	**ACC**	**I**	**160**	**T**
chr17	**7519218**	**TP53**	**C**	**T**	**TGG**	**TAG**	**W**	**146**	**X**
chr5	74057609	GFM2	A	T	TTT	ATT	F	562	I
chr2	165953474	SCN2A	C	T	CGT	TGT	R	1638	C

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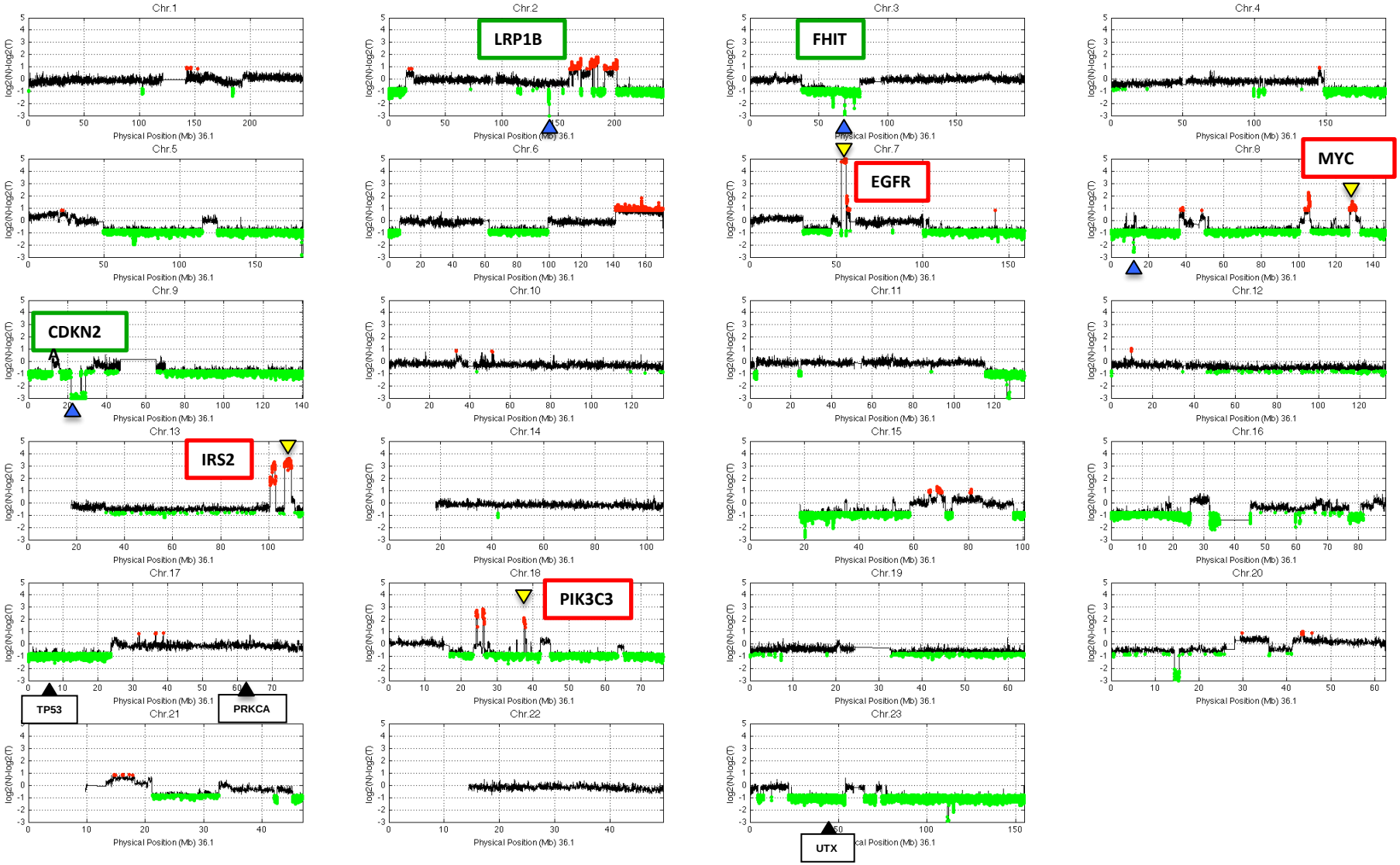
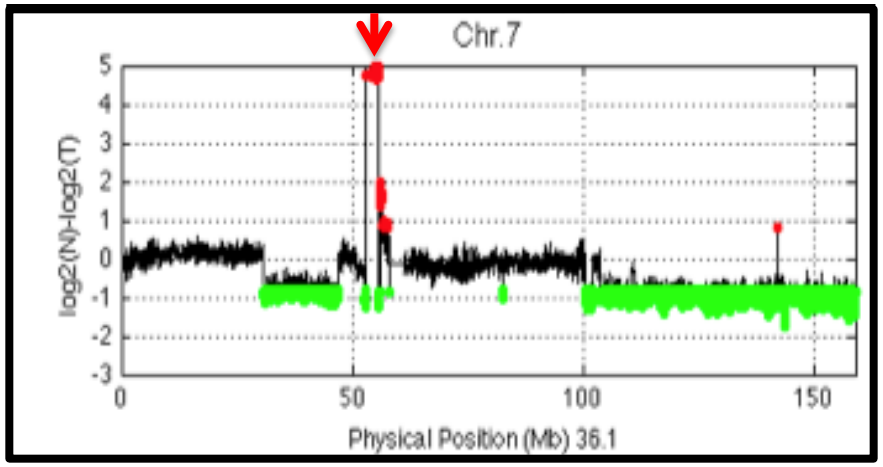
Rare Tumor – Metastatic Uterine Transitional Cell Carcinoma

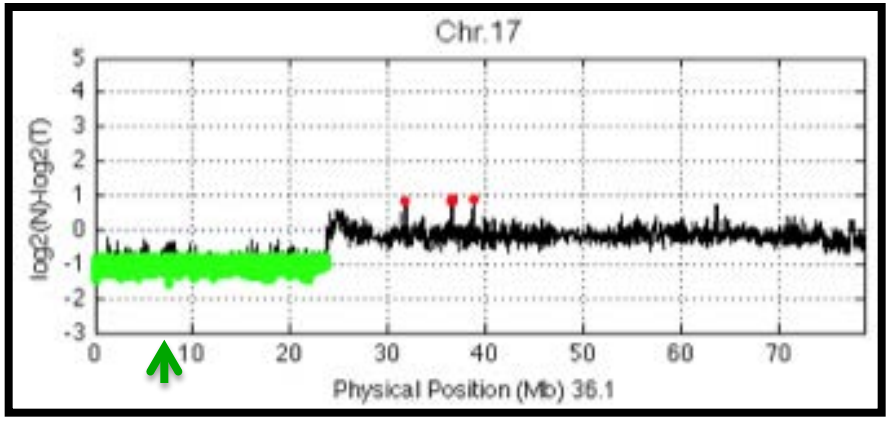
Charts of Each Chromosome Where DNA Has Been Changed



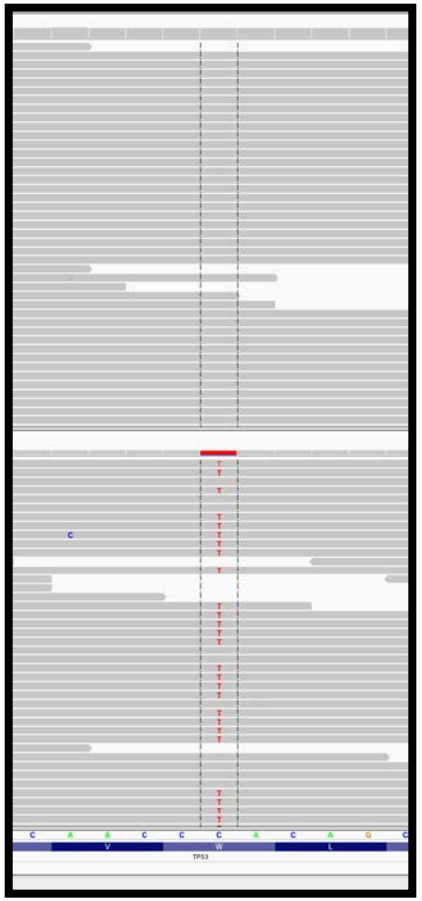
Rare Tumor – Metastatic Uterine Transitional Cell Carcinoma

EGFR

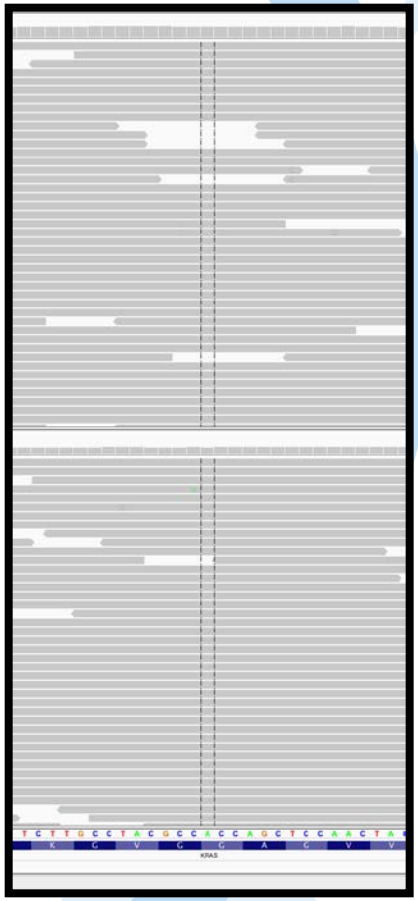




TP53



KRAS



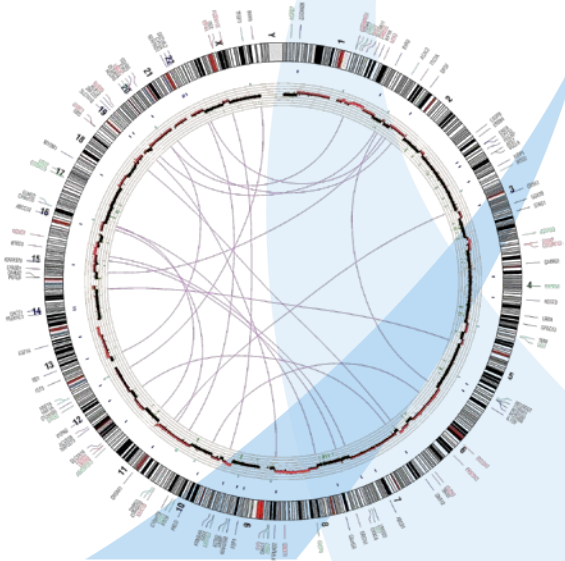
Concomitant TP53 W146X, but no KRAS

Rare Tumor – Metastatic Uterine Transitional Cell Carcinoma

- Cuatrecasas M, et al., 2009. (Am J Surg Pathol;33(4) 556-67).
  - Performed a clinicopathologic, immunohistochemical, and molecular genetic analysis of 19 transitional cell tumors including 13 tumors (5 benign, 7 borderline, and 1 malignant) and 6 TCCs.
    - Malignant Brenner tumors were negative for p16, Rb, and p53, and strongly positive for Cyclin D1, Ras, and EGFR.
    - TCCs had p53 mutations with p53 and p16 protein overexpression and showed a negative immunoreaction for EGFR, Cyclin D1, and Ras.
- Patient tumor demonstrated p16 and p53 loss and high level EGFR amplification more similar to Brenner tumor than TCCs.
- EGFR overexpression and amplification CLIA validated
- Patient on Cetuximab (08/2011) based on EGFR amplification and the absence of KRAS mutation.

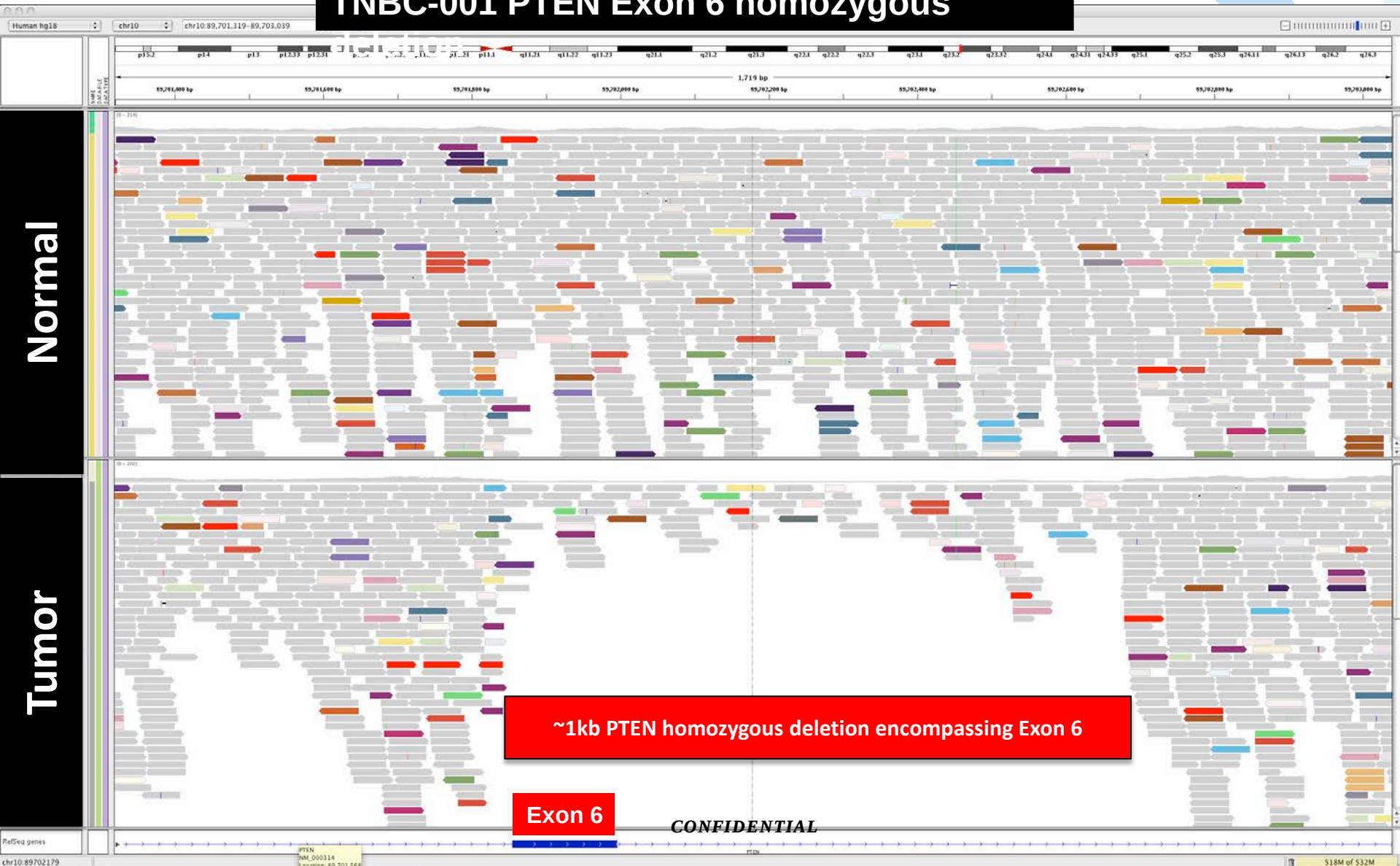
Example 2: Triple Negative Breast Cancer Personalized Genomics Trial

- In collaboration between TGen, Life Technologies and US Oncology and support from Caris Diagnostics, we will sequence the genomes and transcriptomes of tumor and normal tissue from 14 patients with TNBC during the course of clinical management to provide oncologists with additional therapeutic options.
- A subtype of breast cancer that is clinically negative for expression of estrogen and progesterone receptors (ER/PR) and HER2 protein.
- However, there is no effective treatment for chemo-resistant TNBC.



Triple Negative Breast Cancer Personalized Genomics Trial

TNBC-001 PTEN Exon 6 homozygous



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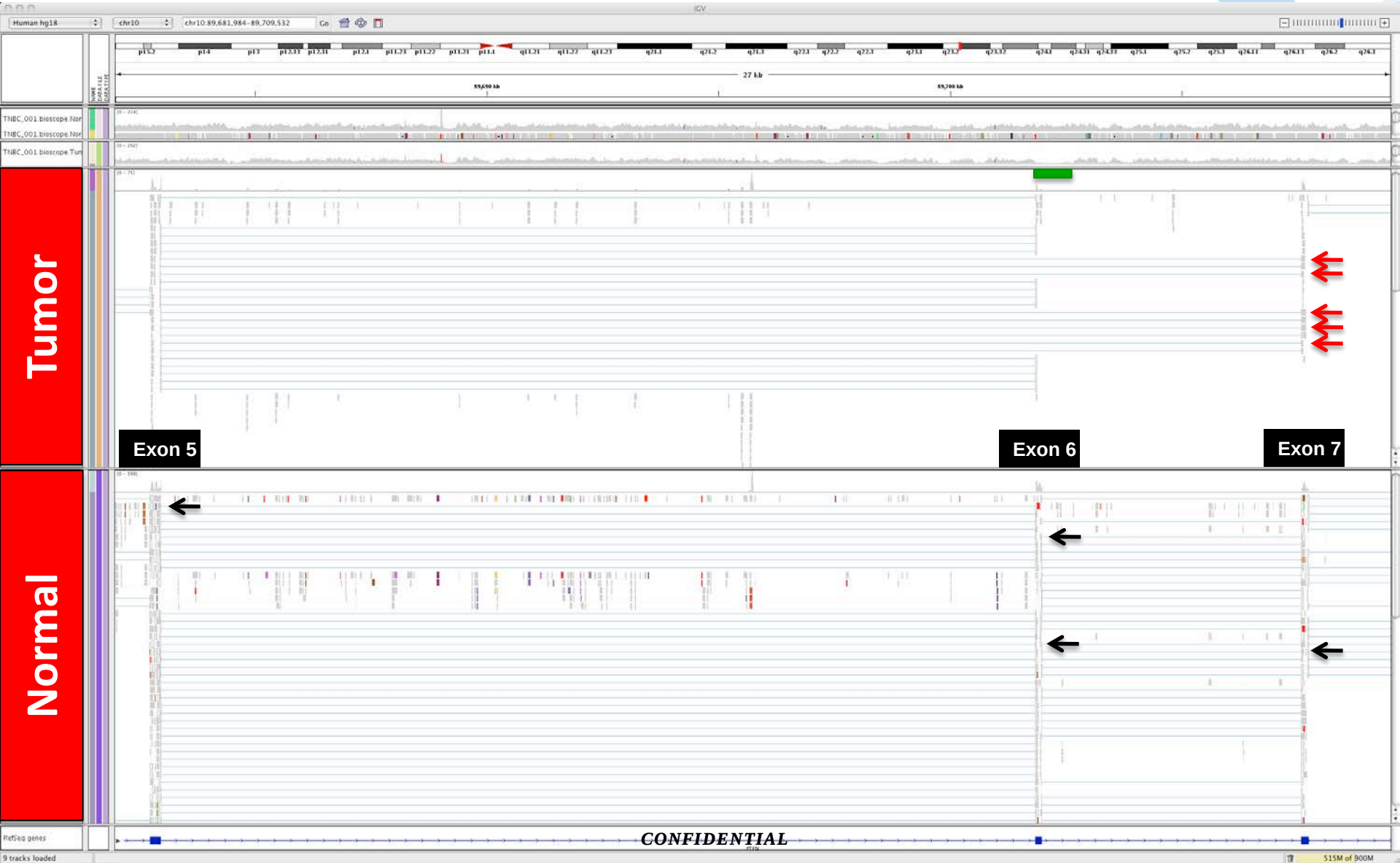
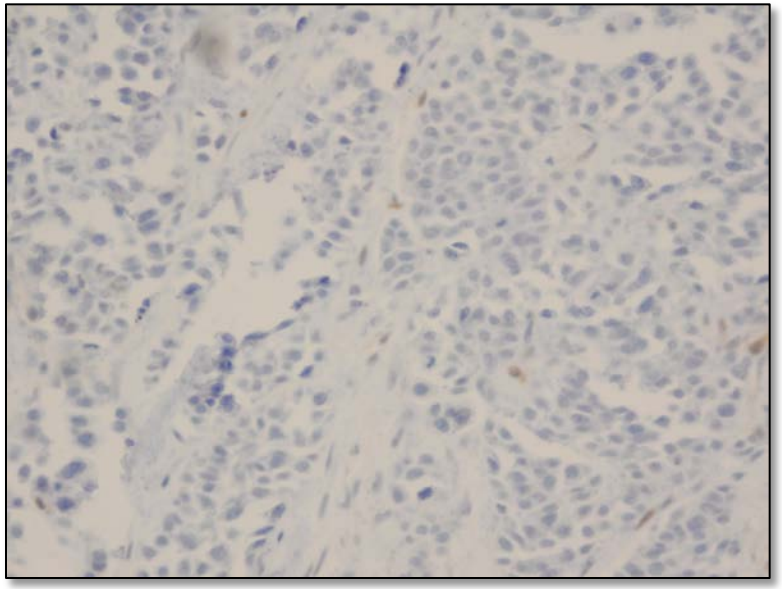
Triple Negative Breast Cancer Personalized Genomics Trial



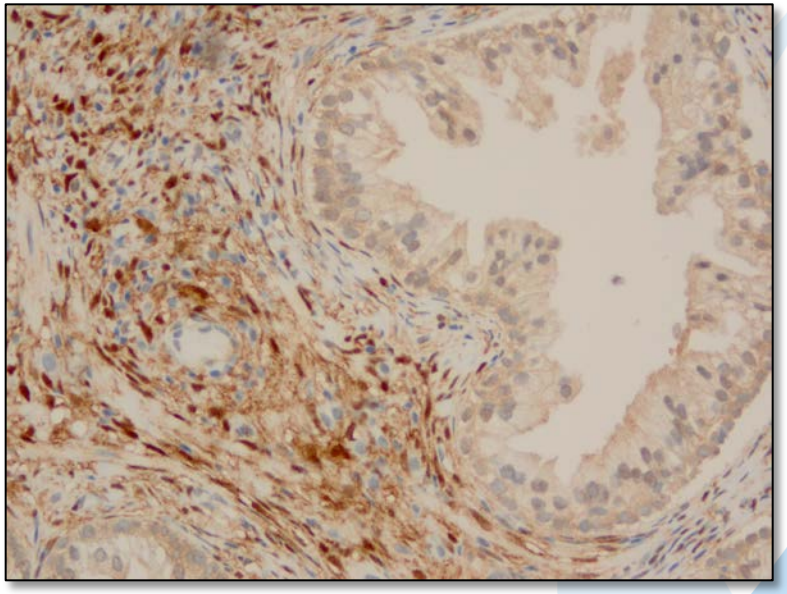
Triple Negative Breast Cancer Personalized Genomics Trial

TNBC-001 PTEN Exon 6 homozygous

PTEN G165Ifs173X protein truncating mutation leads to complete protein loss.



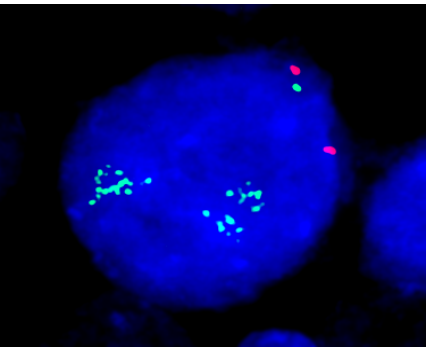
TNBC-001

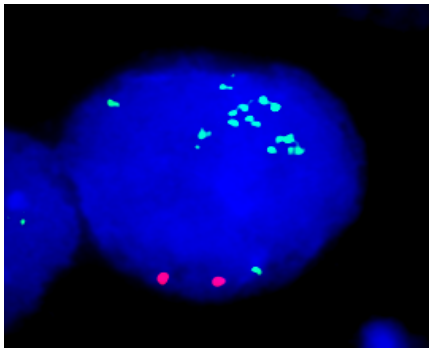


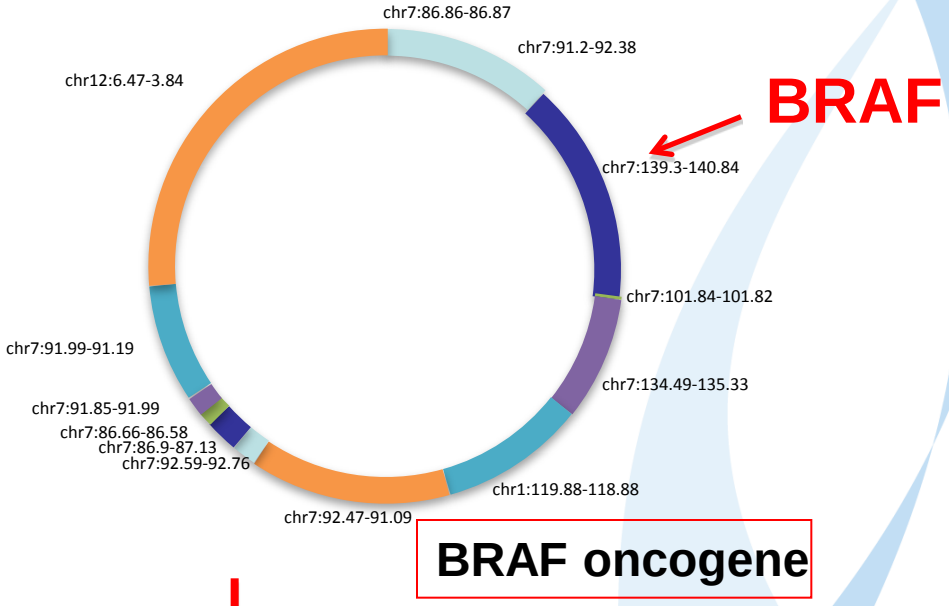
Positive Control

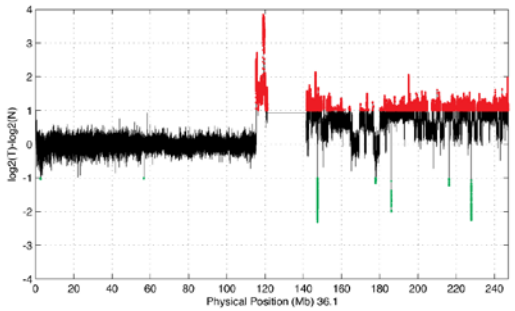
Therapeutic Targets on WGS of mTNBC Cancer TNBC-002

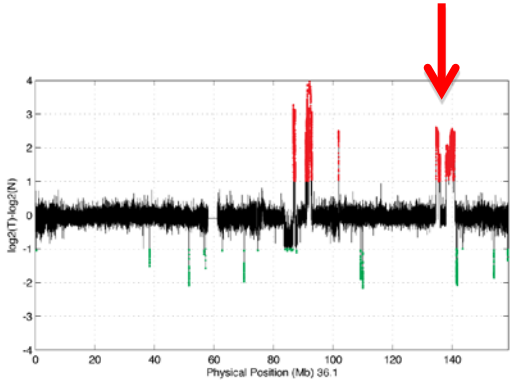
- 58 yo Caucasian transient response preop AC/T, platinum, bevacizumab
- WGS and FISH reveal extrachromosomal DNA BRAF double minute

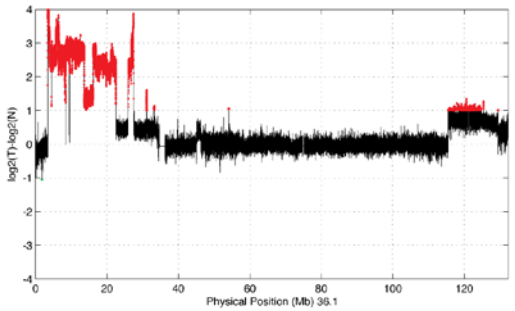












Abstract #2502

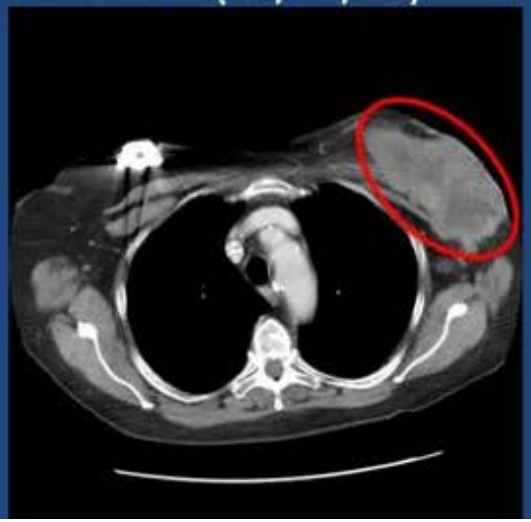
The clinical effect of the dual-targeting strategy involving PI3K/AKT/mTOR and RAS/MEK/ERK pathways in first-in-human phase I studies: The START Center Experience

Toshio Shimizu, Anthony W. Tolcher, Kyriakos P. Papadopoulos, Muralidhar Beeram, Drew Rasco, Lon S. Smith, Shelly Gunn, Leslie Smetzer, Theresa A. Mays, Brianne Kaiser, Michael J. Wick, Cathy Alvarez, Gina L. Mangold, Amita Patnaik

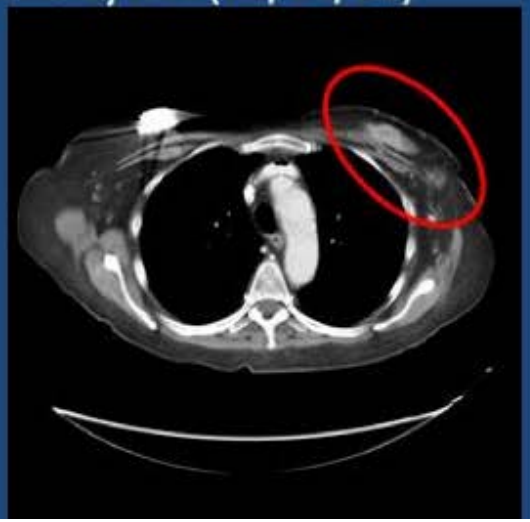
START (South Texas Accelerated Research Therapeutics), San Antonio, TX, U.S.A.

CT 2. TNBC with PTEN deletion (AKT inhibitor + MEK inhibitor)

Baseline (03/07/11)



Post 2 Cycles (05/04/11)



PR,
75% regression
in primary lesion

Shimizu et al., 2011 (ASCO Abstract 2502)

Messages / Areas of Collaboration

- Multiple high utility events are frequently found in metastatic disease
  - *Not always will be simple black/white in clinic*
- Use of WGS in the context of disease management
- Outcomes and Data Sharing


Thank you