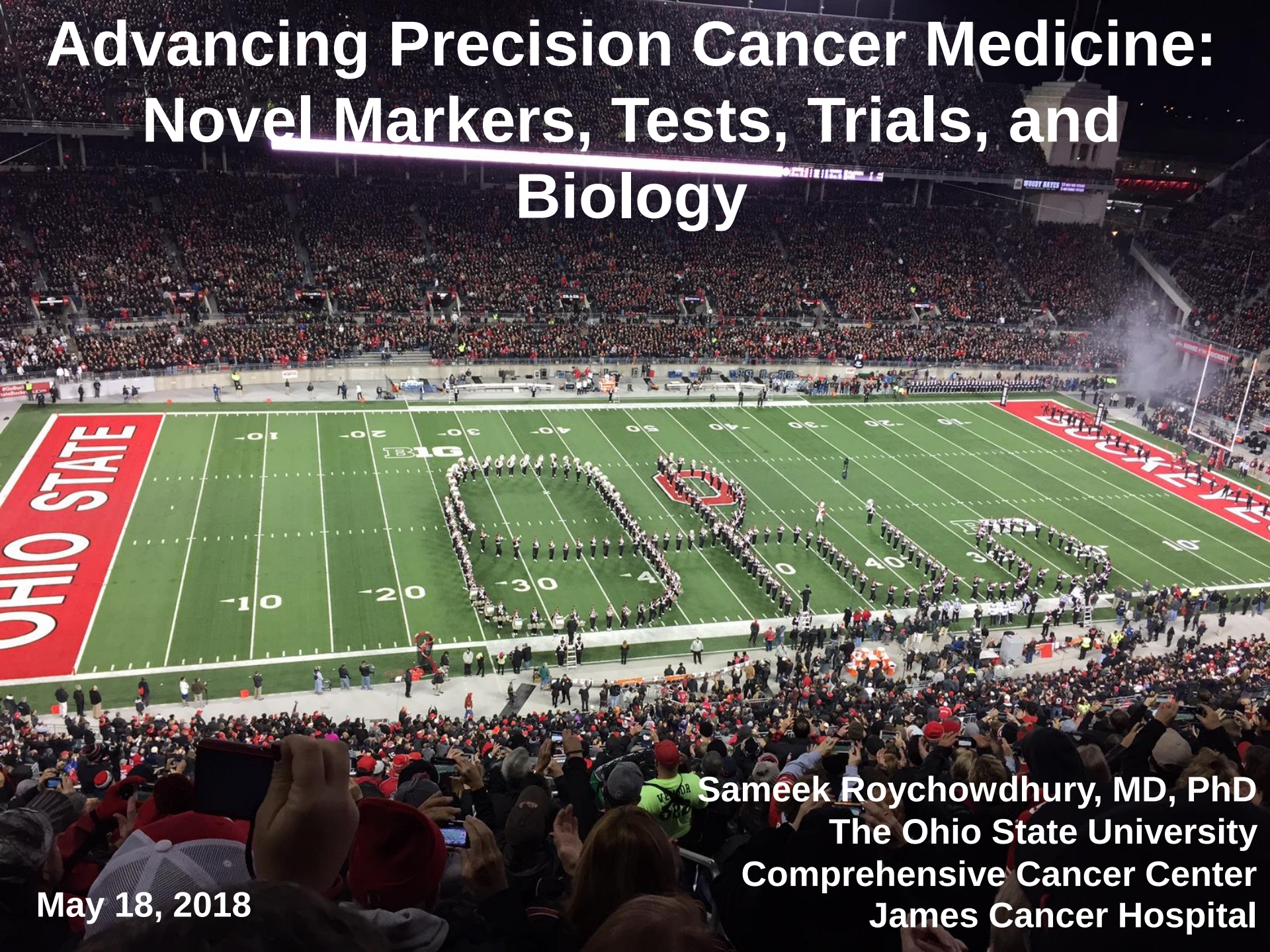
Advancing Precision Cancer Medicine: Novel Markers, Tests, Trials, and Biology



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The Ohio State University
Comprehensive Cancer Center
James Cancer Hospital

May 18, 2018

Disclosure Information

I have the following financial relationships to disclose:

Stockholder in: Johnson and Johnson

Advisory Board: AbbVie, Incyte

Honoraria: IDT DNA technologies

I will not discuss off label use in my presentation.

Precision Cancer Care

Patients

Discovery of Markers

Development of Novel Tests

Clinical Trials with Novel Therapies

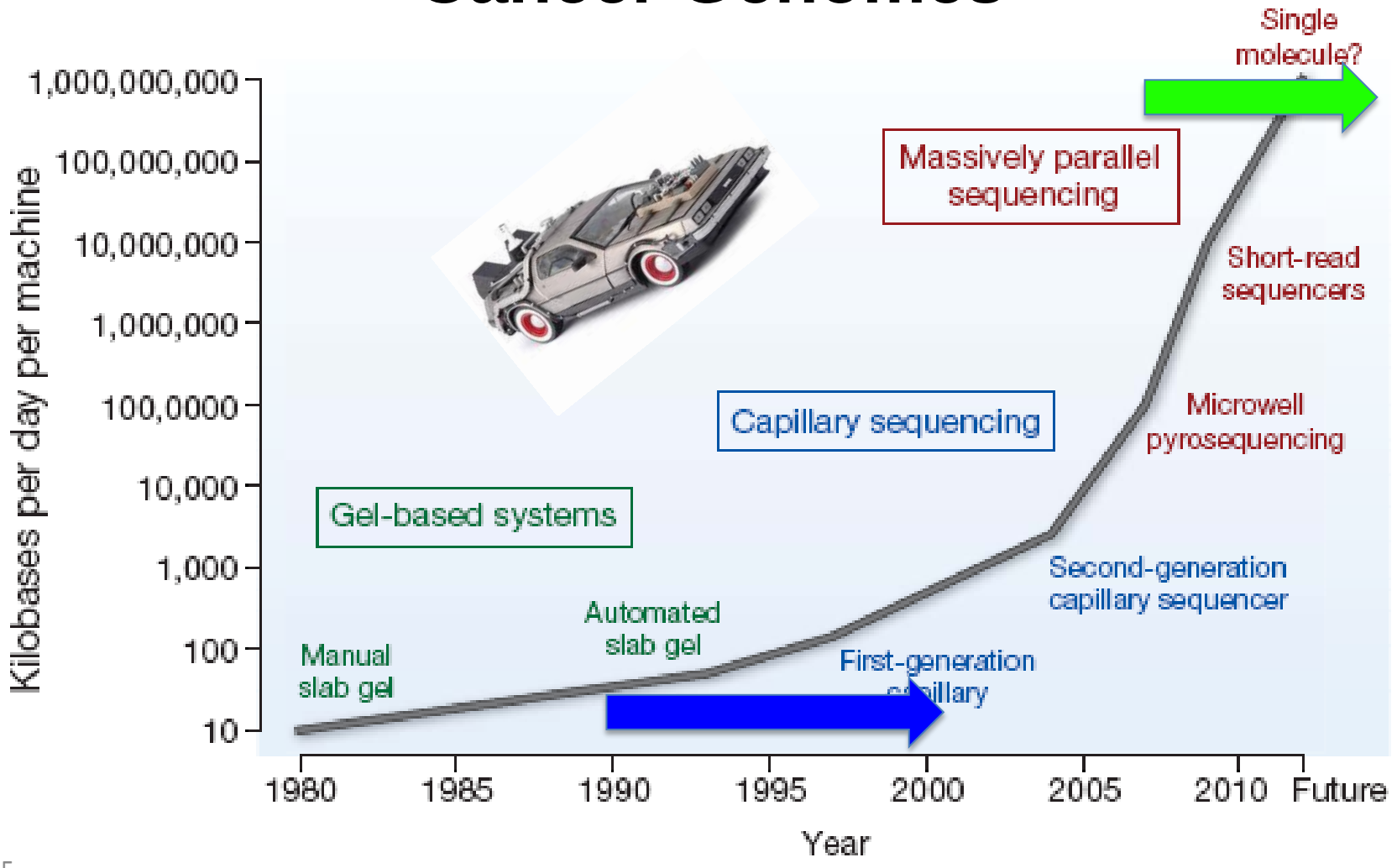
1) What is the right drug for our patient?

2) How can we improve that therapy?

Outline and Goals

- **Precision cancer medicine**
  - **Gene fusions -> Targeted therapies (FGFR)**
  - **Microsatellite instability -> Immunotherapy**
- **Data sharing networks**

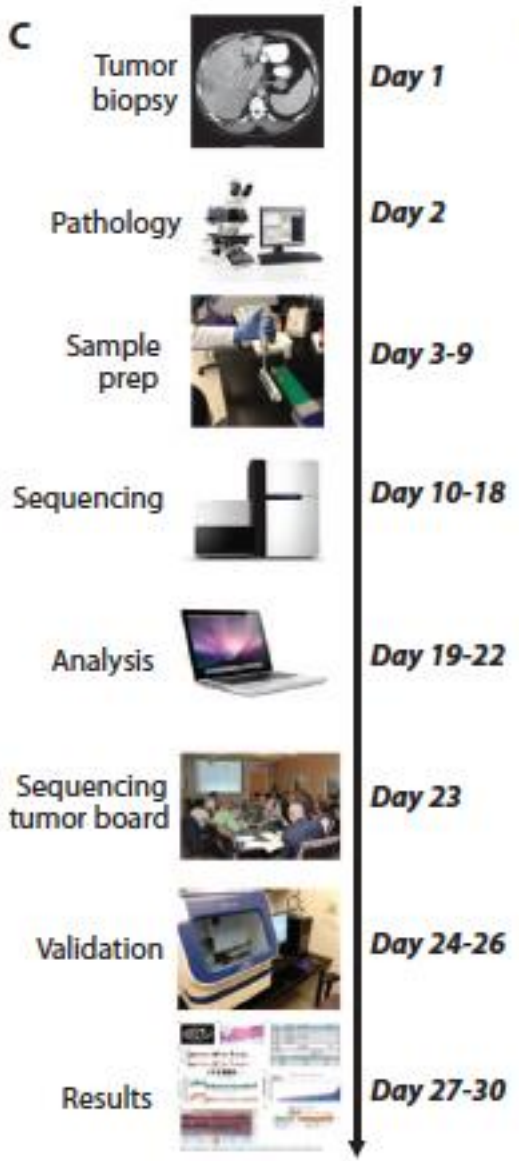
Next Generation Sequencing Technology Enables Rapid Assessment of Cancer Genomes



How do we apply and bring genomic sequencing strategies and bioinformatics to patient care?

Personalized Oncology Through Integrative High-Throughput Sequencing: A Pilot Study

Sameek Roychowdhury,[1,2]* Matthew K. Iyer,[1,3]* Dan R. Robinson,[1,4]* Robert J. Lonigro,[1,3] Yi-Mi Wu,[1,4] Xuhong Cao,[1,4,5] Shanker Kalyana-Sundaram,[1,4,6] Lee Sam,[1,3] O. Alejandro Balbin,[1,3] Michael J. Quist,[1,4] Terrence Barrette,[1,4] Jessica Everett,[7] Javed Siddiqui,[1,4] Lakshmi P. Kunju,[1,4] Nora Navone,[8] John C. Araujo,[8] Patricia Troncoso,[8] Christopher J. Logothetis,[8] Jeffrey W. Innis,[9] David C. Smith,[2,10] Christopher D. Lao,[2,10] Scott Y. Kim,[11] J. Scott Roberts,[11,12] Stephen B. Gruber,[2,10] Kenneth J. Pienta,[1,2,10,13] Moshe Talpaz,[2,10] Arul M. Chinnaiyan[1,3,4,5,13†]



November 2011

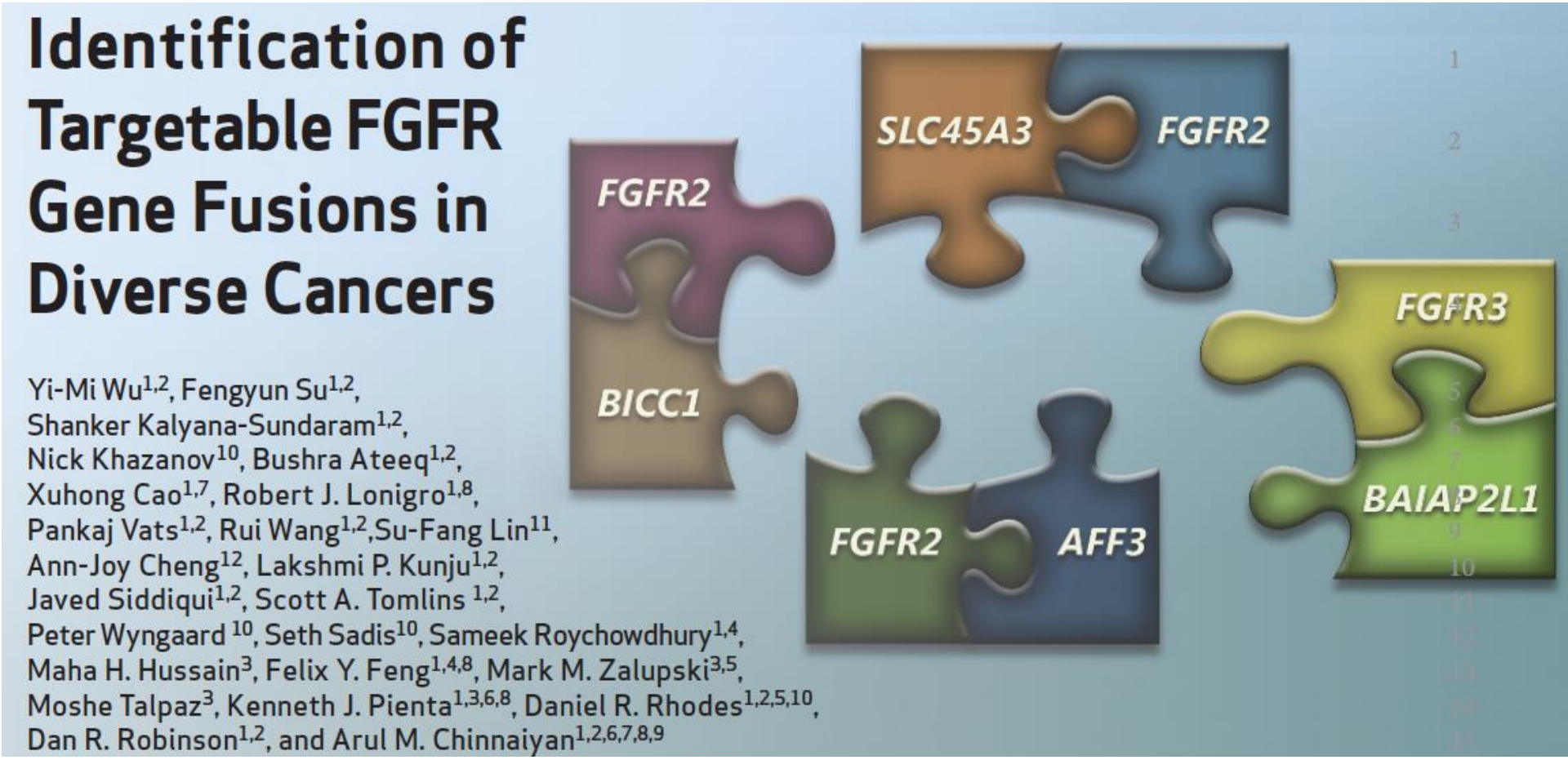
MO_1036: Cholangiocarcinoma

March 2012: 34 year old woman with newly diagnosed metastatic cholangiocarcinoma.

Started therapy in a clinical trial with continuous infusion 5-FU, fixed dose rate gemcitabine, and cisplatin.

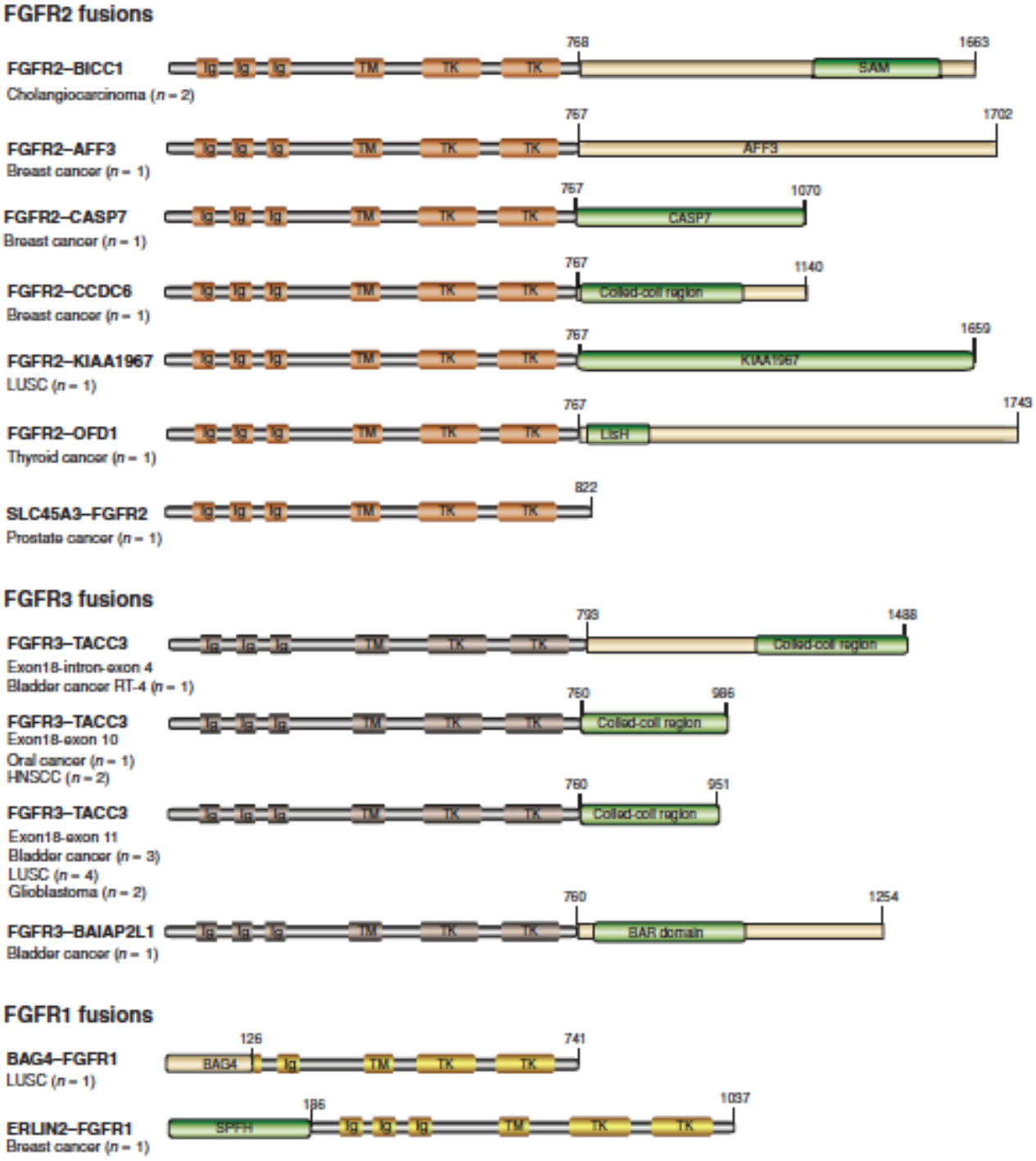
May 2012: Liver biopsy

Fibroblast Growth Factor Receptor (FGFR): *A New Target for Therapy*



Wu et al, Cancer Discovery, 2013

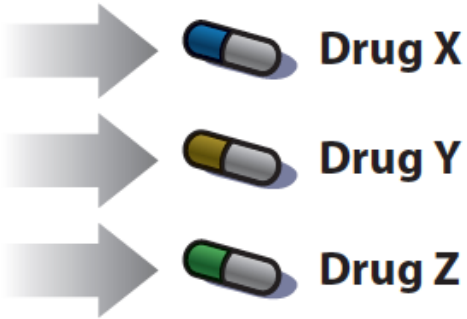
FGFR: *Multiple cancer types*



Genomics is Changing Clinical Trials

One size fits all

Genomics

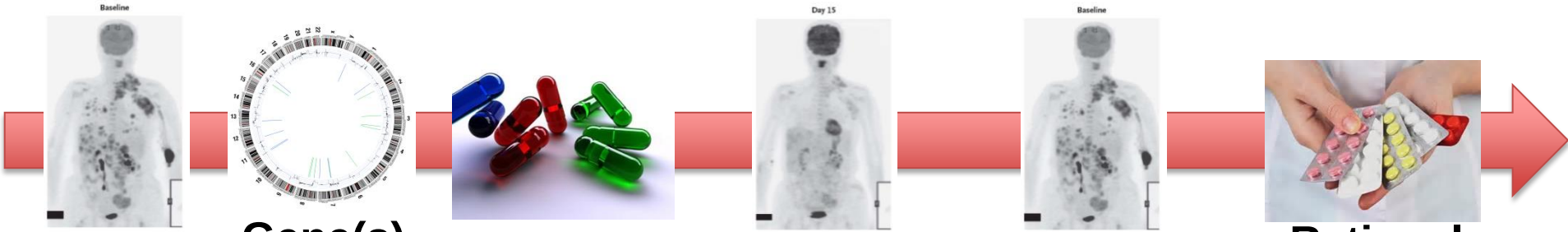


Roychowdhury and Chinnaiyan,
Ann Rev Genomics and Human Genetics, 2014

FGFR: New questions

- Who else has the **marker**?
- How do we leverage **big data for Patients**?
- How do we **diagnose** it across different cancer types?
- What **novel therapies** can we offer them?

Our Team Approach



Patient | Gene(s) Marker(s) | Therapy | Response | Resistance | Rational combinations

Genomics | **Computational Biology**

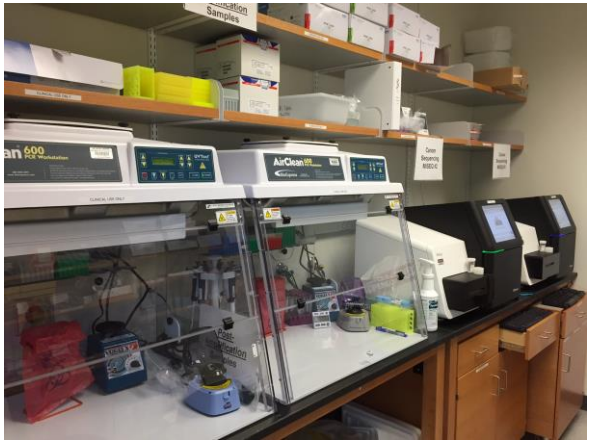
Molecular Diagnostics

Basket Clinical Trials

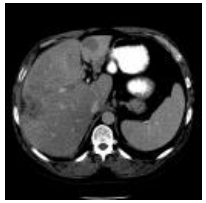
Novel Targets/Resistance | **Autopsy and Heterogeneity** | **Rare Cancers** | **Immunology and Genomics**

CLIA-Cancer Genomics Laboratory

Novel Molecular Diagnostic Tests

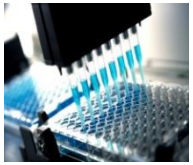


Tumor Biopsy

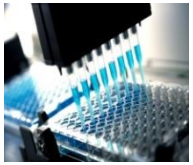


Pathology

DNA & RNA Qty QC



Library Prep(s)

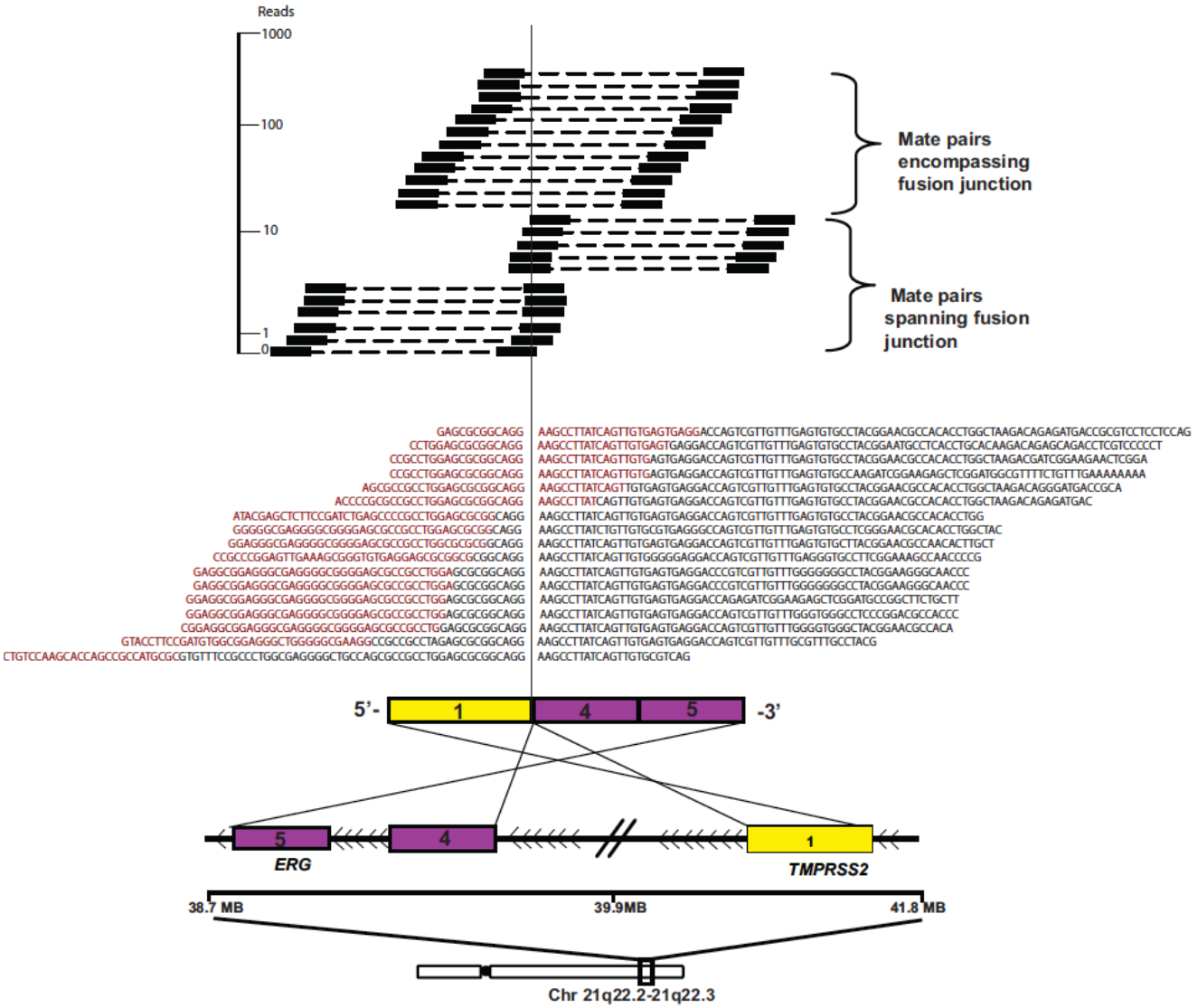


Sequence

Bioinformatics Analysis

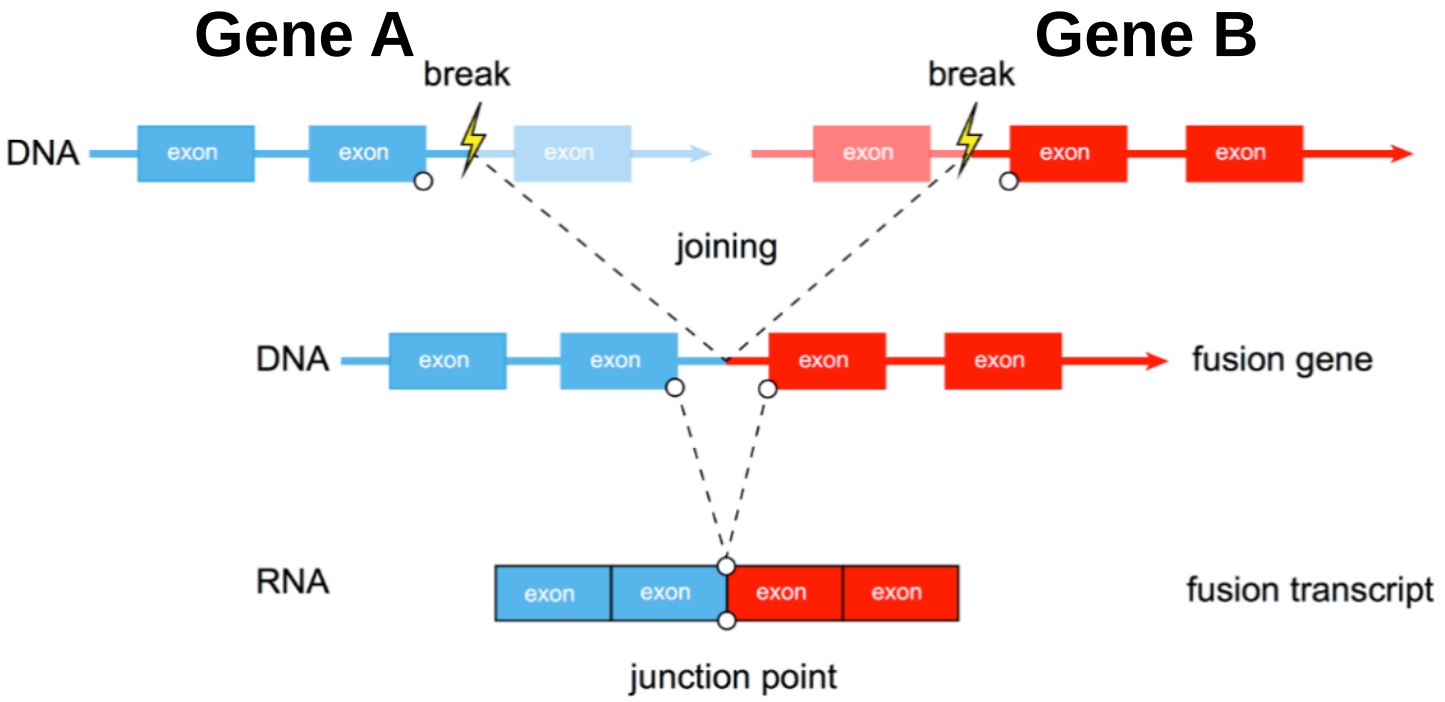
Review and Report

RNAseq to Detect Gene Fusions



Maher et al., PNAS 2009

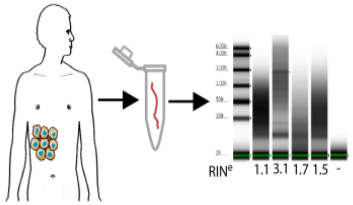
RNA sequencing to detect gene fusions



Advantages	Disadvantages
➢Unbiased (no knowledge of breakpoint/partner gene required) ➢Novel fusion discovery ➢Gene expression information	➢Complex (but focused) data analysis ➢Limited by genes on panel

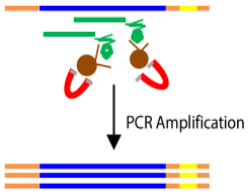
Spanning Actionable RNA Kinase Fusions [OSU-SpARKFuse]

Sample Requirements and RNA Quality Control



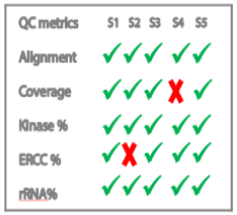
1. Pathologist review
   - Minimum 20-50µm FFPE tissue or single frozen biopsy specimen
   - Tumor content requirement >= 25%
2. RNA Extraction and QC
   - RIN^e and DV200

Library Preparation and Hybridization/ Capture



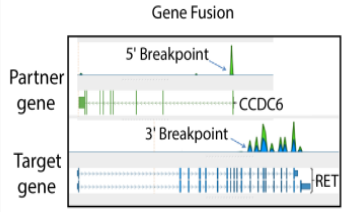
1. 250ng input
2. rRNA depletion, fragmentation, cDNA synthesis, library construction
3. Multiplexed hybridization and capture using biotinylated probes (IDT)

Illumina Sequencing and Quality Metrics



1. 2 x 100 paired end sequencing on MiSeq
2. QC report:
   - Alignment
   - Coverage
   - Kinase %
   - ERCC %
   - rRNA %

Fusion Calling and Report Generation



1. Fusion callers - ChimeraScan and TopHat-Fusion
   - Number of fusion spanning reads
2. Flagging Known fusions

Reeser et al, Journal of Molecular Diagnostics, 2017

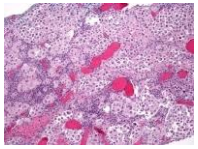
Gene List

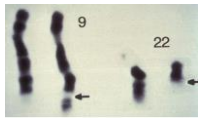
KINASE									
ABL1	ABL2	AKT1	AKT2	AKT3	ALK	AR	ARAF	ATM	AURKA
AURKB	BLK	BRAF	BTK	CDK1	CDK10	CDK2	CDK3	CDK4	CDK5
CDK6	CDK7	CDK8	CDK9	CSF1R	CSF2RA	CSF3R	DDR2	EGFR	EPHA6
EPOR	ERBB2	ERBB3	ERBB4	ERG	ESR1	ETV1	ETV4	ETV5	ETV6
EWSR1	FGFR1	FGFR2	FGFR3	FGFR4	FGR	FLT1	FLT4	FRK	FYN
HCK	HRAS	IGF1R	IGF2R	IL7R	ITK	JAK1	JAK2	JAK3	KDR
KIT	KRAS	LCK	LYN	MAP2K1	MAP2K2	MAPK1	MAPK3	MET	MPL
MTOR	MYC	NRAS	NTRK1	NTRK2	NTRK3	PDGFB	PDGFRA	PDGFRB	PIK3CA
PIK3R1	PIK3R2	RAF1	RARA	RET	ROS1	SRC	STK11	SYK	TSC1
TSC2	TYK2	YES1							
HOUSE KEEPING									
ASCC3	CNTF	EPM2A	HEATR4	NOL10	PRPSAP1	RPGRIP1	SFT2D3	SPDYA	
ERCC									
ERCC-00017	ERCC-00025	ERCC-00039	ERCC-00057	ERCC-00060	ERCC-00084	ERCC-00108	ERCC-00109	ERCC-00154	ERCC-00164

Genomics Closes the Gap from Discovery to Patients

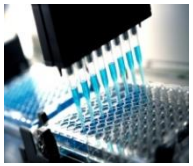
Microscopy

Immunohistochemistry



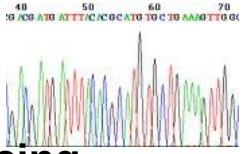


Karyotype

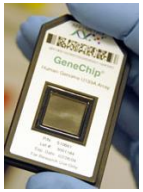


PCR

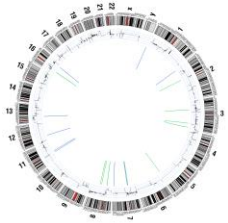
Sanger sequencing



FISH



Microarray



Next Generation sequencing

1900s 1960s 1970s 1980s 1990s 2000s 2010s

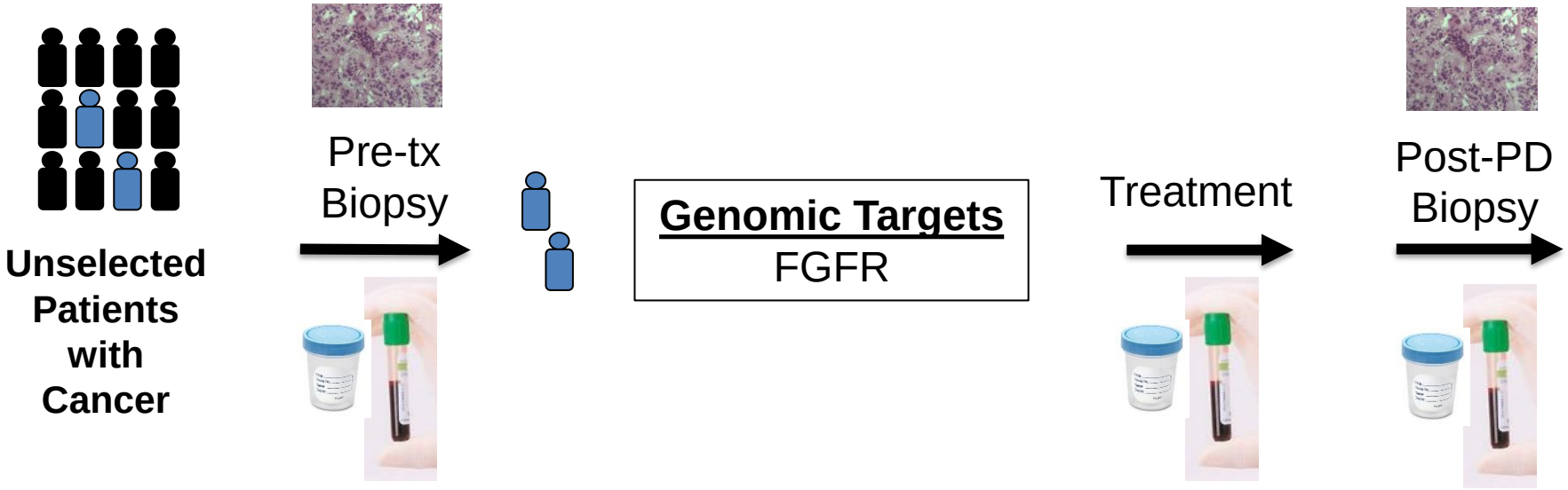
BCR-ABL (Leukemia) 1960 → IMATINIB 2001

BRAF (Melanoma) 2002 → VEMURAFENIB 2010

ALK (Lung) 2007 → CRIZOTINIB 2010

FGFR and **Trials** 2013 → 2015

Three FGFR inhibitor trials for patients with activating FGFR gene alterations

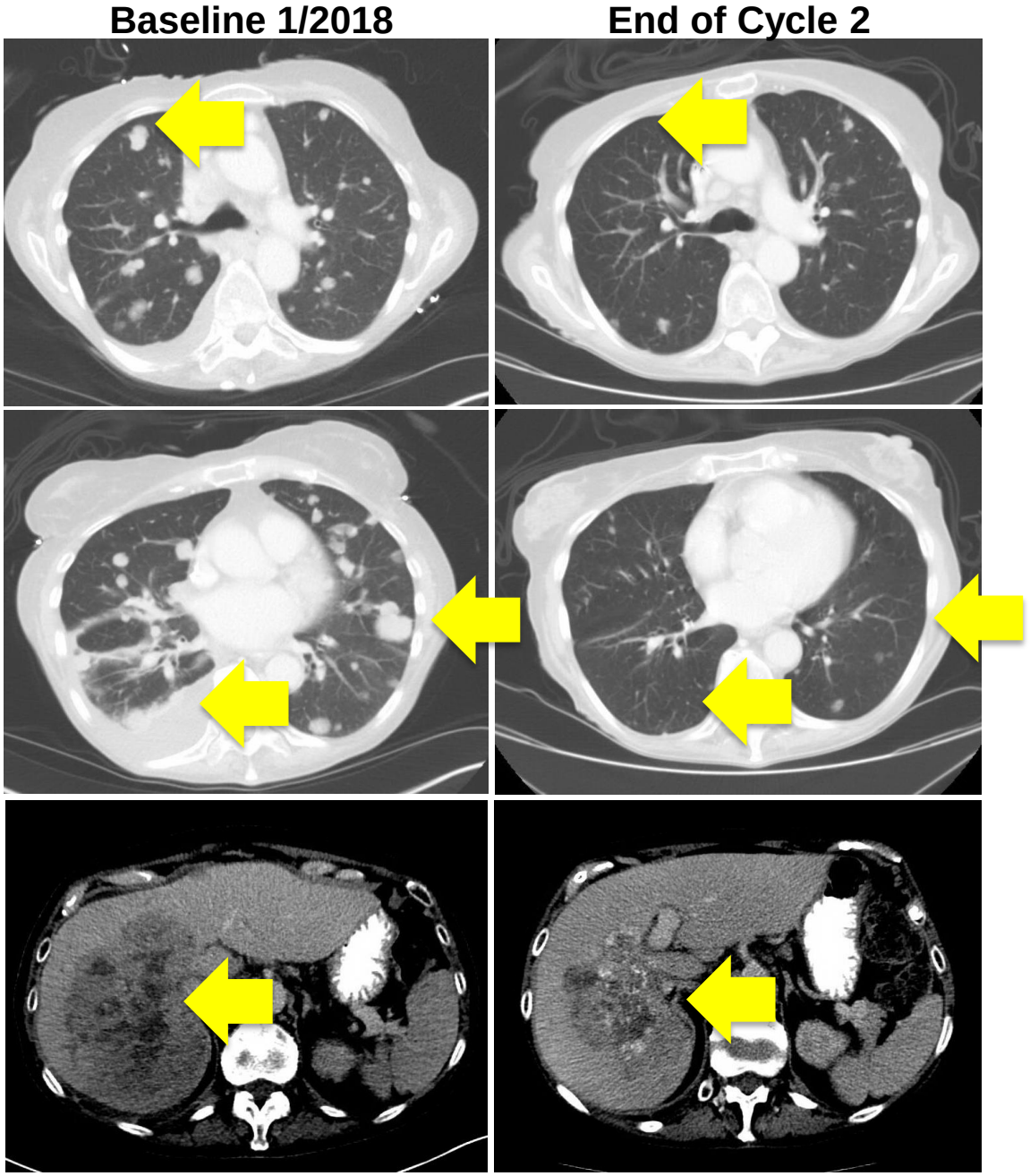


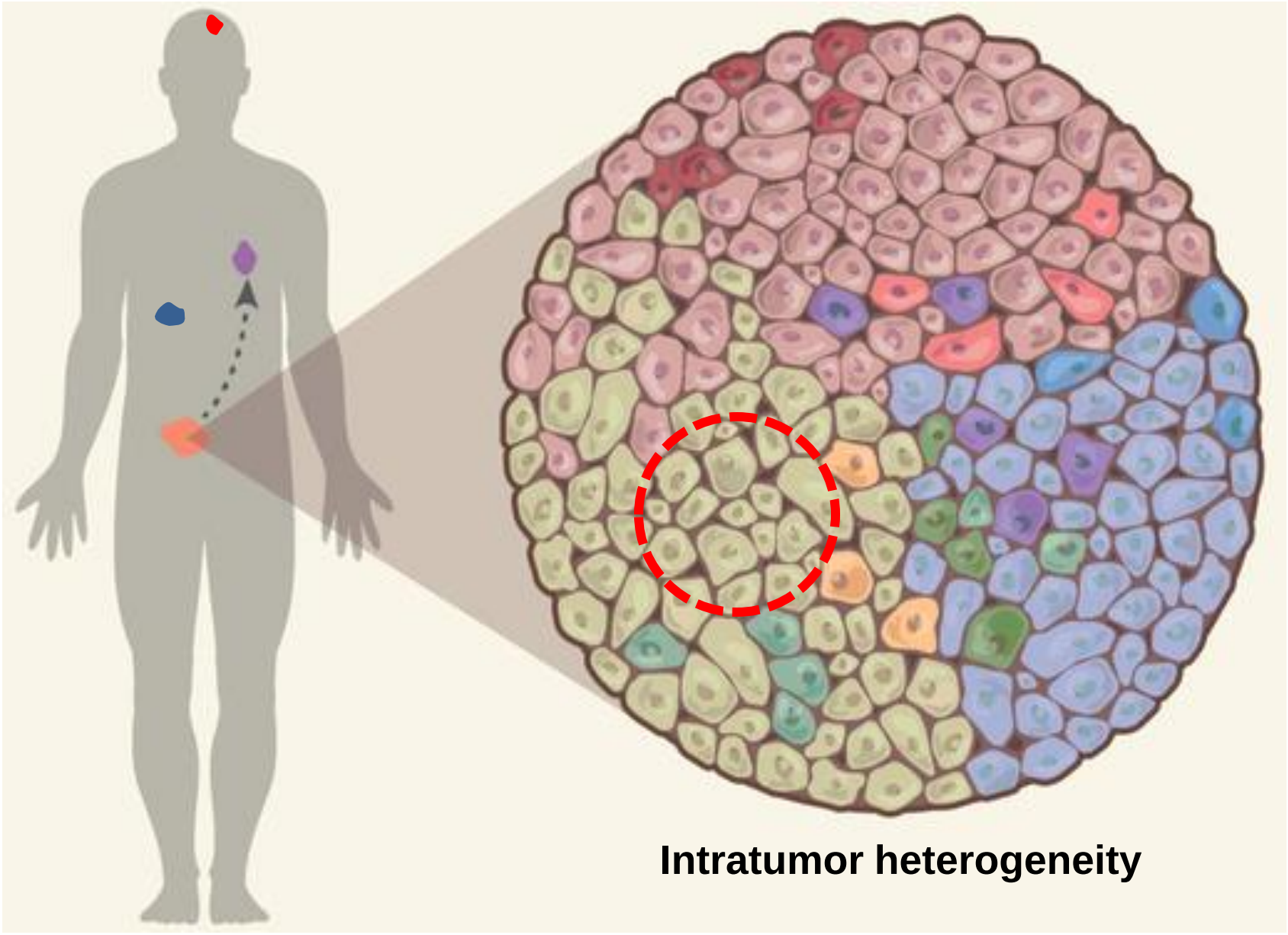
***1) Ponatinib** for **Any** Cancer with **FGFR** gene alterations*

***2) BGJ398** for **cholangiocarcinoma** with **FGFR** gene alterations*

***3) INCB054828** for **Any** Cancer with **FGFR** gene alterations*

Clinical response to FGFR inhibitor in patient with FGFR2 fusion-positive metastatic cholangiocarcinoma




Intratumor heterogeneity

Rapid Research Autopsy

Informed Consent

Transport to Morgue

Autopsy

Tissue Procurement

Return to Funeral Home

Genomics

Clinical Research Team

Hui-Zi Chen, MD, PhD
Melanie Krook, PhD
Julie Reeser, PhD
Michele Wing, PhD,FNP

Autopsy Team

Patricia Allenby, MD
Jen Sachire
Jakob Durakovic

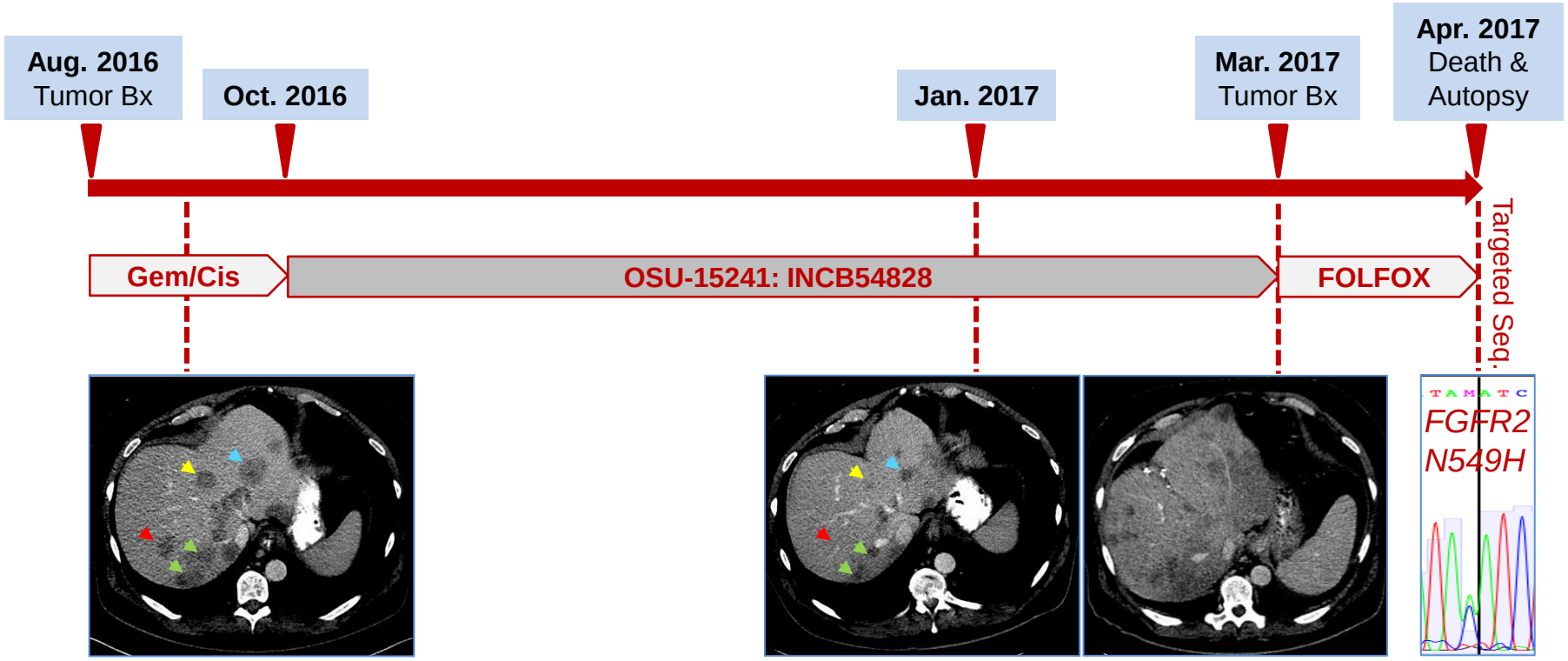
Tissue Procurement Team

Kelly Hamilton

- Tumor Heterogeneity
- Drug Resistance
- Patient Derived Xenografts

PELOTONIA

Acquired Resistance to INCB54828



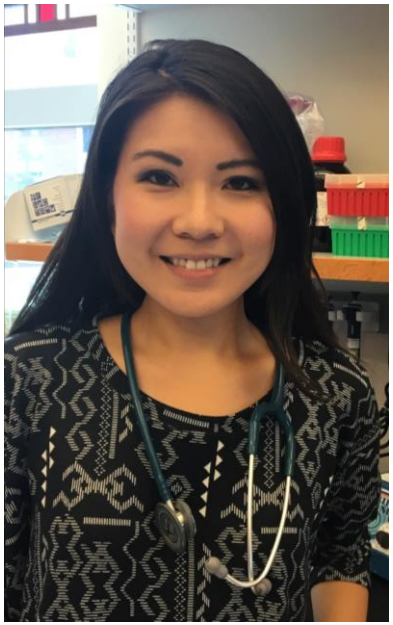
PELOTONIA

Summary:
Patients teaching us about gene fusions

- Novel FGFR fusions
- 3 FGFR inhibitor Trials
- Acquired Resistance
- Research Autopsy
- Tumor Heterogeneity in Cholangiocarcinoma

Melanie Krook, PhD
Postdoctoral Fellow
Cancer Biology

Melanie is studying mechanisms of resistance to FGFR inhibitors and how to overcome this resistance.



Hui-Zi Chen, MD, PhD
Medical Oncology Fellow
Medical Oncology

Hui-Zi is treating patients with FGFR inhibitors on trial and leading research autopsy

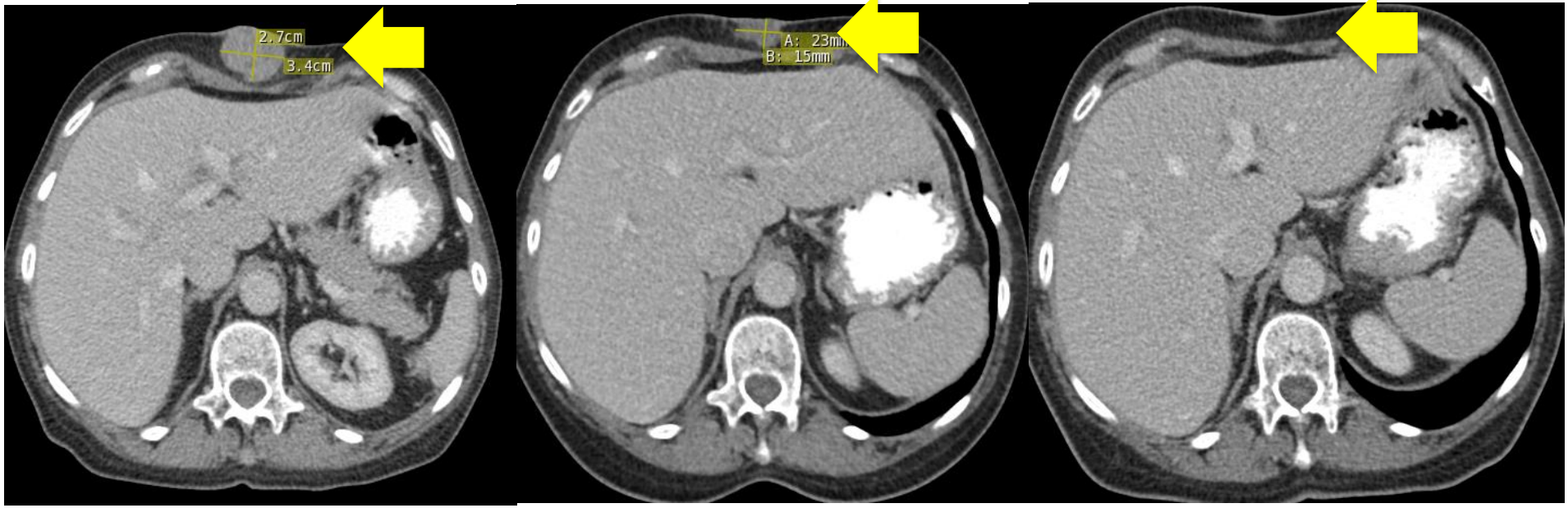
Outline and Goals

- **Precision cancer medicine**
  - **Gene fusions -> Targeted therapies (FGFR)**
  - ***Microsatellite instability -> Immunotherapy***
- **Data sharing networks**

Rhonda Ball

- Metastatic adenocarcinoma of unknown primary, summer of 2015.
- Radiation, chemotherapy, surgery
- Found to have MSI-H+ marker on her tumor.
- Started immunotherapy trial. Complete response.

7/25/2016 **9/12/2016** **10/28/2016**



Microsatellites are short, repeating DNA sequences

- 1-5 bp repeat, for 10-60 bp total

- Dispersed throughout the genome

- Repeat count must be preserved through repeated cell divisions
  - By DNA mismatch repair (MMR) system

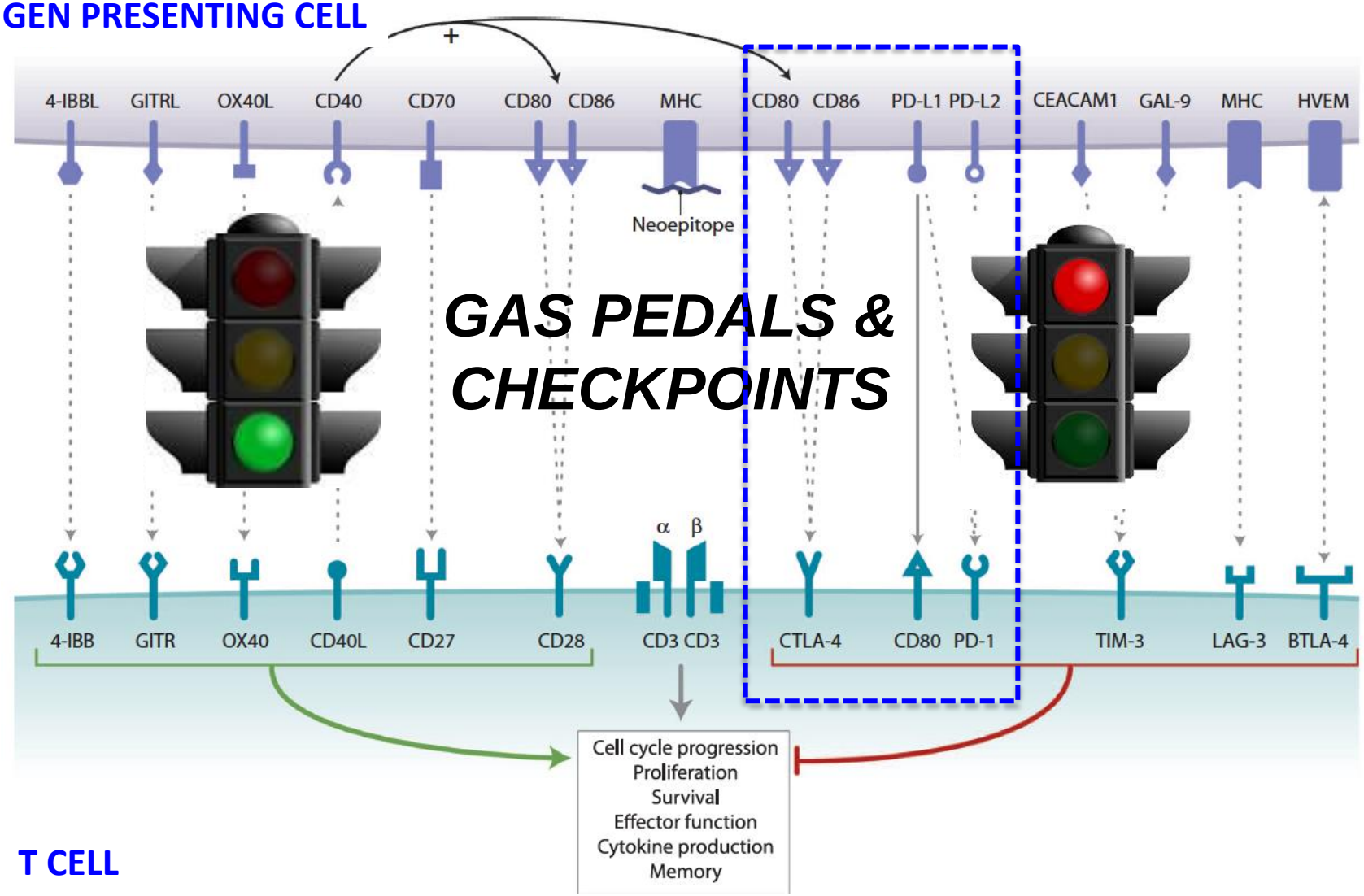
DNA repair deficiency leads to hypermutation

- Cancer cells with **deficient** DNA mismatch repair (MMR) system have lots of mutations

- **Hypermutated** cancer cells have resulting **Neo-antigens** that can be recognized by the immune system

- But the immune system needs a little help…

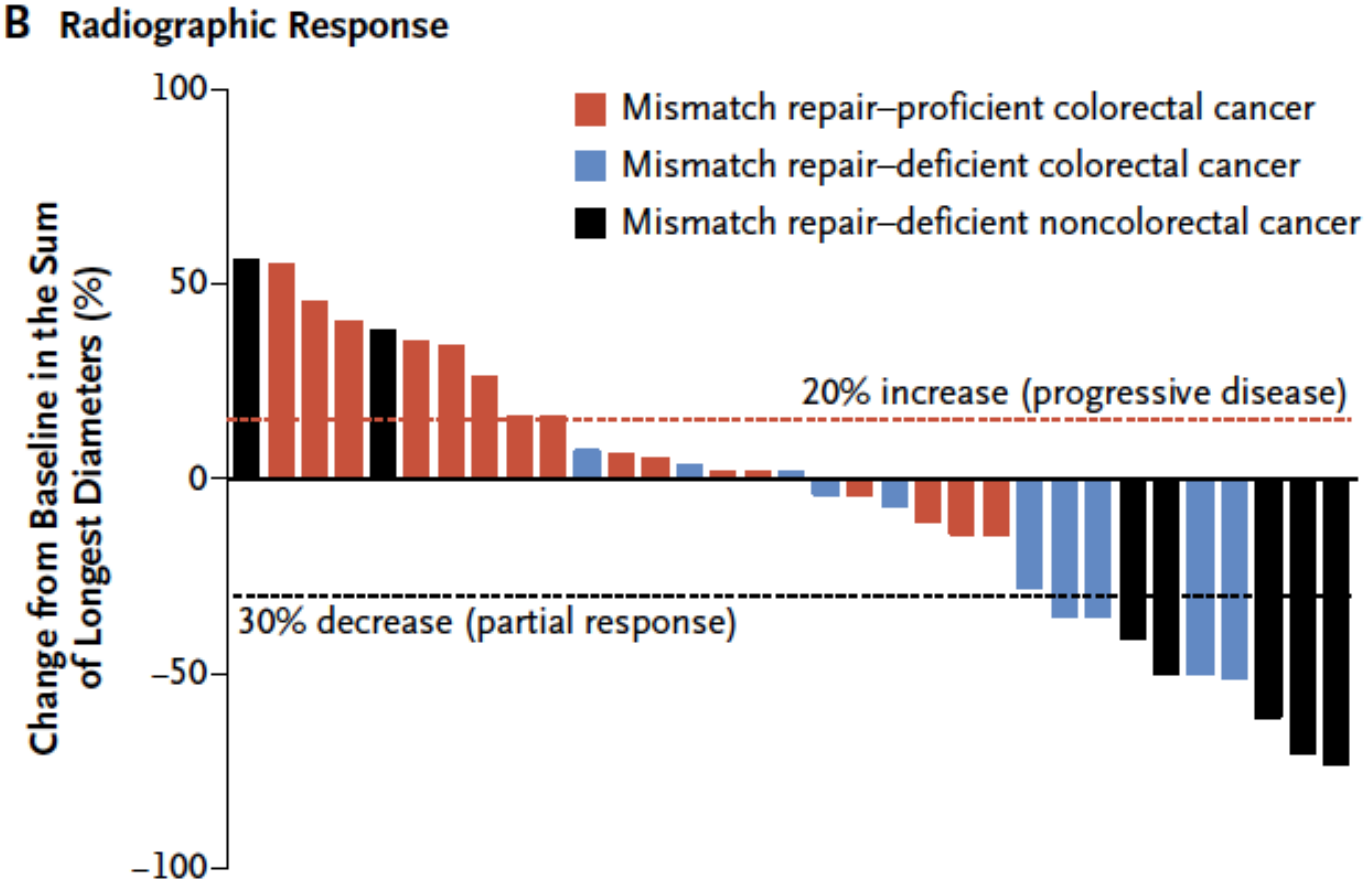
T cells have many gas pedal(s) and brake(s): Implications for cancer immunotherapy



Lesokhin et al, Science Translational Medicine 2015

PD-1 Blockade in Tumors with Mismatch-Repair Deficiency

D.T. Le, J.N. Uram, H. Wang, B.R. Bartlett, H. Kemberling, A.D. Eyring, A.D. Skora, B.S. Luber, N.S. Azad, D. Laheru, B. Biedrzycki, R.C. Donehower, A. Zaheer, G.A. Fisher, T.S. Crocenzi, J.J. Lee, S.M. Duffy, R.M. Goldberg, A. de la Chapelle, M. Koshiji, F. Bhaijee, T. Huebner, R.H. Hruban, L.D. Wood, N. Cuka, D.M. Pardoll, N. Papadopoulos, K.W. Kinzler, S. Zhou, T.C. Cornish, J.M. Taube, R.A. Anders, J.R. Eshleman, B. Vogelstein, and L.A. Diaz, Jr.



NEJM 2015

One of five clinical trials that helped lead to ….

FDA News Release

FDA approves first cancer treatment for any solid tumor with a specific genetic feature

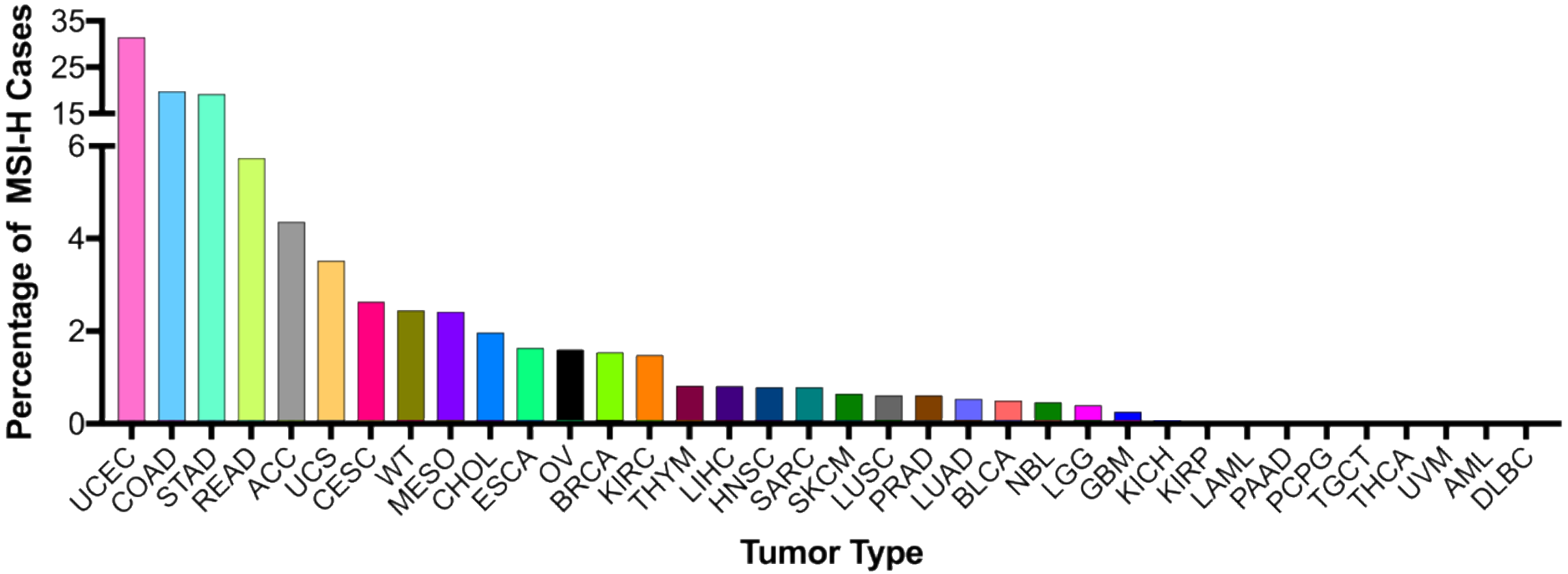
SHARE | TWEET | LINKEDIN | PIN IT | EMAIL | PRINT

For Immediate Release May 23, 2017

MSI: New questions

- Who else has the **marker MSI-H** ?
- How do we leverage **big data for Patients**?
- How do we **diagnose** it across different cancer types??
- What **novel therapies** can we offer them?

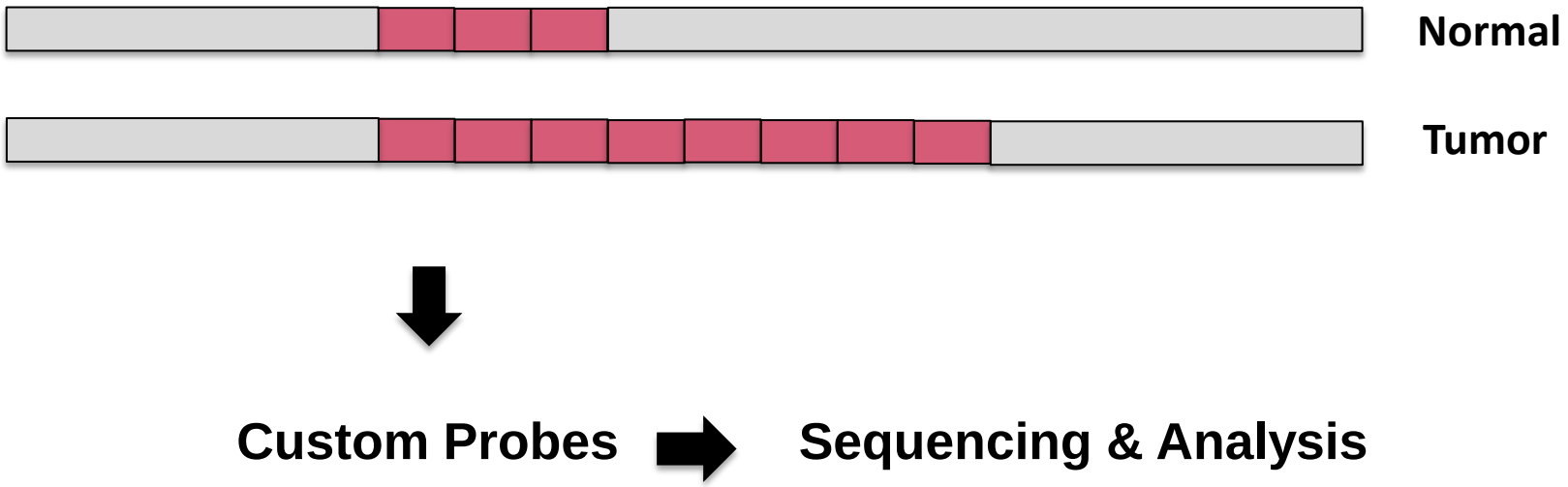
Landscape of Microsatellite Instability Across 11,000+ cancers



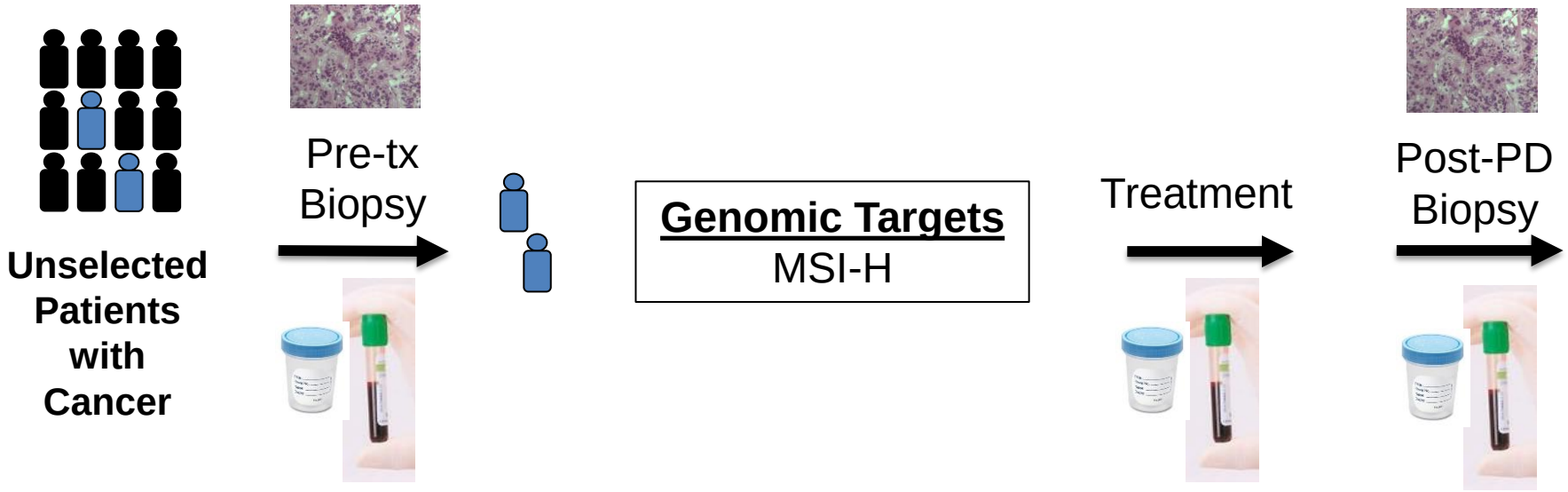
Bonneville, Krook, et al, JCO Precision Oncology, 2017

MSIDx

Next generation sequencing to detect MicroSatellite Instability-High (MSI-H)



Phase 2 Trial of Combination IDO-1 inhibitor and Pembrolizumab immunotherapy for any tumor with MSI-H



- ***Tumor:*** *Pretreatment and Post-treatment Tumor Biopsies, Research Autopsy (resistance)*
- ***Host:*** *Serial blood and urine (immune cells, circulating markers)*
- ***Extrinsic:*** *Stool Microbiota*

The James
THE OHIO STATE UNIVERSITY
COMPREHENSIVE CANCER CENTER

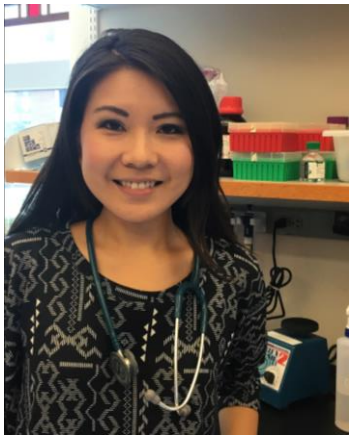
Novel Diagnostics and Therapy

Algorithm to Detect MSI-H → **Novel Diagnostic Test: MSIDx** → **Clinical Trial Immunotherapy**

Russell Bonneville
Graduate Student
Computational Biology

Michele Wing, PhD, FNP
Research Scientist
Cancer Molecular Diagnostics

Julie Reeser, PhD
Technical Director
Cancer Molecular Diagnostics



Hui-Zi Chen, MD, PhD
Medical Oncology Fellow
Medical Oncology

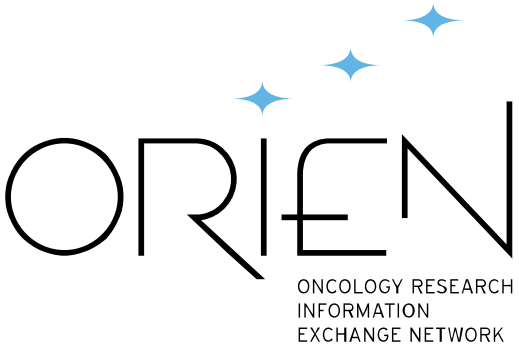
- Published Landscape of MSI-H marker across 39 Cancer Types (June 2017)
- Developed concept for pan-cancer test (“MSIDx”)
- UH2/UH3 funding for developing MSIDx (Sept 2017)
- New clinical trial for Immunotherapy

Outline and Goals

- **Precision cancer medicine**
  - **Gene fusions -> Targeted therapies (FGFR)**
  - ***Microsatellite instability -> Immunotherapy***
- **Data sharing networks**

What can we expect from advanced genomic testing for our patients?

- **~3%** will have a germline alteration that may confer **heritable risk**
- **~10%** will have an actionable genomic alteration that leads to **new therapy**



A National Cancer Center Alliance to integrate "Big Data" and Data Sharing For Cancer Research and Care

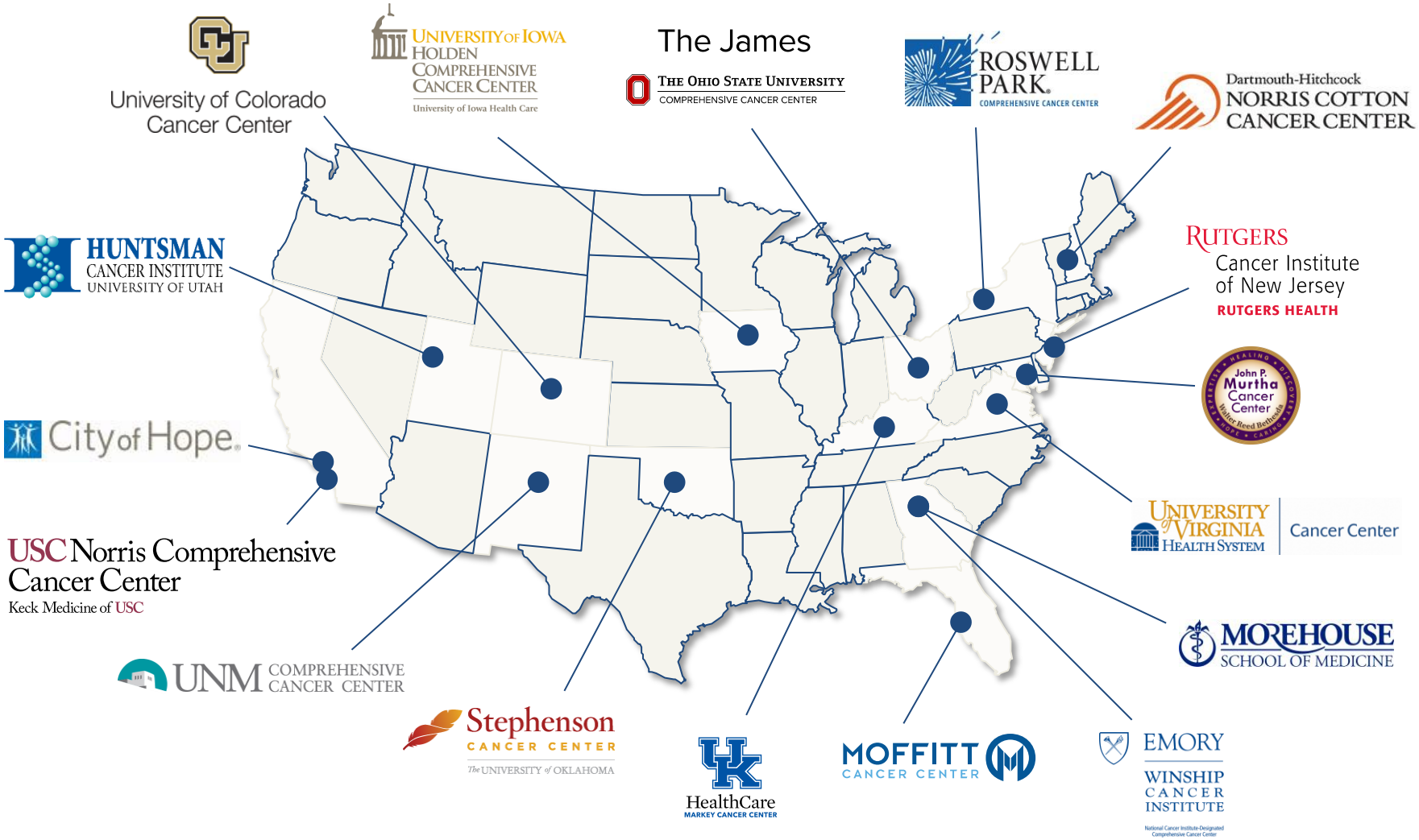
MOFFITT CANCER CENTER

The James
THE OHIO STATE UNIVERSITY
COMPREHENSIVE CANCER CENTER

Mission:

Accelerating cancer discovery and delivering hope through collaborative learning and partnerships

Oncology Research Information Exchange Network (ORIEN)



February 2018

Oncology Research Information Exchange Network (ORIEN): Investigator Initiated Trials for Marker+ patients

- ***MSI-H Hypermutated***
- ***FGFR fusions***
- ***ALK and ROS1 fusions***

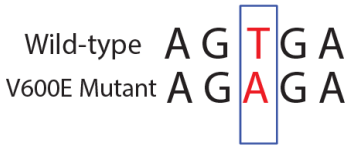
Analysis of Whole Exome and RNAseq → MARKER+ Candidates? → CLIA Testing → Trial Therapy → Drug Resistance

Looking Ahead to Novel Diagnostics and Targets

OSU-IGNITE (DNA)

Point Mutations and InDel's

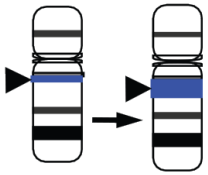
- Missense
- Nonsense
- Frameshift



BRAF

Copy Number Alterations

- Amplifications
- Deletions
- LOH

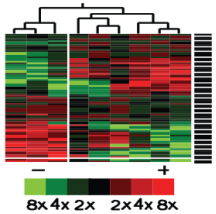


HER2

OSU-SpARKFuse (RNA)

Gene Expression

- Outlier Expression
- Signatures
- Pathways



Structural Rearrangements

- Translocations
- Gene Fusions
- Inversions

EML4-ALK

Novel Biomarkers and Diagnostics

OSU Undisclosed	OSU MSIDx	OSU Microbiome	OSU T cell
Methylation	MSI-H	?	?
⇩	⇩	⇩	⇩
Undisclosed	Immunotherapy	Diet?	Combination Immunotherapy

Summary

- Patients first

Examples:

- Biomarkers to predict response to therapy
- Novel Diagnostic tests
- Therapies in clinical trials

- Team work
- Data Sharing Networks
- Training

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Thank you!

Questions?

Molecularly Matched Therapeutic Trials at OSUCCC-James *(Examples)*

Alteration	**Trials**
FGFR alterations	FGFR inhibitors (3)
RET alterations	RET (3)
ALK alterations	ALK (3+)
ROS1 alterations	ROS1 (2)
NTRK alterations	NTRK (1)
MYC alterations	Bromodomain inhibitors (2)
BRCAness	PARP inhibitors (1+)
MSI-H	PD1 inhibitors, Multiple