



Understanding the Concept of “Precision Oncology”

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Department of Surgery

Moore's UCSD Cancer Center

a Systemic chemotherapy



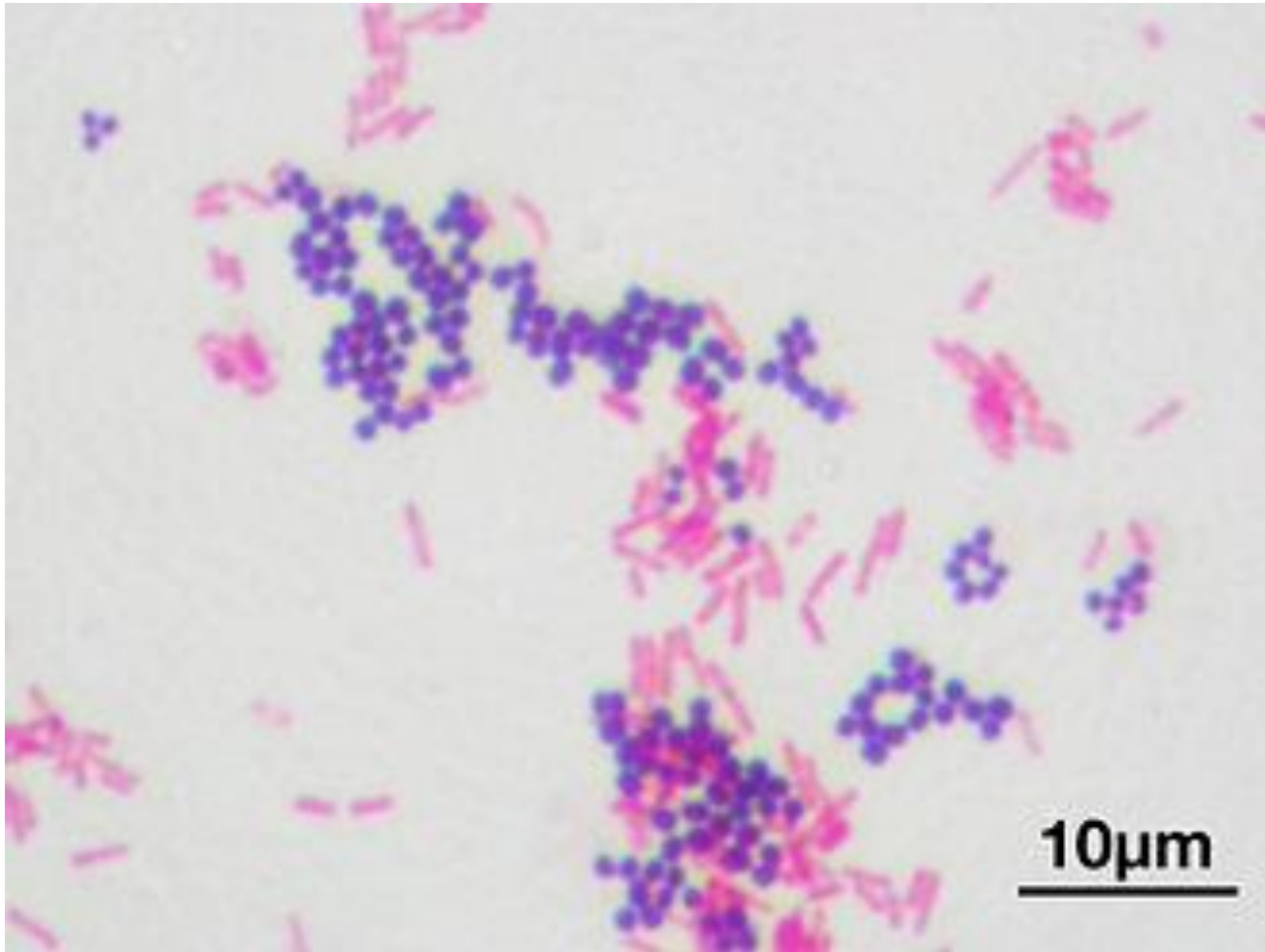
b Targeted monotherapy



c Targeted combination therapy



1884



Hans Christian Gram, Berlin, 1884.

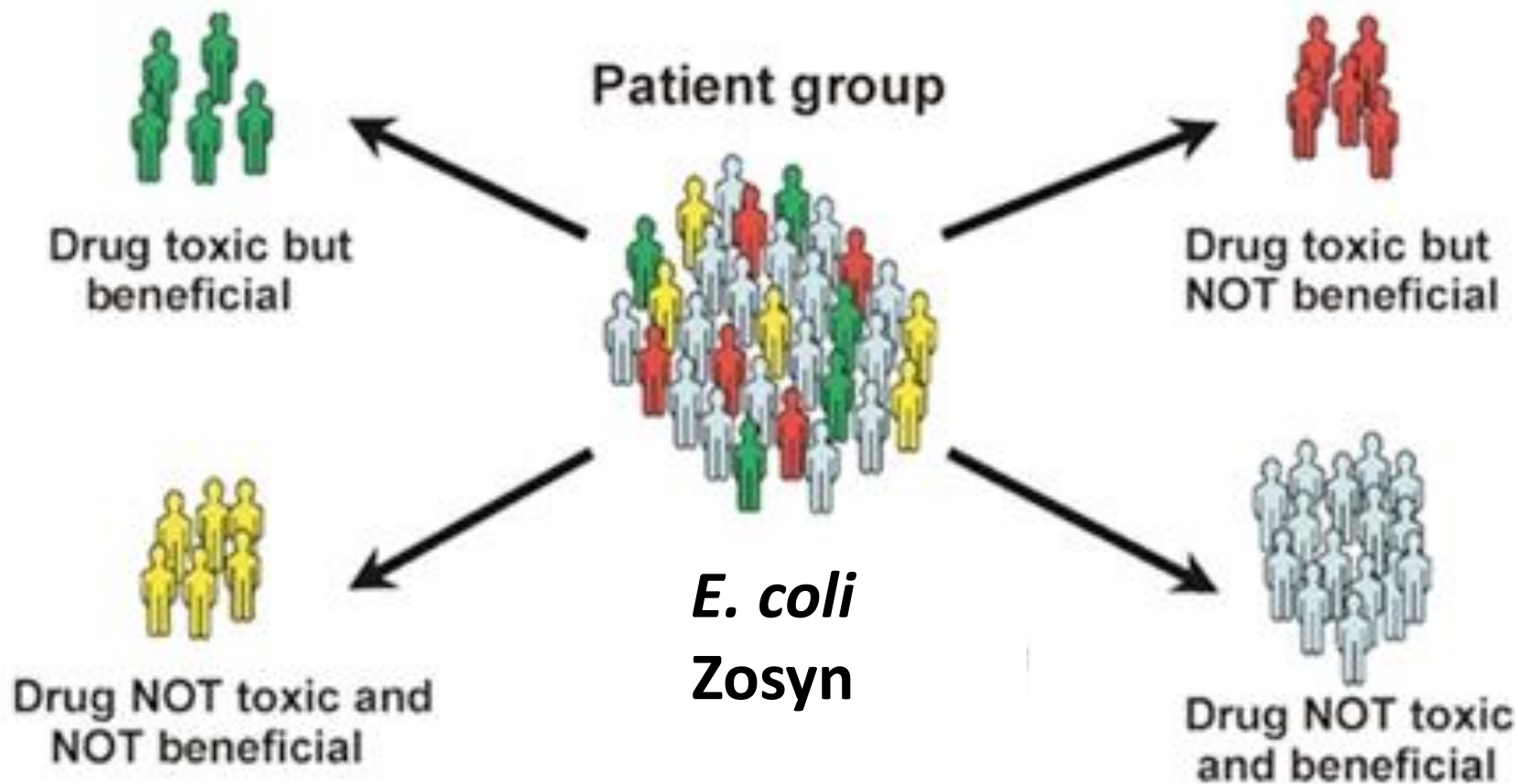
E. Coli in 1885



Hans Christian Gram, Berlin, 1884.




























Anything else to know?

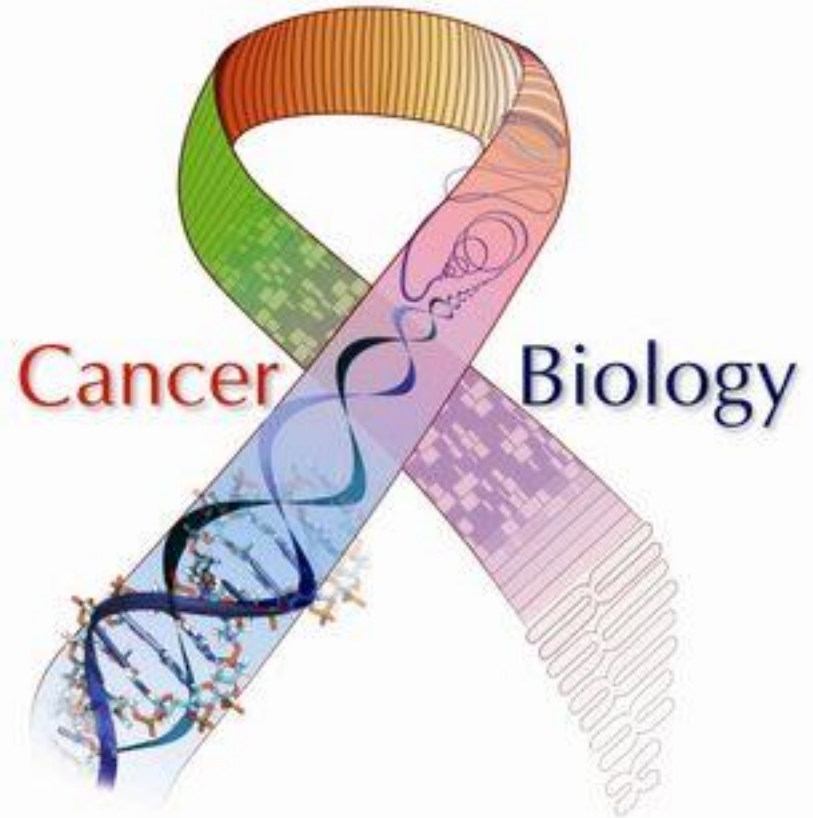
<i>ESCHERICIA COLI</i>
AMPICILLIN
AMPICILLIN/SULBACTAM
CEFAZOLIN
CEFEPIME
CEFTAZIDIME
CEFTRIAZONE
CEFUROXIME SODIUM
CIPROFLOXACIN
COLISTIN
ERTAPENEM
GENTAMICIN
PIPERACILLIN/AZOBACTAM
TIGECYCLINE
TOBRAMYCIN
TRIMETHOPRIM/SULFAMETHOXAZOLE



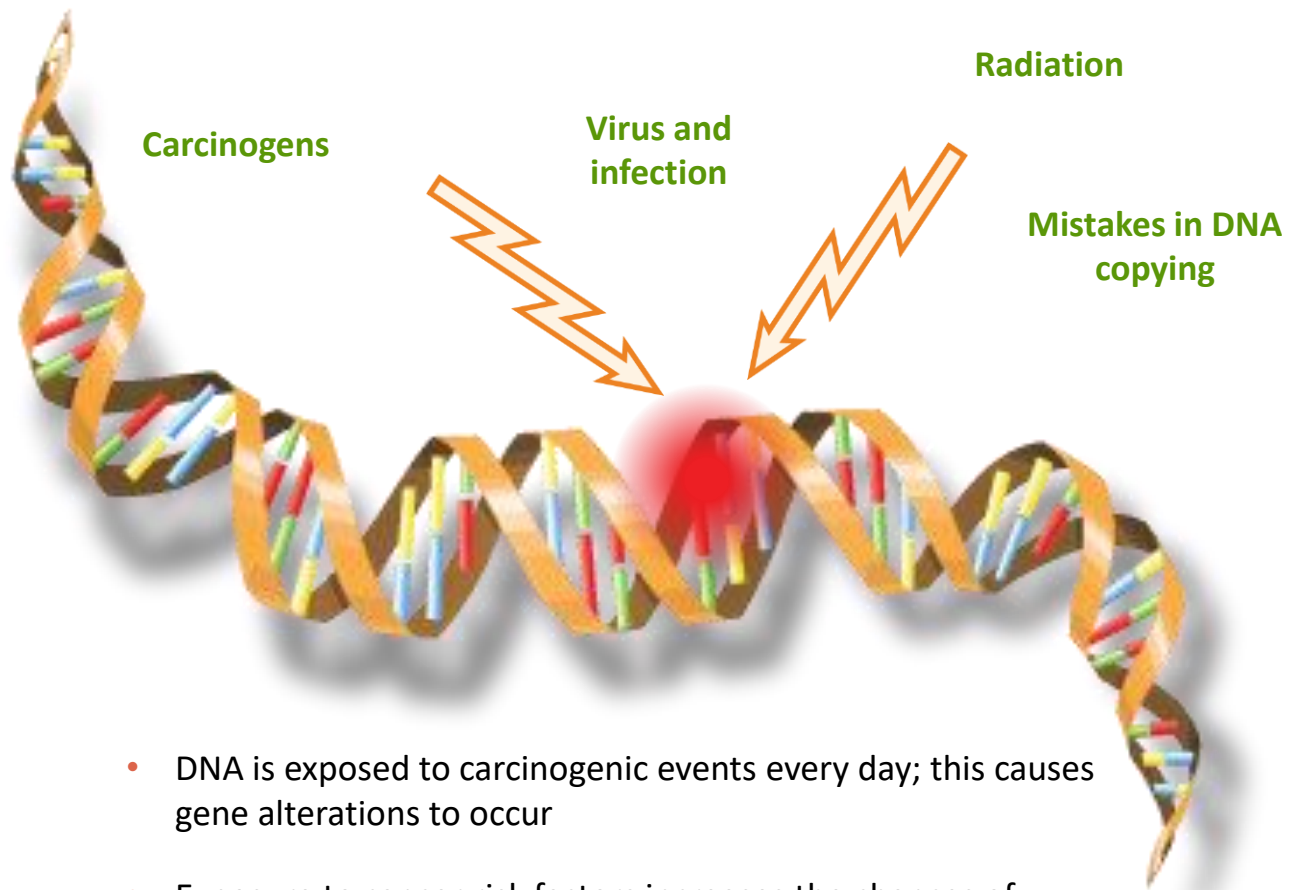
Why is Personalizing Cancer Care Becoming Important?

Histology Agnostic

 All Cancers Lavender	 Kidney Cancer Orange	 Pancreatic Cancer Purple
 Bladder Cancer Yellow	 Leiomyosarcoma Purple	 Prostate Cancer Light Blue
 Brain Cancer Gray	 Leukemia Orange	 Sarcoma/Bone Cancer Yellow
 Breast Cancer Pink	 Liver Cancer Emerald	 Stomach Cancer Periwinkle
 Cervical Cancer Teal/White	 Lung Cancer White	 Testicular Cancer Orchid
 Childhood Cancer Gold	 Lymphoma Lime	 Thyroid Cancer Teal/Pink/Blue
 Colon Cancer Dark Blue	 Melanoma Black	 Uterine Cancer Peach
 Esophageal Cancer Periwinkle	 Multiple Myeloma Burgundy	 Honors Caregivers Plum
 Head/Neck Cancer Burgundy/Ivory	 Ovarian Cancer Teal	 Printable PDF Color Chart

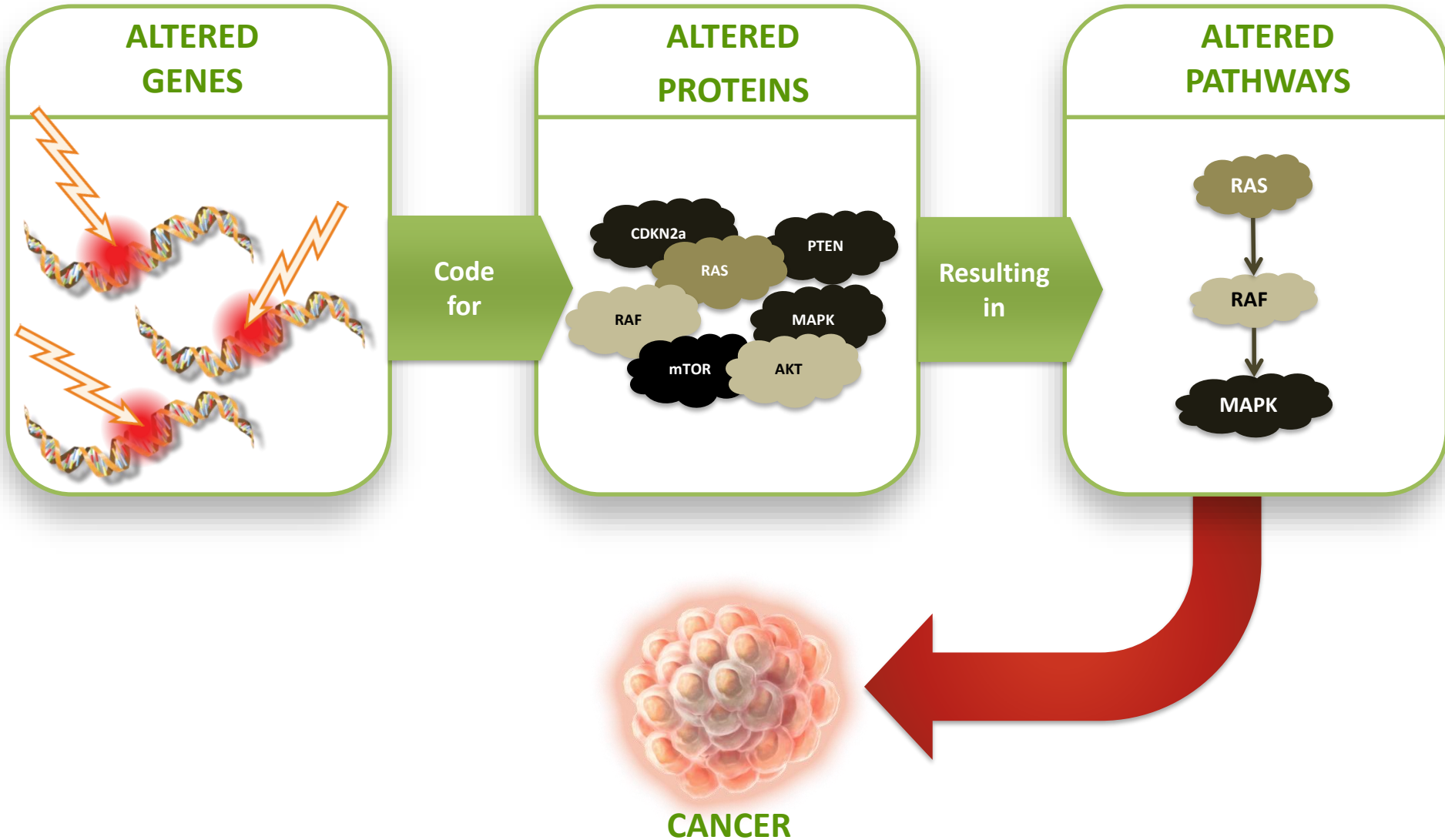


Cancer is a Disease of the Genome

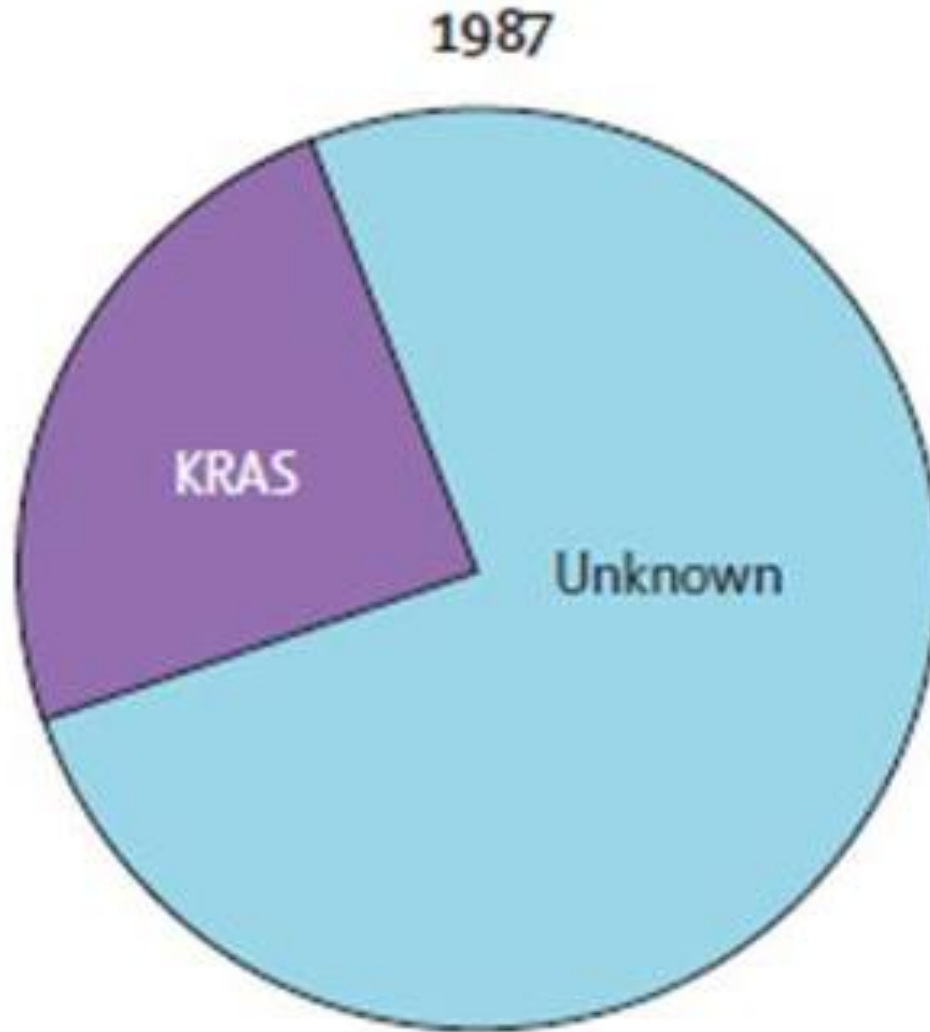


- DNA is exposed to carcinogenic events every day; this causes gene alterations to occur
- Exposure to cancer risk factors increases the chances of gene alterations

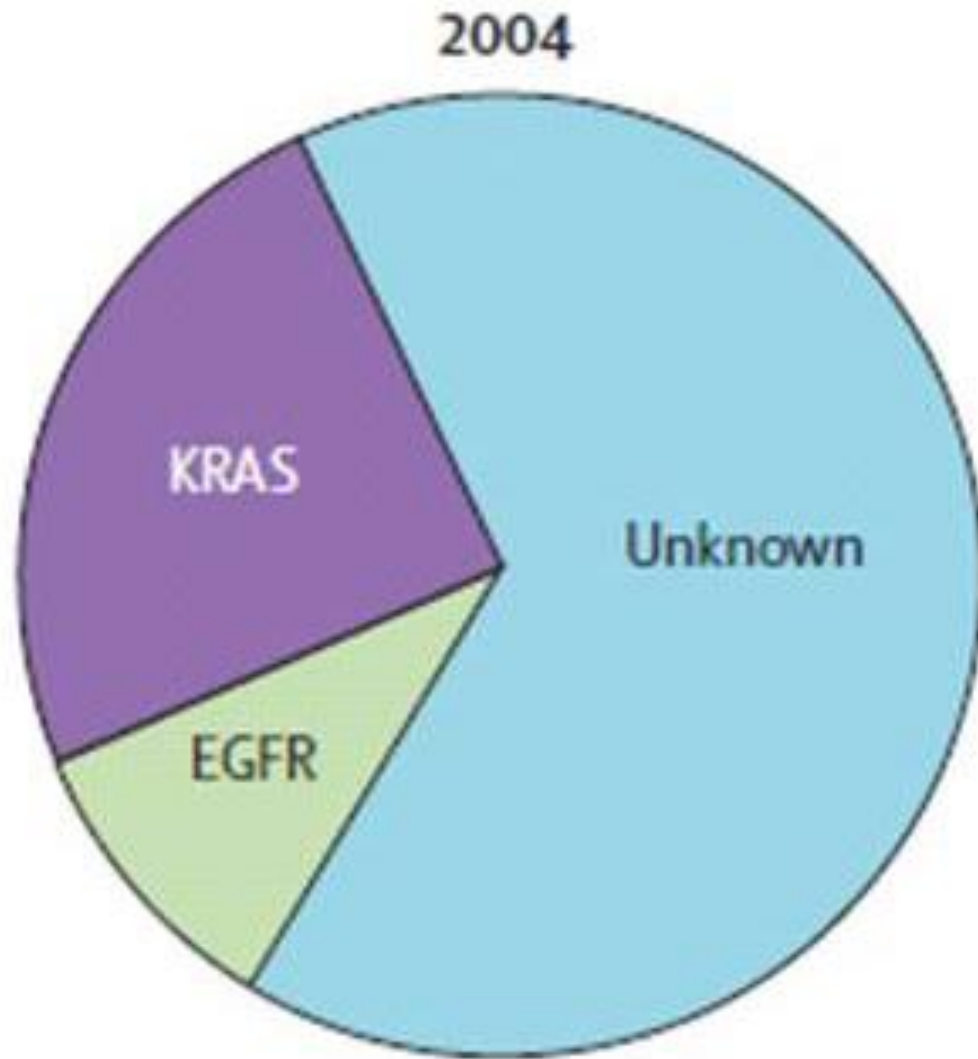
How Gene Alterations Can Cause Cancer



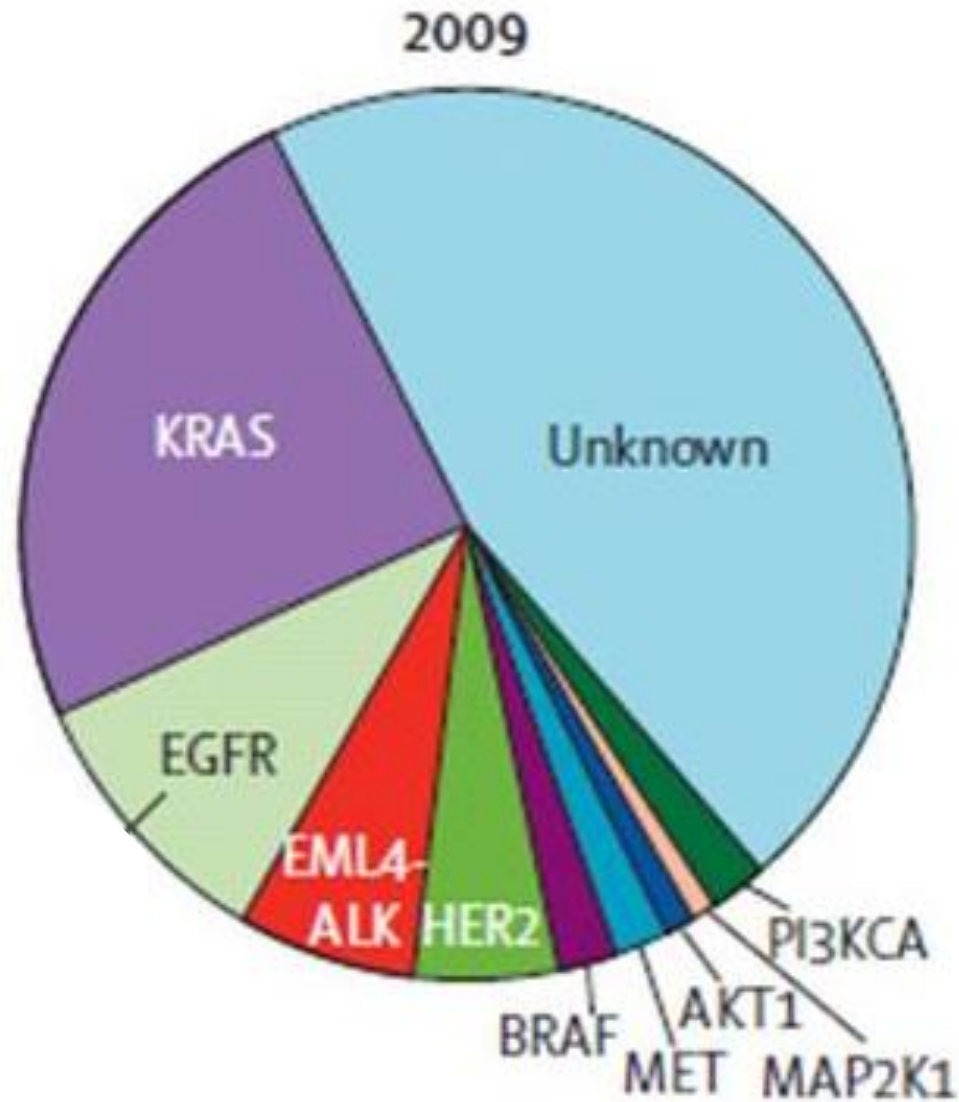
Lung Cancer



Changing Paradigms

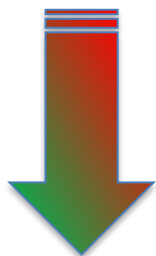


Changing Paradigms



Analysis of 85,000 Patients in Phase I/II Clinical Trials

Worst outcome



Best outcome

	POOLED Analysis			Meta-analysis		
<i>ARMS type</i>	<i>RR (%)</i>	<i>PFS (mos)</i>	<i>OS (mos)</i>	<i>RR (%)</i>	<i>PFS (mos)</i>	<i>OS (mos)</i>
Non-precision targeted	4	2.6	8.7	7.5	2.5	8.3
Cytotoxic	12	3.3	9.4	16.1	3.3	9.3
Precision targeted	30	6.9	15.9	31.3	6.1	13.7

Schwaederle et al., *JCO*, 2015.


Jardim et al., *JNCI*, 2015.

Schwaederle et al., *JAMA Oncology*, 2016.



Worldwide innovative networking
in personalized cancer medicine

SHIVA

 Molecularly targeted therapy based on tumour molecular profiling versus conventional therapy for advanced cancer (SHIVA): a multicentre, open-label, proof-of-concept, randomised, controlled phase 2 trial

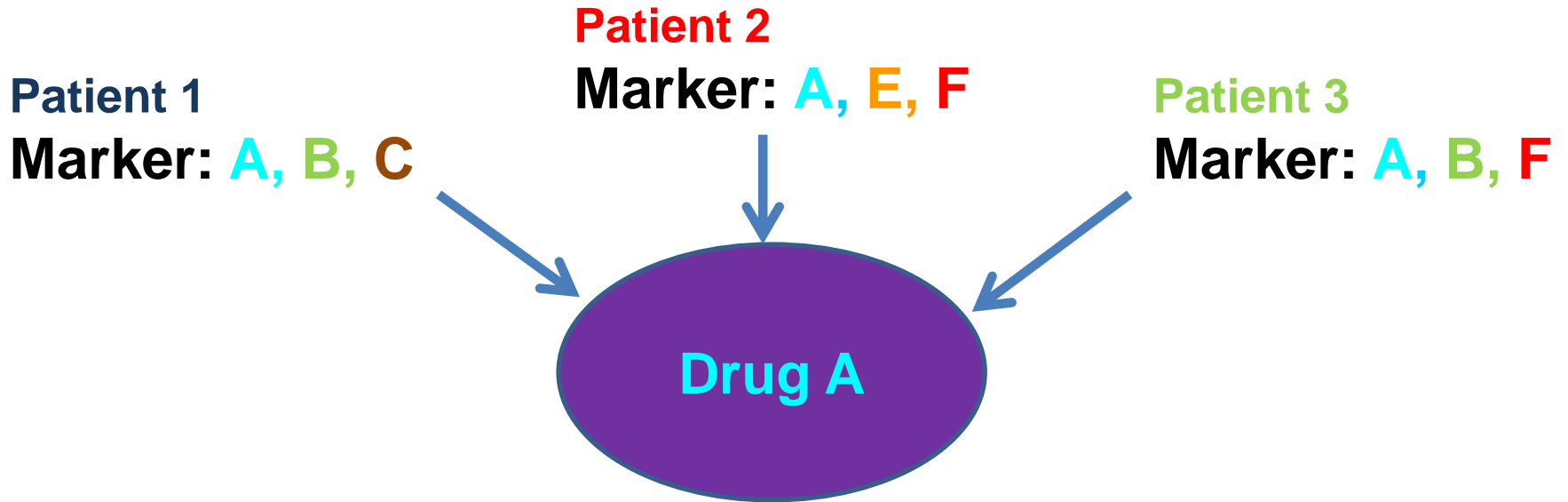
IMPACT



Precision Oncology Trials



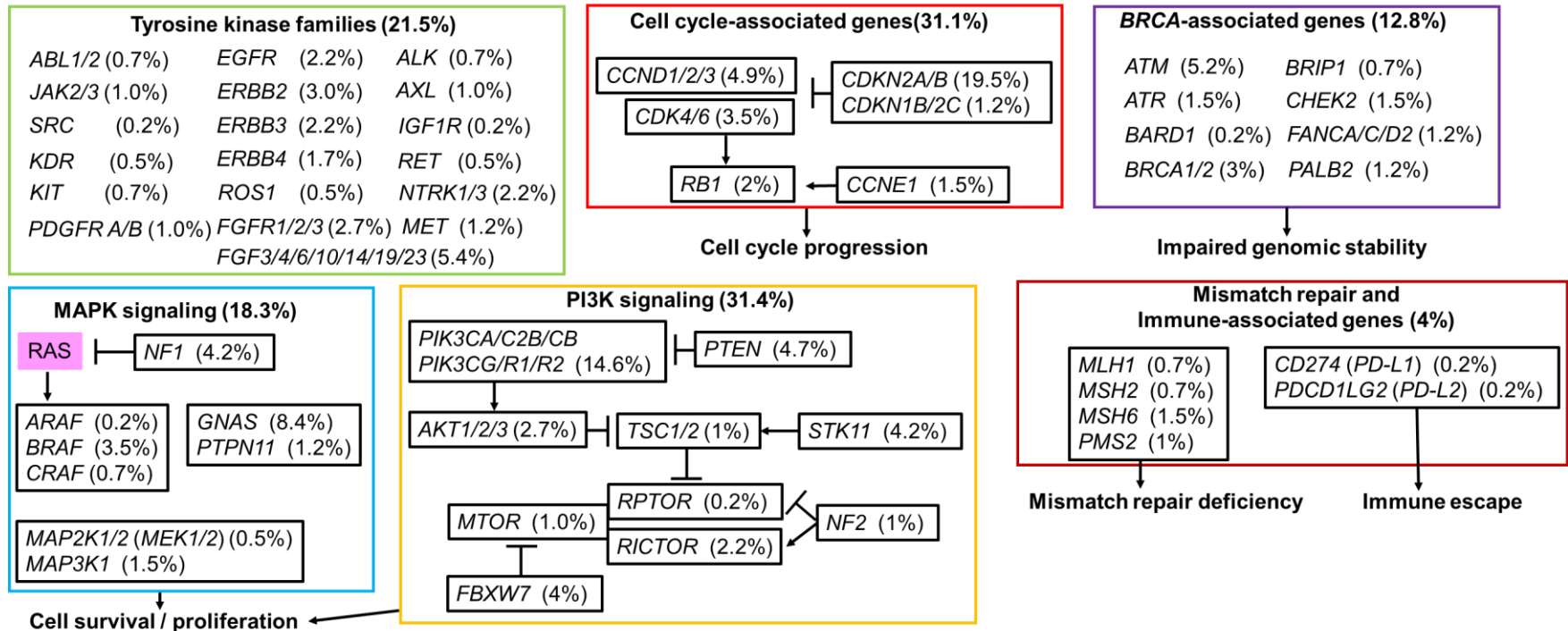
Drug-Centric (Traditional Precision Trials)



Strategy: Find 1 common feature between patients and treat with the same drug

Co-altered Oncogenic Pathways Associated with *RAS* Alterations

1,526 Patients



Challenges to Targeted Therapy Approach

1

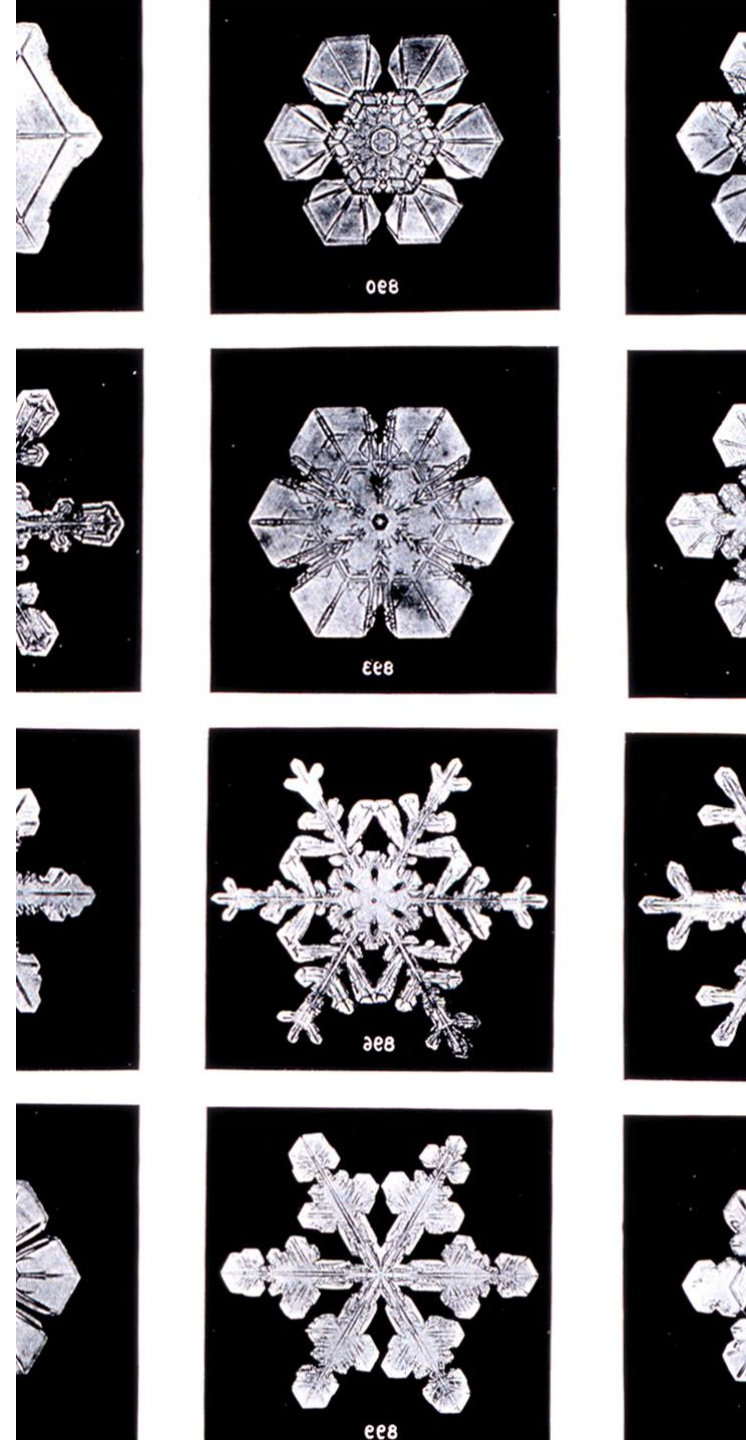
Malignant Snowflakes

2

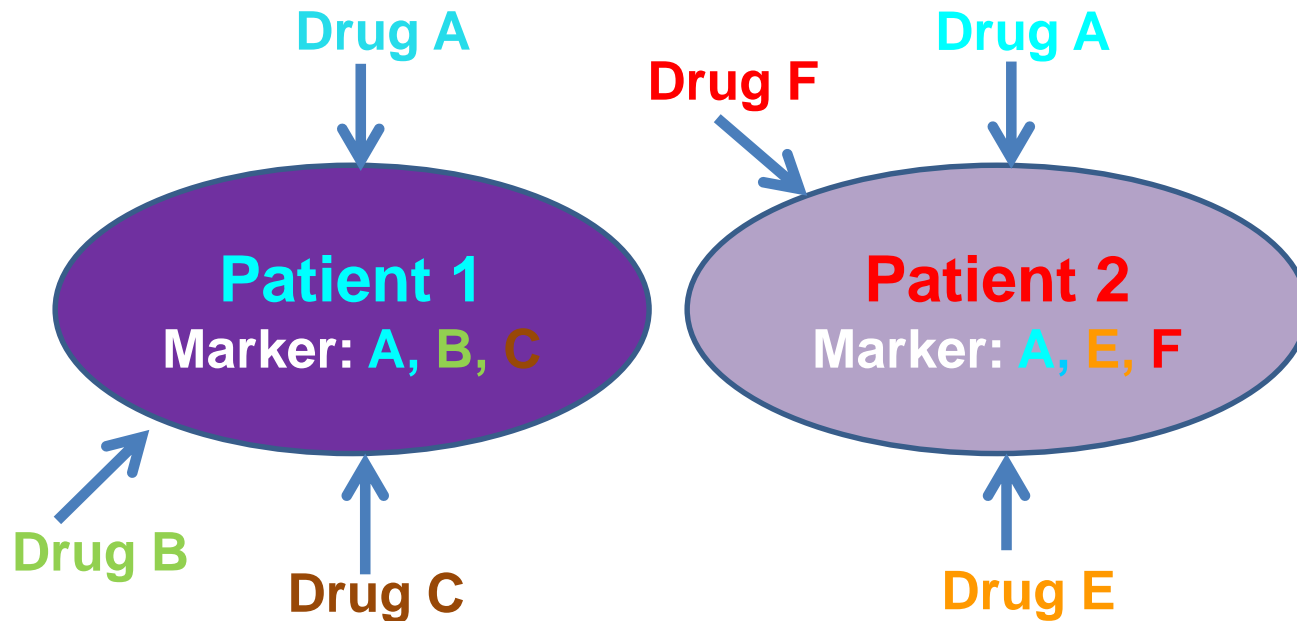
Co-genomic Alterations

3

Low Matching Rates



Patient-Centric: Personalized and Precision (N-of-1 Trial)



Strategy: Molecular and immune marker matching for each patient with customized combination therapy

I-PREDICT

Investigation of Profile-Related
Evidence Determining
Individualized Cancer Therapy



Razelle Kurzrock



Jason Sicklick

***Feasibility Study In Patients with Incurable Malignancies:
Treatment Naïve and Previously Treated Patients with Advanced Cancers***

Activation Date: February 13, 2015

Consented: $N = 435$ (as of May 1, 2019)

Treatment Decisions Guided by:

FoundationOne (Heme), Foundation ACT (ct DNA), PD-L1 IHC,
Tumor Mutational Burden (TMB), Microsatellite (MS) Status

Study Population

2014 National Cancer Database	Stage III 2-yr Mortality	Stage IV 2-yr Mortality
Gallbladder	89.5%	94.8%
Pancreas*	86.5%	93.3%
Liver	83.0%	93.3%
Intrahepatic bile duct	79.1%	92.8%
Esophagus	70.6%	90.3%
Bile duct (other)	70.5%	92.2%
Lung, Bronchus - Non small cell carcinoma	65.3%	88.7%
Stomach	63.9%	90.0%
Small intestine	57.1%	70.7%
Ovary	35.2%	60.8%
Urinary*	34.2%	69.9%
Soft tissue sarcoma including heart	31.9%	72.0%
Melanoma	24.1%	77.8%
Head and Neck*	21.9%	43.9%
Breast*	14.2%	52.1%
Colorectal	13.4%	58.6%

* UCSD-specific data; others are all NCDB cases

Matching Score

$$\frac{\text{\# Alterations Targeted}}{\text{\#Total Alterations}} = \text{Matching Score (\%)}$$

Examples:

*BRCA2 N319fs*8* → Carboplatin

PIK3R1 splice site 1300-11_1308del20 and *PTEN V45fs*7* → Everolimus

3/3 = 100% Matching Score

*BRCA2 N319fs*8* → Cisplatin (Gemcitabine)

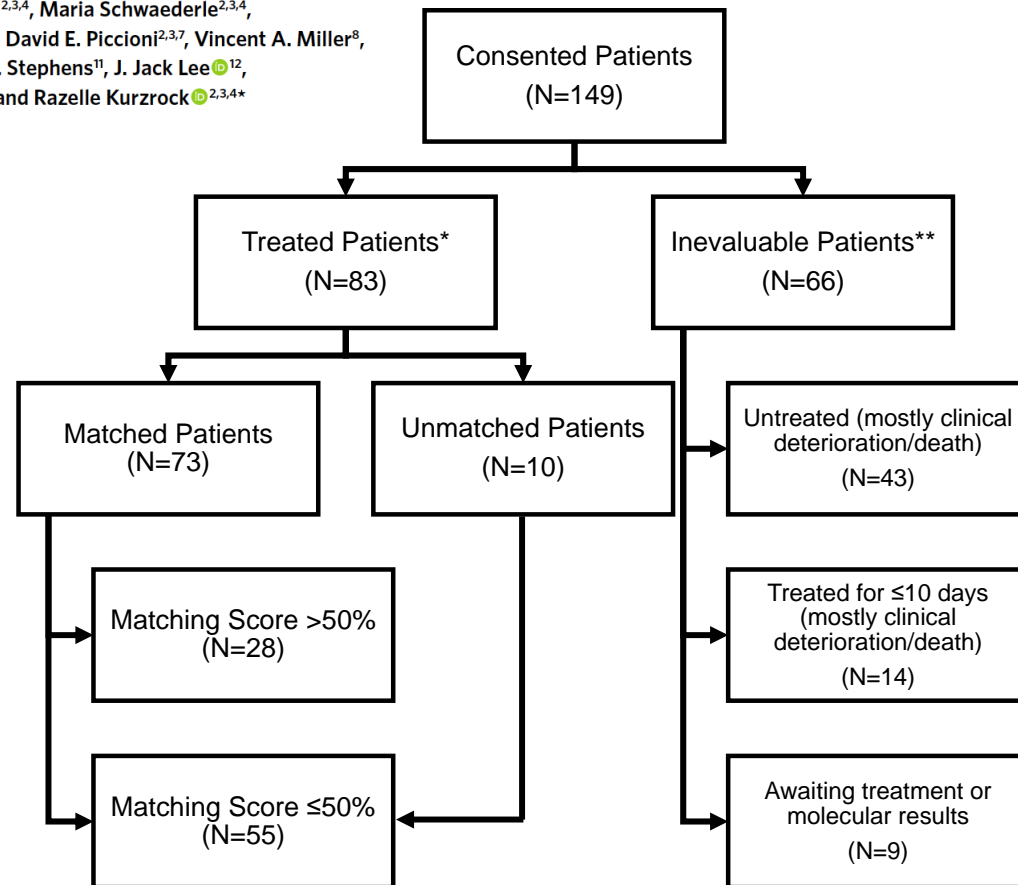
PIK3R1 splice site 1300-11_1308del20 and *PTEN V45fs*7*

1/3 = 33% Matching Score

Wheler *et al.*, Cancer Therapy Directed by Comprehensive Genomic Profiling: A Single Center Study. *Cancer Research*. 2016.

Molecular profiling of cancer patients enables personalized combination therapy: the I-PREDICT study

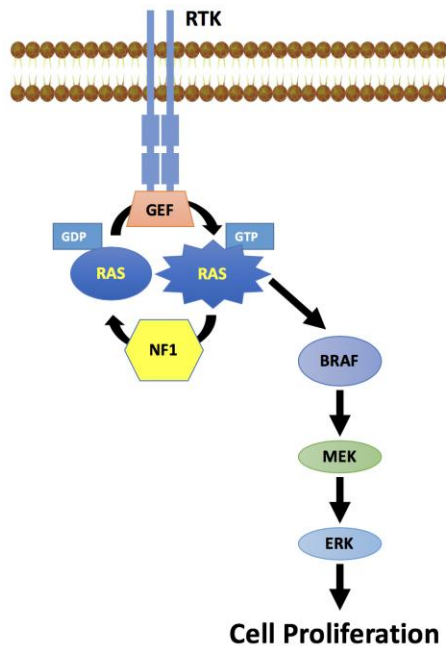
Jason K. Sicklick^{1,2,3*}, Shumei Kato^{2,3,4}, Ryosuke Okamura^{2,3,4}, Maria Schwaederle^{2,3,4}, Michael E. Hahn⁵, Casey B. Williams⁶, Pradip De⁶, Amy Krie⁶, David E. Piccioni^{2,3,7}, Vincent A. Miller⁸, Jeffrey S. Ross^{8,9}, Adam Benson¹⁰, Jennifer Webster⁸, Philip J. Stephens¹¹, J. Jack Lee¹², Paul T. Fanta^{2,3,4}, Scott M. Lippman^{2,3,4}, Brian Leyland-Jones⁶ and Razelle Kurzrock^{2,3,4*}



68 year old man with gastrointestinal stromal tumor (GIST)

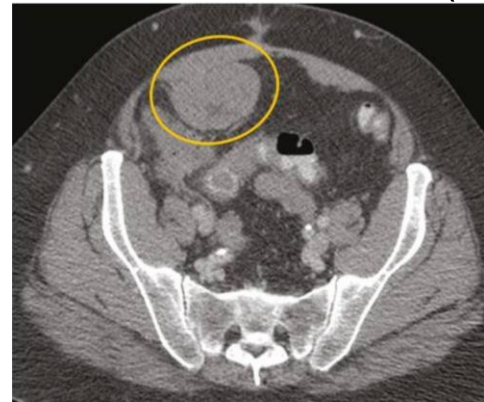
Tissue NGS (at initial diagnosis in 2007)

- *BRAF* V600E



Treatment

- Dabrafenib (GSK2118436)



Baseline

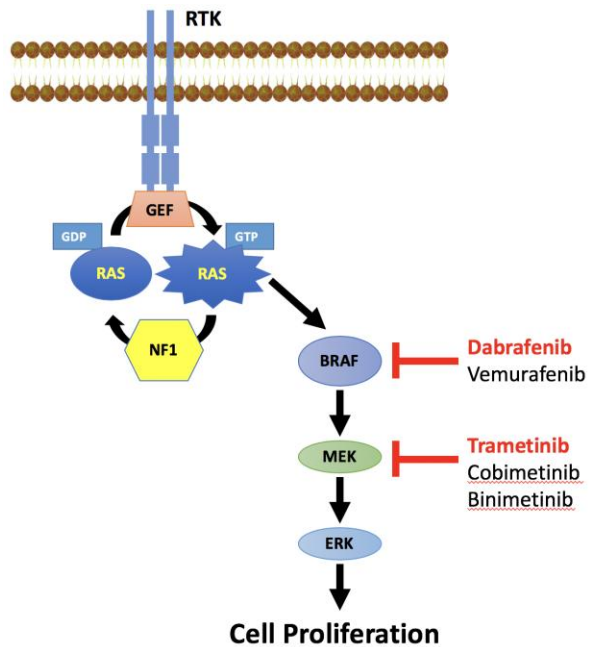


Week 24

Fallchook et al., *Oncotarget* 2013.

68 year old man with GIST

Progression

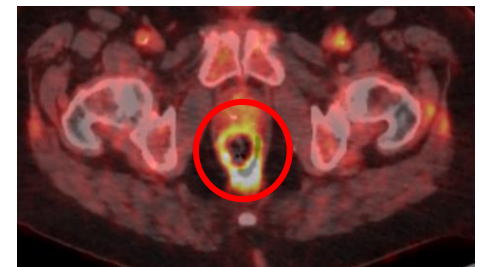
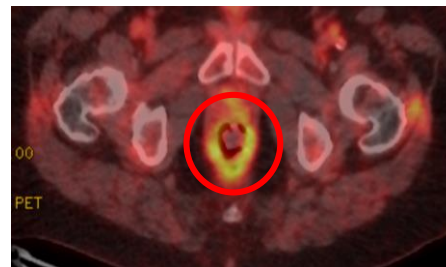
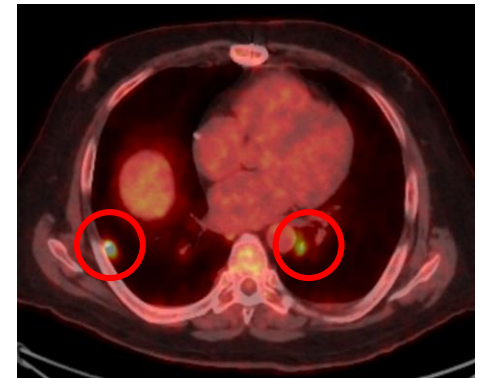
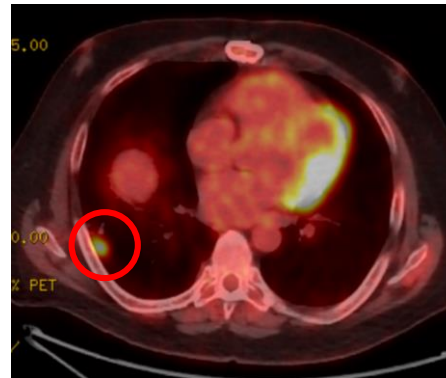


Dabrafenib + Trametinib

2/7/2018

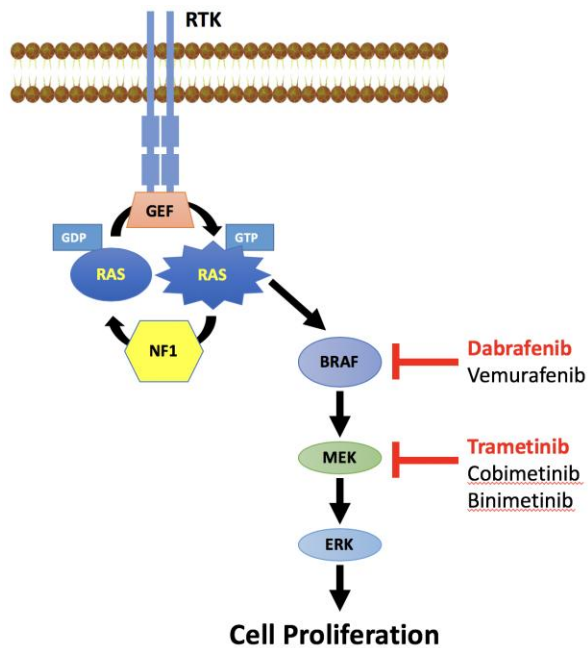


4/10/2018



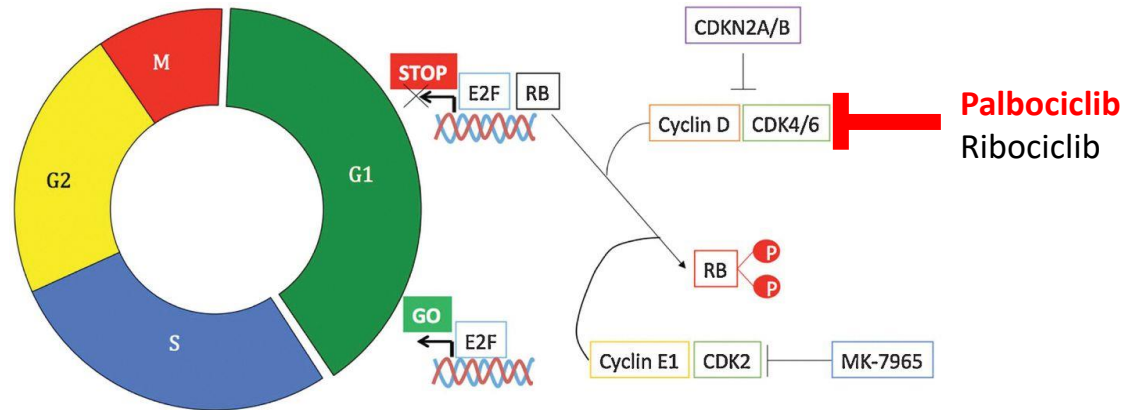
68 year old man with GIST

Subsequent Progression



Tissue NGS (during Dabrafenib + Trametinib)

- *BRAF* V600E
- *CDKN2A* p16INK4a splice site 150+1G>A



Dabrafenib
Trametinib

Dabrafenib
Trametinib
Palbociclib

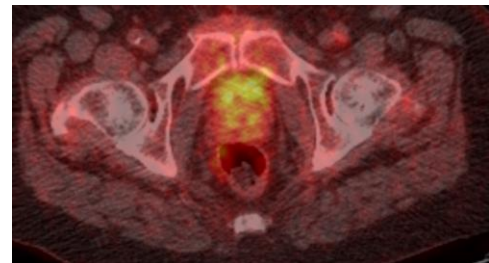
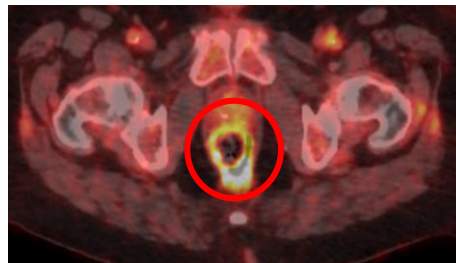
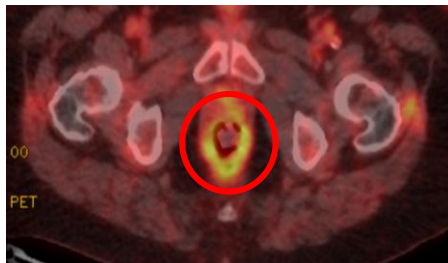
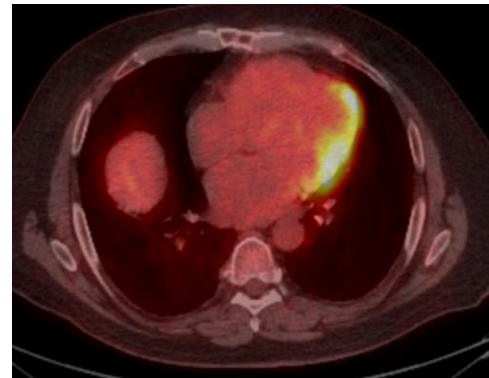
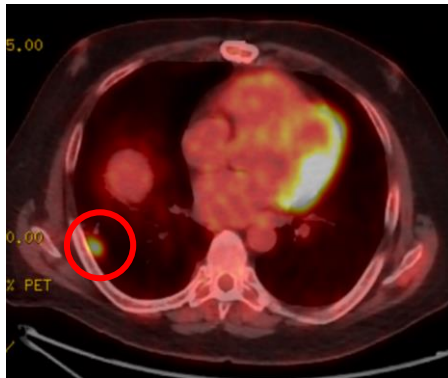
2/7/2018



4/10/2018



6/27/2018



Stage IV IHCC

Genomics (Tissue NGS):

KRAS G12D → Trametinib

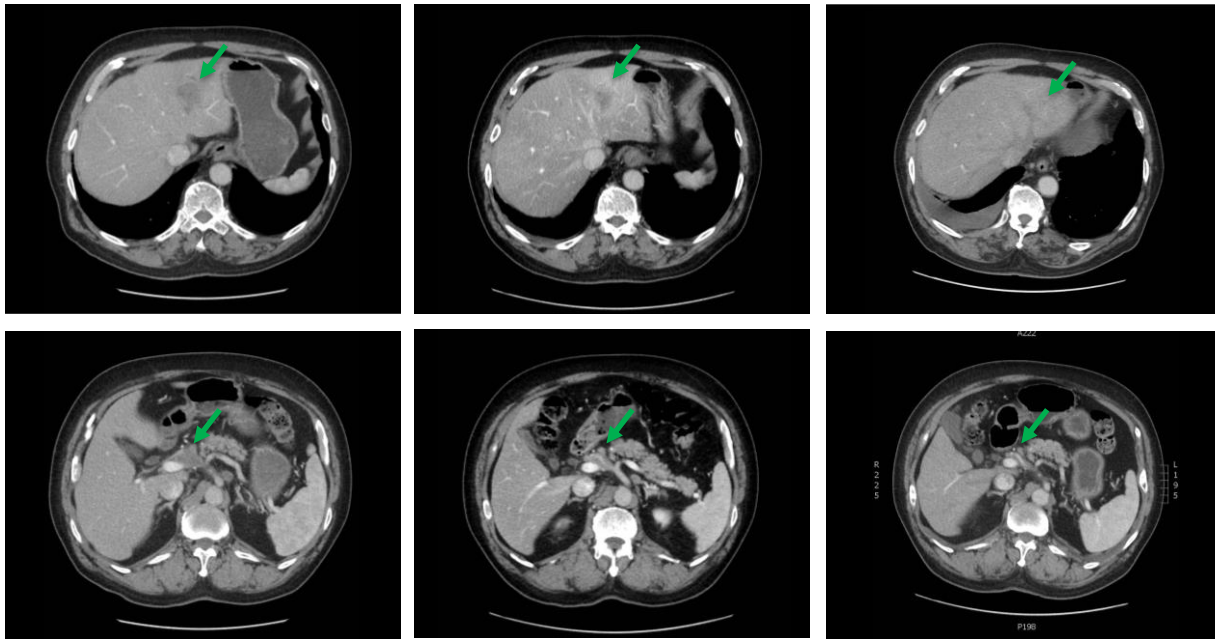
MLH1 splice site 1989+1G>T → Nivolumab

TP53 R248Q

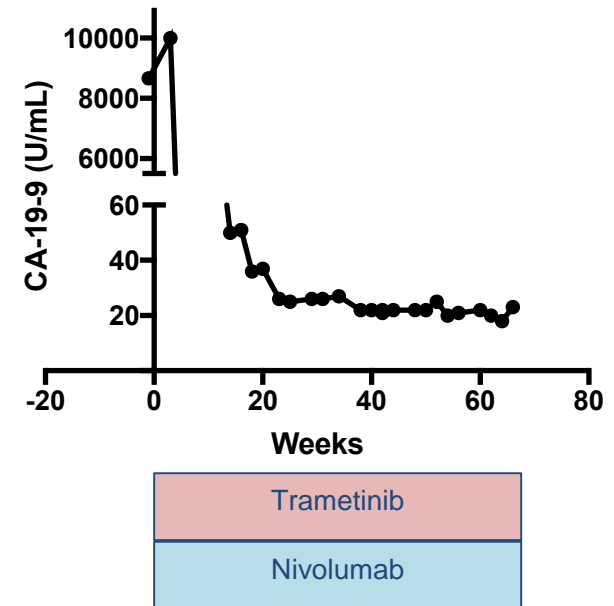
Pre-treatment

11 weeks

12.4 months

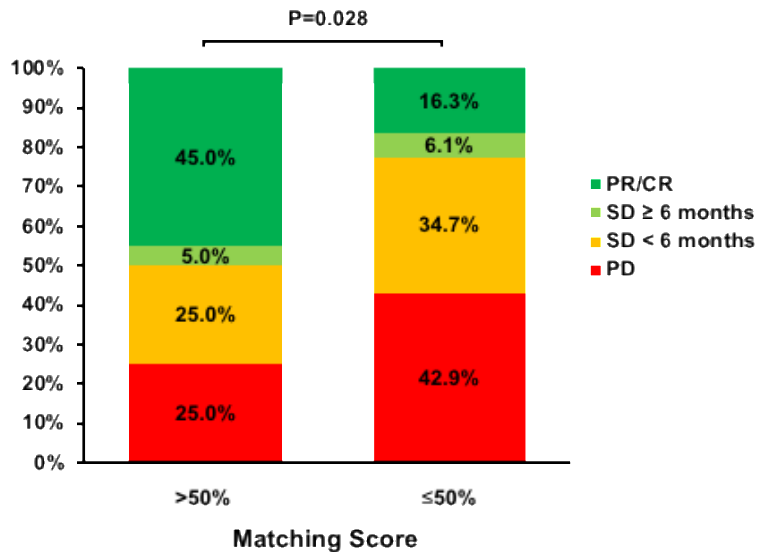


Near Complete Response



Outcomes by Matching Score

A



I-PREDICT Lessons

Single agent matched therapy is *often* inadequate to treat many lethal cancers

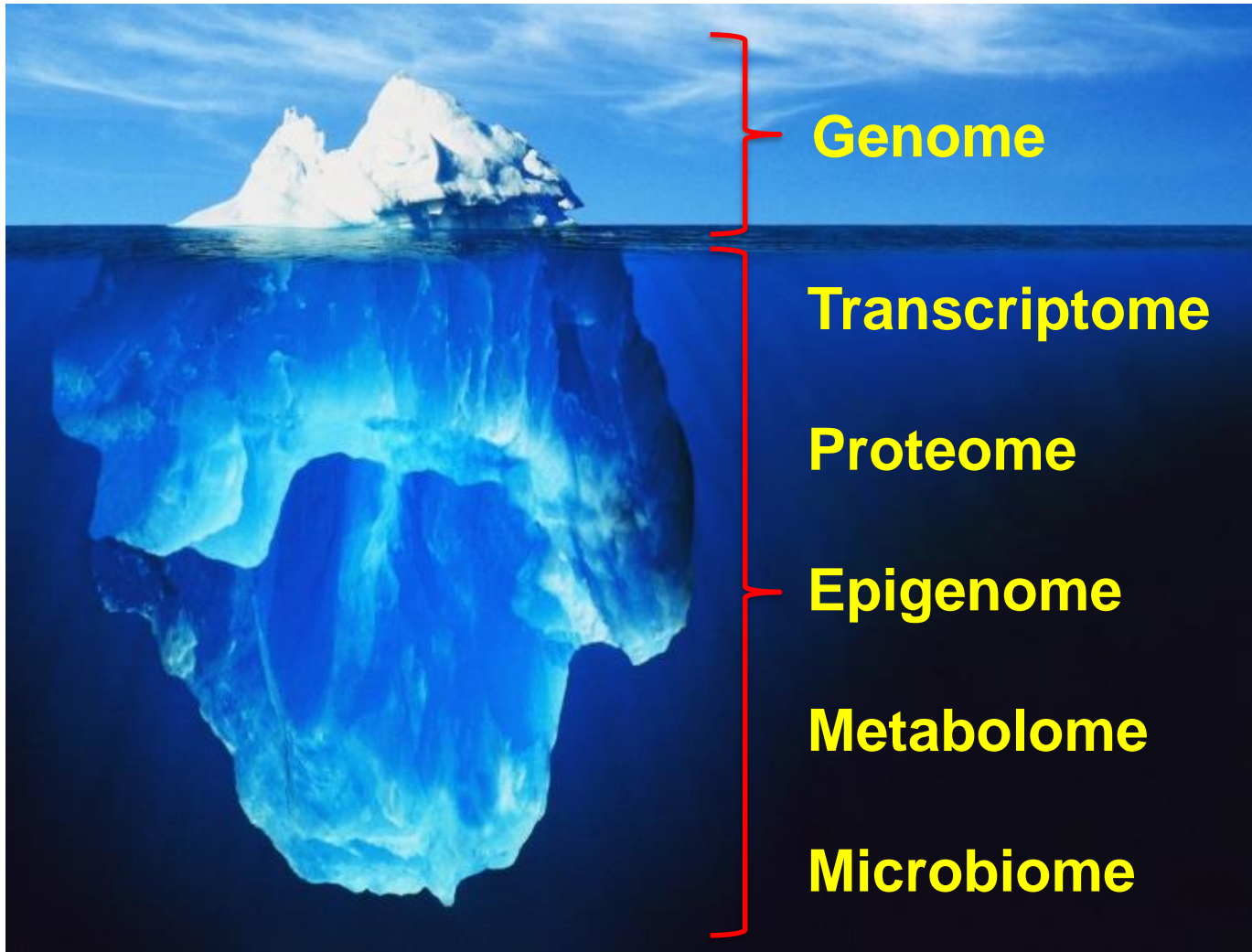
We can safely treat each malignant snowflake and its co-genomic alterations:
customized, molecularly matched combination therapies

We can increase matching rates:
nearly 50% of pts treated with molecularly matched regimens

Appreciate the pillars of precision medicine by combining both genomically targeted therapies and immunotherapies

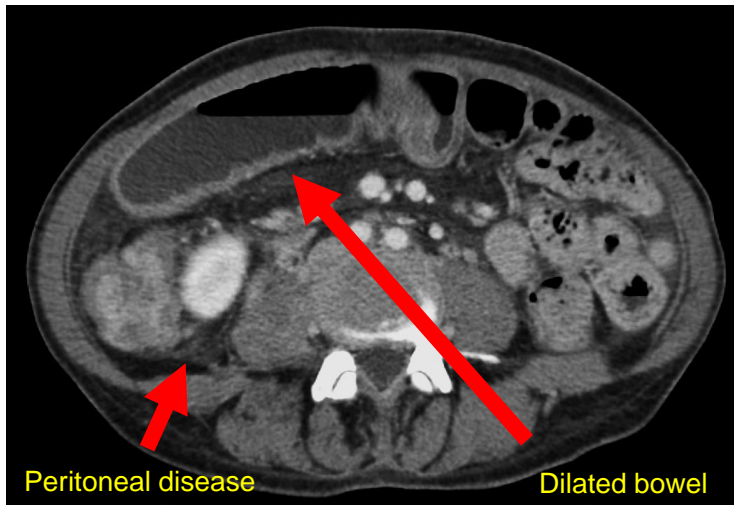
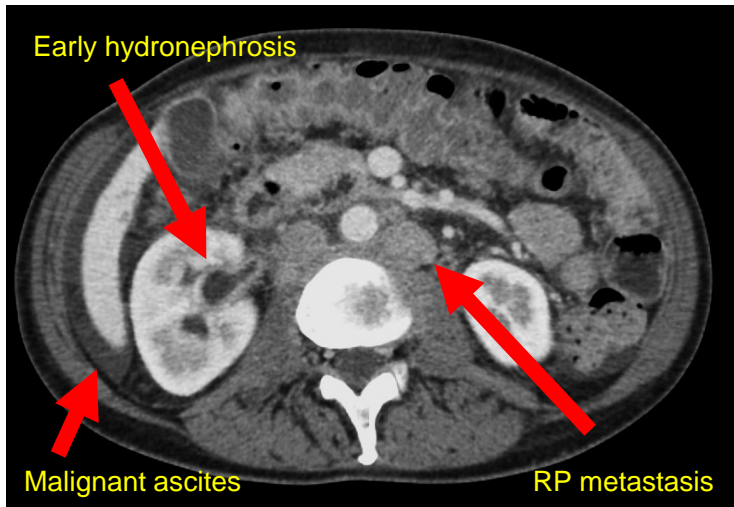
Continuing to enroll both previously treated and treatment naive patients to the study

Future Precision-Personalized Medicine



Stage IV TNBC

Initial Presentation



Prior Treatment

6 lines of therapy

(including 10 different drugs)

Laparoscopy



November 2016

Stage IV TNBC



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Genomic Alterations (13)	TMB*	MS Status
<i>ATM</i> R3008H <i>BCOR</i> S1717 <i>BRIP1</i> R798Q <i>CDH1</i> P260L <i>CDKN1B</i> splice site 476-1G>T <i>ERBB2</i> D769H – subclonal <i>MAP2K4</i> S184L <i>MTOR</i> T1834_T1837del <i>PIK3CA</i> E545K <i>SMAD4</i> E337K <i>TP53</i> E285Q <i>TP53</i> R280K <i>TP53</i> E287	High (76 Muts/Mb) * Definitions <i>Low</i> : ≤ 5 <i>Intermediate</i> : 6-19 <i>High</i> : >19	Stable

Immunotherapy

Companion Diagnostic, Pharmacogenomic, and Cancer Biomarkers

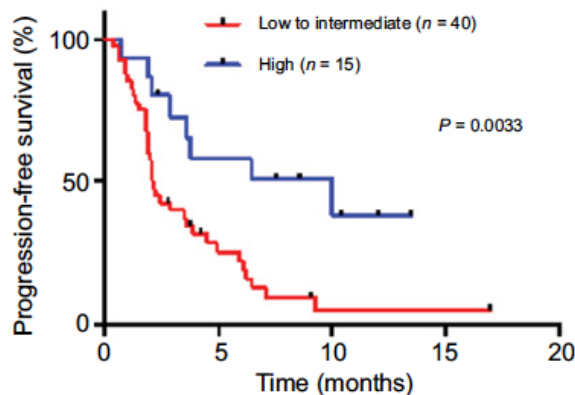
Molecular
Cancer
Therapeutics

Tumor Mutational Burden as an Independent Predictor of Response to Immunotherapy in Diverse Cancers

Aaron M. Goodman^{1,2,3}, Shumei Kato^{1,2}, Lyudmila Bazhenova¹, Sandip P. Patel¹, Garrett M. Frampton⁴, Vincent Miller⁴, Philip J. Stephens⁴, Gregory A. Daniels¹, and Razelle Kurzrock^{1,2}



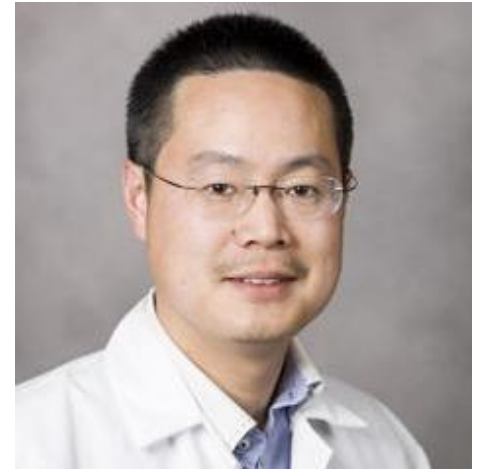
	All Patients (N=151)	TMB Low-Intermediate (N=113)	TMB High (N=38)	P-value
CR/PR	45 (30%)	23 (20%)	22 (58%)	0.0001



I-PREDICT

Investigation of Profile-Related
Evidence Determining
Individualized Cancer Therapy

Feasibility Study In Newly Diagnosed, Treatment Naïve Patients with Incurable Malignancies and Previously Treated Patients with Advanced Cancers



Co-I: Shumei Kato, MD
Assistant Professor
Division of Medical Oncology

Consented: January 13, 2017

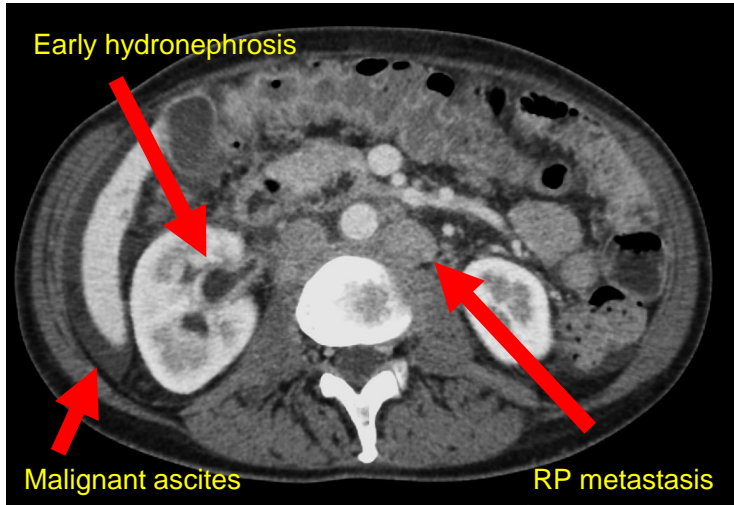
Match: High Tumor Mutation Burden (TMB) to immunotherapy (nivolumab, Opdivo)*

Treatment Started: February 13, 2017

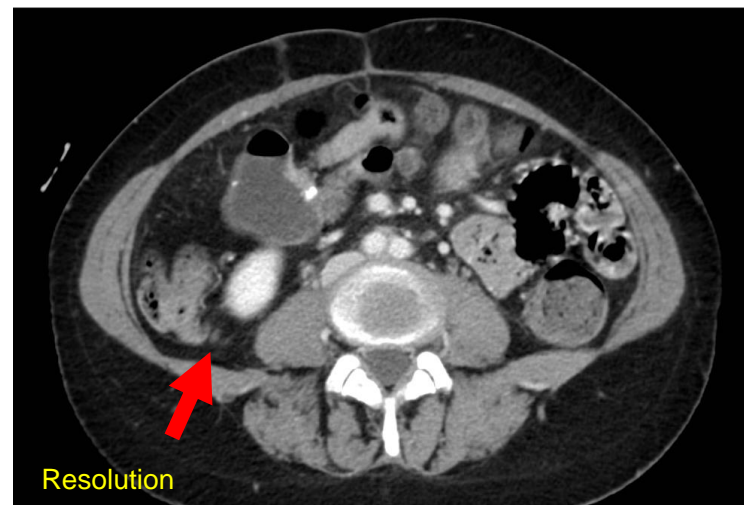
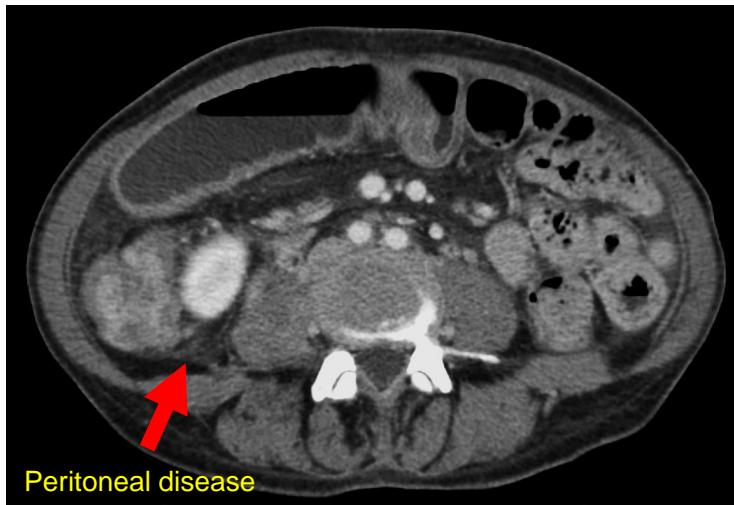
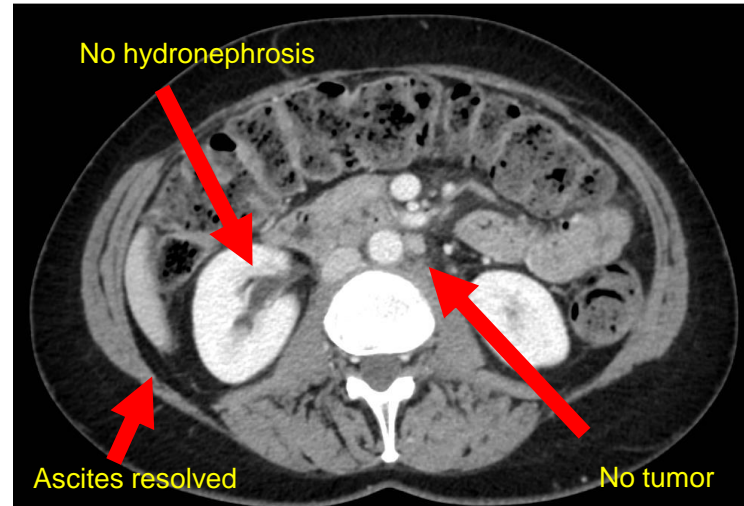
* Goodman, Kato, et al....Kurzrock, *Molecular Cancer Therapeutics*. 2017

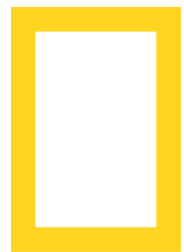
Complete Response

Initial Presentation



14 Months Later (2018)





NATIONAL GEOGRAPHIC

How personalized medicine is transforming your health care

I-PREDICT

Investigation of
Profile-Related
Evidence Determining
Individualized Cancer
Therapy

MAGAZINE | THE FUTURE OF MEDICINE

How personalized medicine is
transforming your health care

Stunning advances in gene research and data mining will predict diseases and devise
treatments tailored to each of us.



**FOUNDATION
MEDICINE**

Summary

- Personalized-precision medicine represents in a paradigm shift in oncology
- We are just in the process of defining the true feasibility of this approach with NGS technology
- While it does not completely account for tumor heterogeneity, the potential exists for obtaining data from multiple distinct tumor sites or primary and metastasis
- Ultimately, we need to start somewhere...GIST, CML, and melanoma have been successful examples of matched targeted approaches
- Potential for applications in other fields including anesthesia, internal medicine, and surgery