THE UNIVERSITY OF ALABAMA AT BIRMINGHAM

HEERSINK SCHOOL OF MEDICINE

Precision Pathology

Challenges and Opportunities

George J. Netto, M.D.

Professor and Robert and Ruth Anderson Endowed Chair of Pathology

HEERSINK SCHOOL OF MEDICINE

University of Alabama at Birmingham (UAB)

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Precision Pathology

A Journey of Transformation and Innovative Disruption

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Disclosures

I have the following **financial relationships to disclose**:

TERT Promoter Mutations in Urothelial Neoplasia
Patents: (US201660208340A1) (PCT/US2014/051808)

UroSEEK; **CancerSEEK; PapSEEK**

- Methods and Materials for Assessing and Treating Cancer
  Patents: (US16/250,703) (PCT/US2018/045669)
- Financial Interest in "**Thrive Early Detection Corp" and "Exact Sciences Inc"**

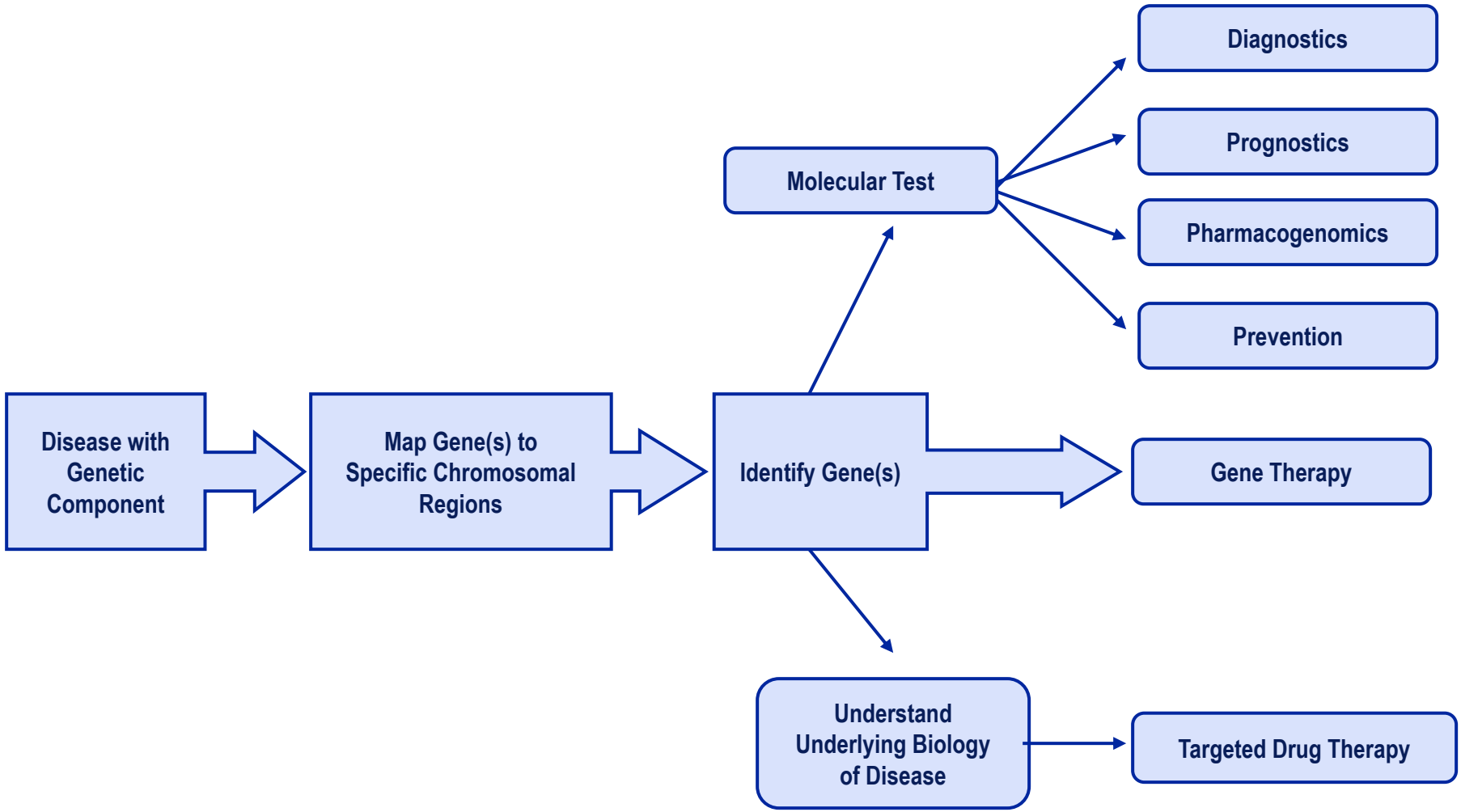
Genentech Advisory Pathology Board

Why bullish on the future of our field?

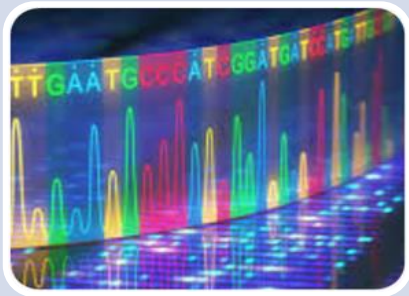
- Optimist by nature, but fully believe we are heading for a bright future …
- Recent technological and interdisciplinary advances (**Precision Medicine**) present unprecedented **opportunities** for Pathology and Lab Med
- **Disruptive changes** in healthcare environment (technological, financial and operational) pose significant **challenges but open new doors** for our specialty

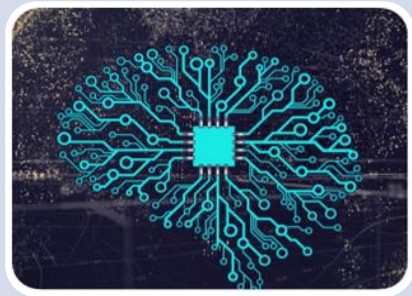
Implications of the Human Genome Project for Medical Science

Francis Collins and Victor McKusick, *JAMA February 2001*



Disruptive Advances in Path & LM as Opportunities





Omics Technology & Bioinformatics

Digital & Computational Pathology

Laboratory Informatics & Big Data

https://health.usf.edu
https://www.datanami.com
https://theconversation.com

Advances in Genomic Technologies & Bioinformatics

Genomic Technology

&

Bioinformatics

Pathology and Lab Med Opportunities

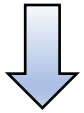
- Familial/Genetic risk
- Targeted Rx

- Immunotherapy/Immuno-genomics
- Liquid Biopsy

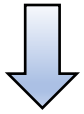
- Single Cell-Spatial Omics
- Cell Rx

Omics: Coming Together…

- Genomic advances paved the way to Precision Medicine

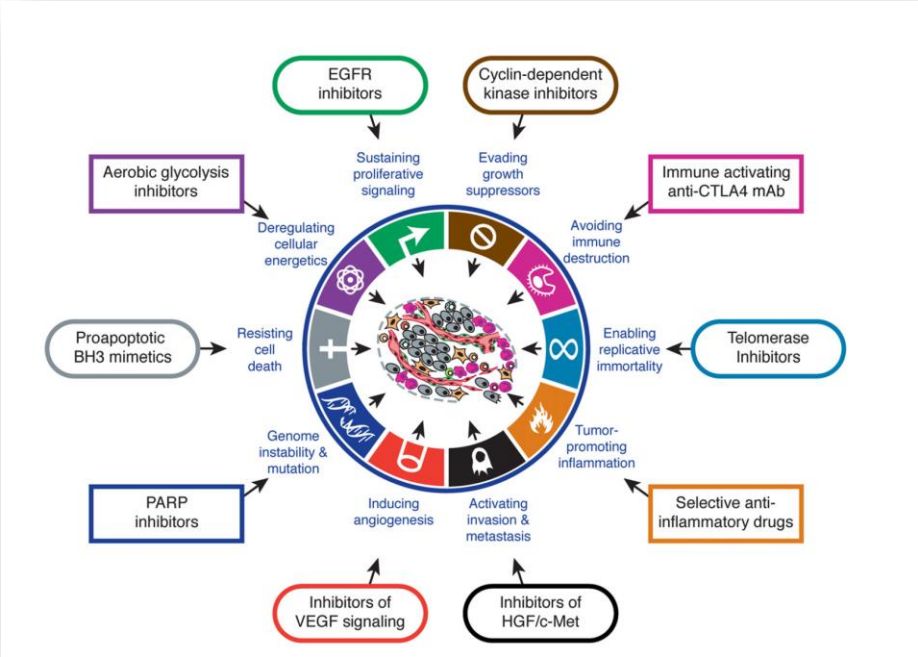


- Multiparametric Analyses (e.g. TCGA studies)
  - DNA
  - RNA
  - Protein
  - Epigenetics

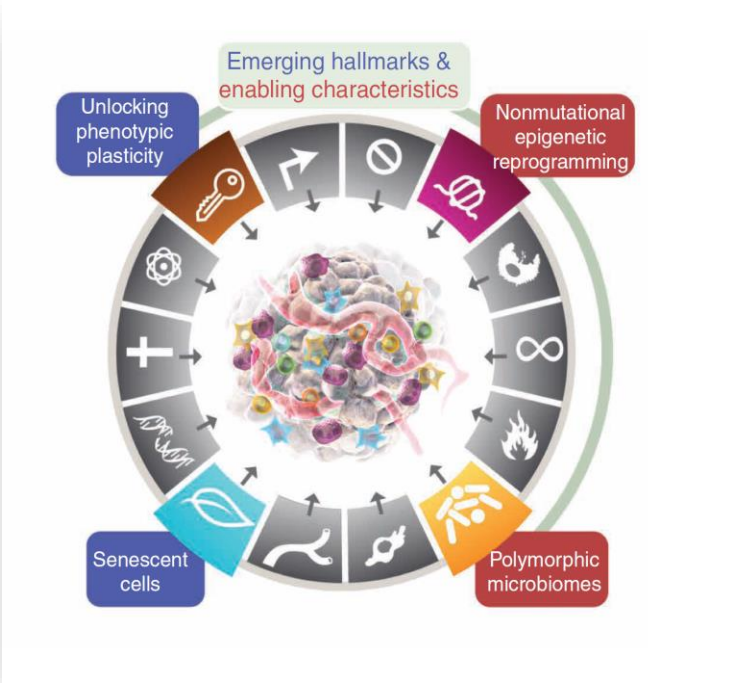


- Robust Molecular Classifications
  - Functional role of molecular alterations across tumor types
  - Druggable targets

Toward Personalized Oncology Care



Hanahan and Weinberg Cell 2011



Hanahan CANCER DISCOVERY 2022

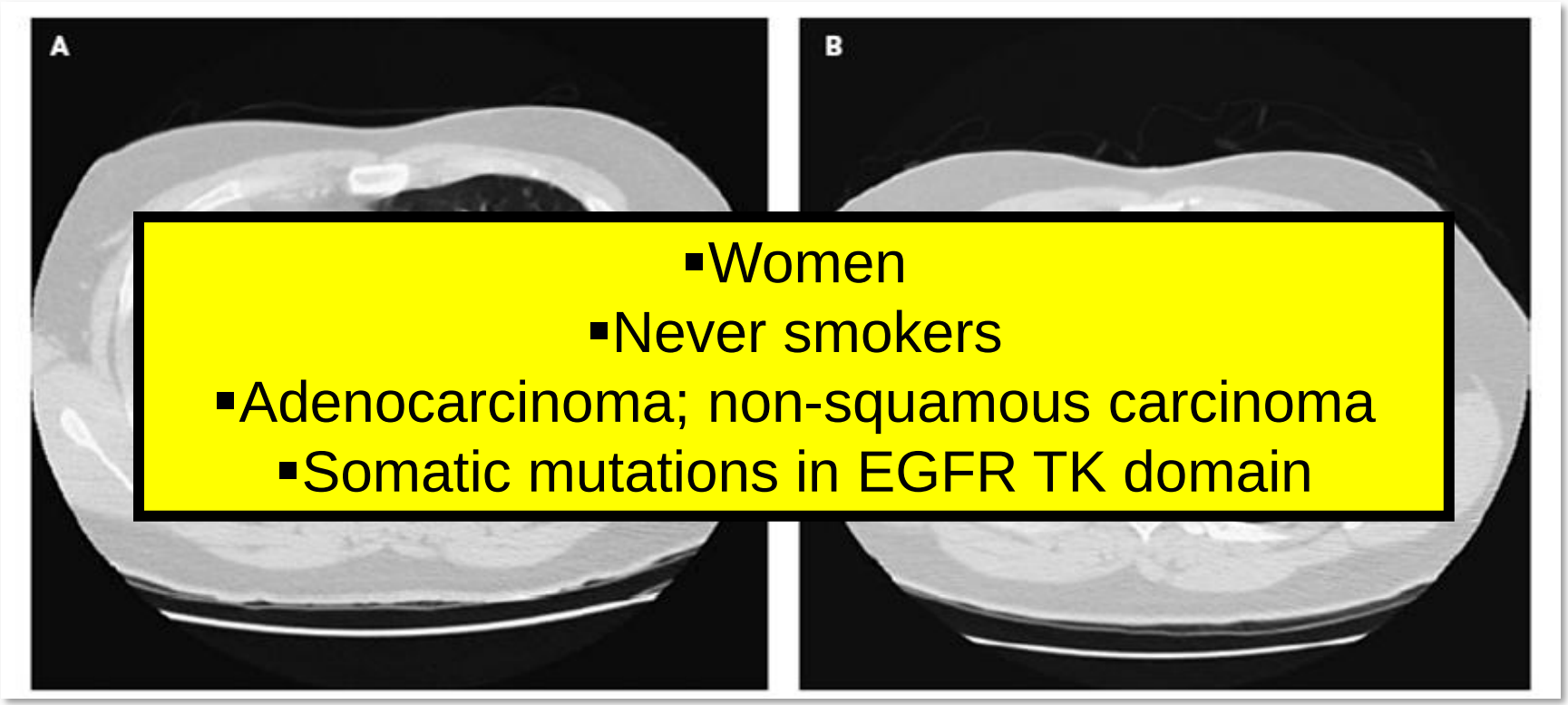
Molecular Diagnostic Pathology in NSCLC

A model for future cancer management of solid tumors

EGFR Mutation Predicts Response to TKI (Gefitinib)

Lynch et al NEJM 2004; 350:2129-39

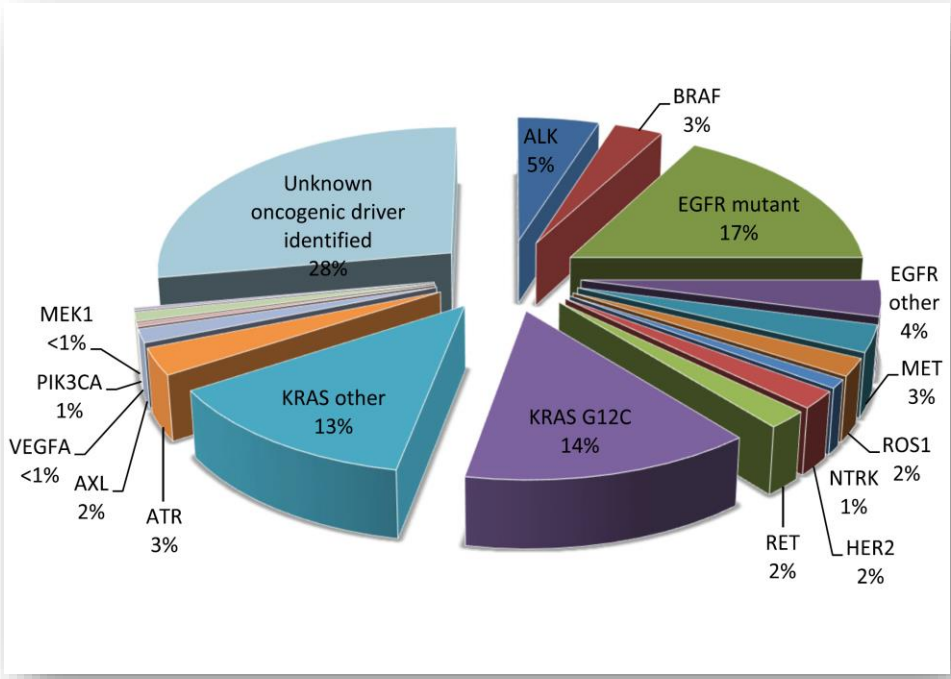
- **8/9 NSCLC with EFGR mutation Vs 0/7 EGFR wild type tumors had evidence of Iressa Rx response**
- **8% EGFR mutation rate in 25 tested NSCLC pts**



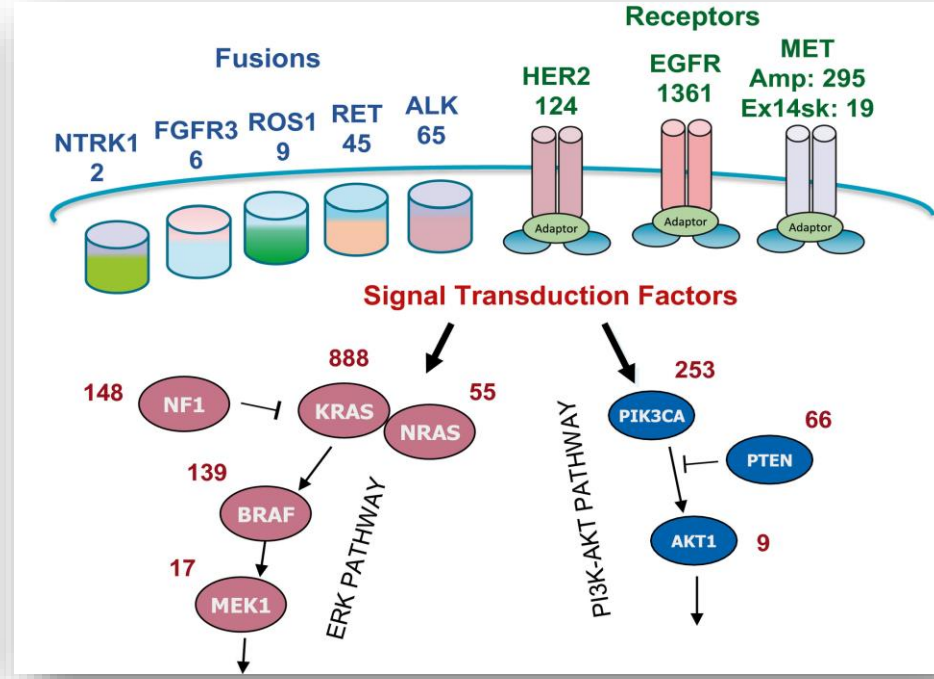
- Women
- Never smokers
- Adenocarcinoma; non-squamous carcinoma
- Somatic mutations in EGFR TK domain

Genetic Alterations in Lung Adenocarcinoma

AACR / GENIE / Lung Cancer Mutation Consortium

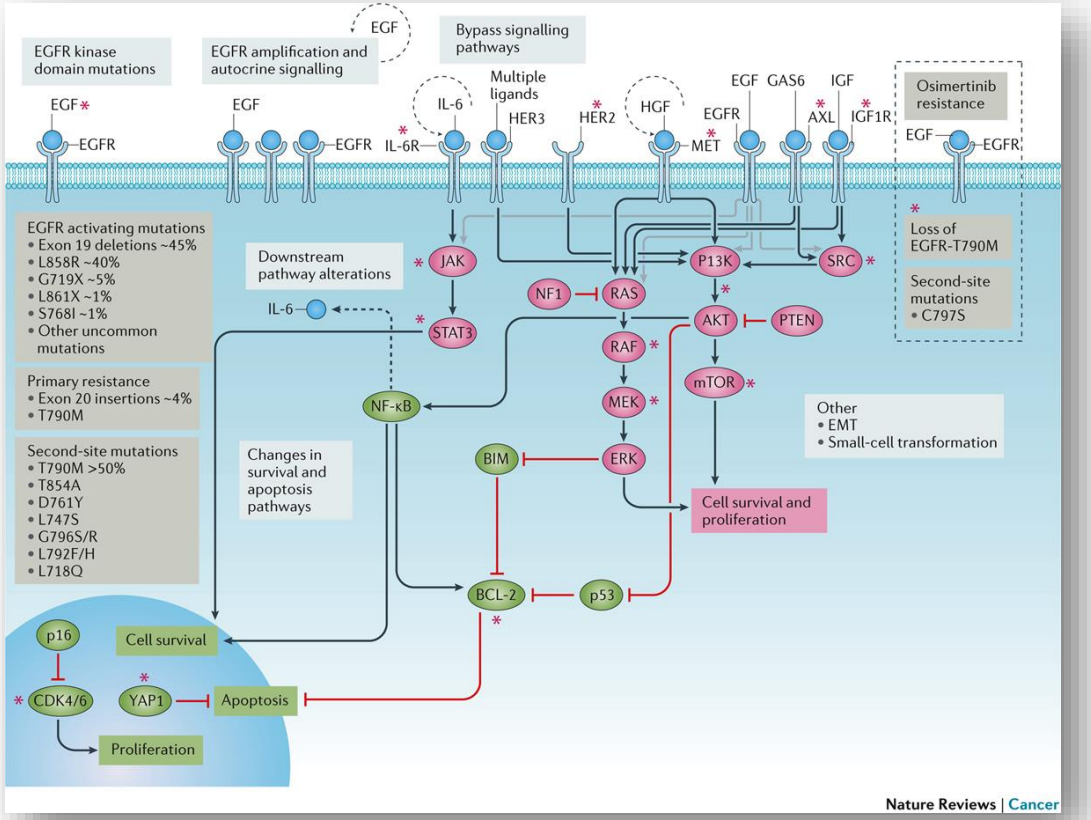


Chen et al. Journal of Hematology & Oncology 2020



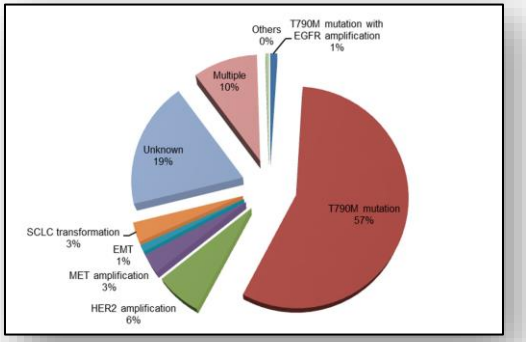
Macks PH et al . Cancer 2020

Mechanisms of Acquired Resistance to NSCLC TKI

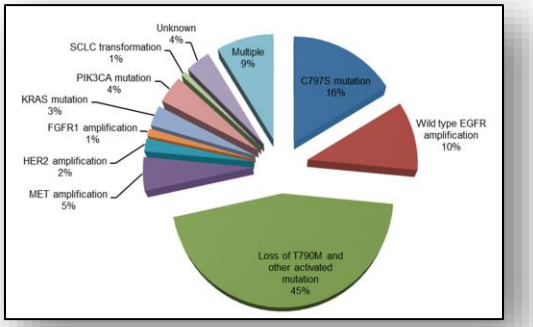


Rotow, J., Bivona, T. Nat Rev Cancer 2017

Mechanisms of acquired resistance to **1st generation TKI** (gefitinib/erlotinib)



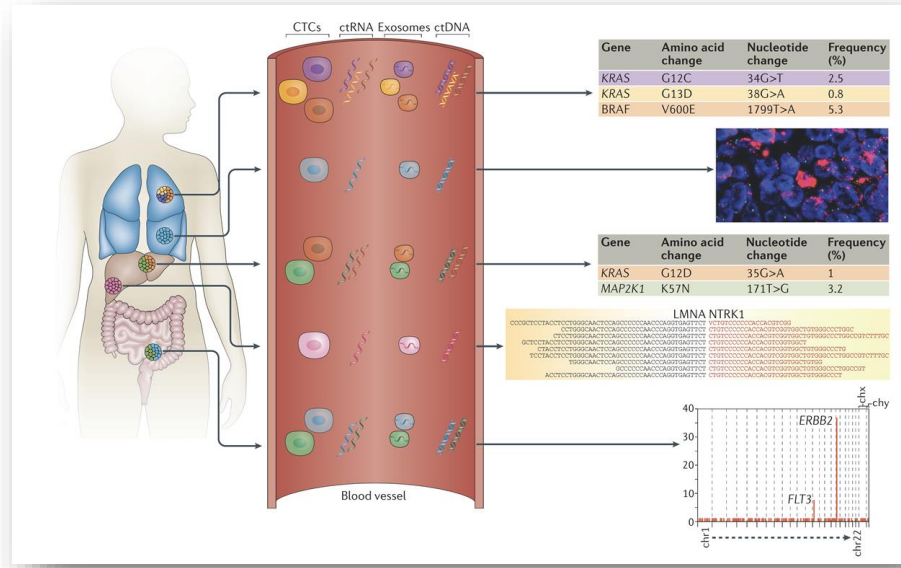
Mechanisms of acquired resistance to **3rd generation TKI** (osimertinib)



Nagano t et al. Cells (2018)

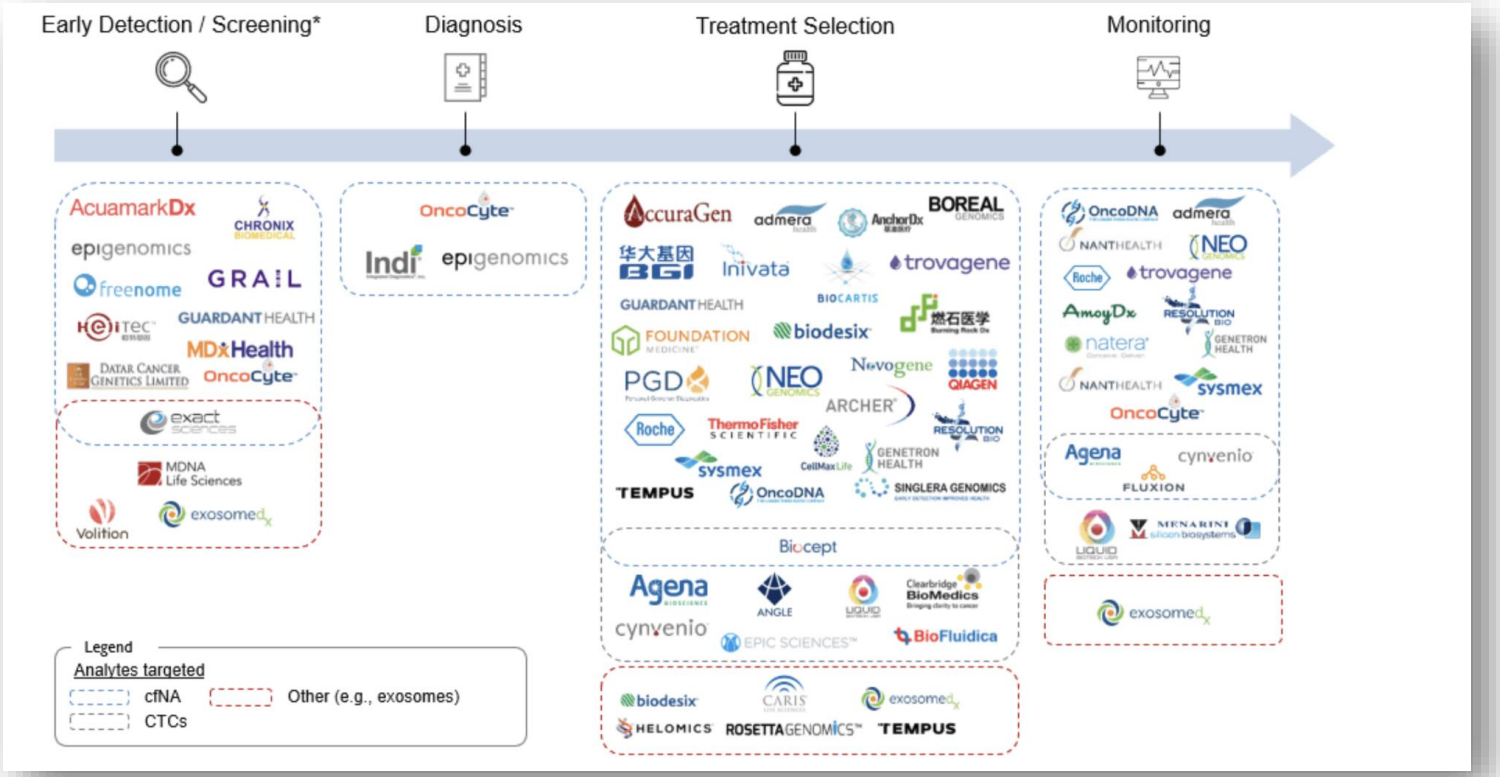
Liquid Biopsy
Minimally Invasive Tumor Monitoring

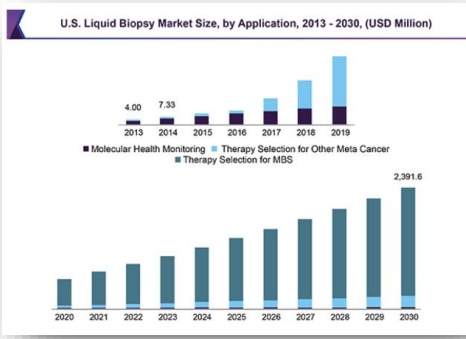
- Tumor genomic landscape is heterogeneous within primary and metastatic sites
- Longitudinal surveillance of clonal evolution (eg. selective pressure of targeted Rx) is essential for precision medicine
- Blood contains tumor-derived materials:
  - Circulating cell-free tumor DNA **(ctDNA)**
  - Circulating tumor cells **(CTC)**
- Advantages
  - Lower Cost $$
  - Avoid FFPE cross linking artifacts
  - Repeatable
  - Clones with metastatic potential (CTC)

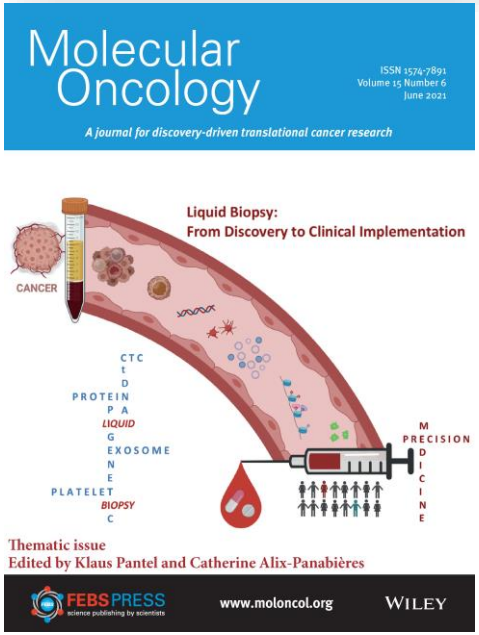


Siravegna G. et al. Nature Reviews clinical oncology 2017

Liquid Biopsy Commercial Landscape







UroSEEK/CancerSEEK/PapSEEK

CANCER

Detection and localization of surgically resectable cancers with a multi-analyte blood test

Joshua D. Cohen,[1,2,3,4,5] Lu Li,[6] Yuxuan Wang,[1,2,3,4] Christopher Thoburn,[3] Bahman Afsari,[7] Ludmila Danilova,[7] Christopher Douville,[1,2,3,4] Ammar A. Javed,[8] Fay Wong,[1,3,4] Austin Mattox,[1,2,3,4] Ralph. H. Hruban,[3,4,9] Christopher L. Wolfgang,[8] Michael G. Goggins,[3,4,9,10,11] Marco Dal Molin,[4] Tian-Li Wang,[3,9] Richard Roden,[3,9] Alison P. Klein,[3,4,12] Janine Ptak,[1,2,3,4] Lisa Dobbyn,[1,3,4] Joy Schaefer,[1,3,4] Natalie Silliman,[1,2,3,4] Maria Popoli,[1,3,4] Joshua T. Vogelstein,[13] James D. Browne,[14] Robert E. Schoen,[15,16] Randall E. Brand,[15] Jeanne Tie,[17,18,19,20] Peter Gibbs,[17,18,19,20] Hui-Li Wong,[17] Aaron S. Mansfield,[21] Jin Jen,[22] Samir M. Hanash,[23] Massimo Falconi,[24] Peter J. Allen,[25] Shibin Zhou,[1,3,4] Chetan Bettegowda,[1,3,4] Luis A. Diaz Jr.,[1,3,4*] Cristian Tomasetti,[3,6,7†] Kenneth W. Kinzler,[1,3,4†] Bert Vogelstein,[1,2,3,4†] Anne Marie Lennon,[3,4,8,10,11†] Nickolas Papadopoulos[1,3,4†]

Cohen, J.D., et al. Science, 2018

SCIENCE TRANSLATIONAL MEDICINE | RESEARCH ARTICLE

CANCER

Evaluation of liquid from the Papanicolaou test and other liquid biopsies for the detection of endometrial and ovarian cancers

Yuxuan Wang,[1] Lu Li,[2] Christopher Douville,[1] Joshua D. Cohen,[1,3] Ting-Tai Yen,[4] Isaac Kinde,[5] Karin Sundfelt,[6] Susanne K. Kjær,[7,8] Ralph H. Hruban,[9] Ie-Ming Shih,[9] Tian-Li Wang,[9] Robert J. Kurman,[9] Simeon Springer,[1] Janine Ptak,[1] Maria Popoli,[1] Joy Schaefer,[1] Natalie Silliman,[1] Lisa Dobbyn,[1] Edward J. Tanner,[4] Ana Angarita,[4] Maria Lycke,[6] Kirsten Jochumsen,[10] Bahman Afsari,[2] Ludmila Danilova,[2] Douglas A. Levine,[11] Kris Jardon,[12] Xing Zeng,[12] Jocelyne Arseneau,[12] Lili Fu,[12] Luis A. Diaz Jr.,[1] Rachel Karchin,[13] Cristian Tomasetti,[2*] Kenneth W. Kinzler,[1*] Bert Vogelstein,[1,14*] Amanda N. Fader,[4*] Lucy Gilbert,[12*] Nickolas Papadopoulos[1*]

Wang Y., et al. Sci Trans Med, 2018

Non-invasive detection of urothelial cancer through the analysis of driver gene mutations and aneuploidy

Simeon U Springer[1,2†], Chung-Hsin Chen[3†], Maria Del Carmen Rodriguez Pena[4,5†], Lu Li[6], Christopher Douville[7], Yuxuan Wang[1,2], Joshua David Cohen[1,2], Diana Taheri[4,8], Natalie Silliman[1,2], Joy Schaefer[1,2], Janine Ptak[1,2], Lisa Dobbyn[1,2], Maria Papoli[1,2], Isaac Kinde[1,2], Bahman Afsari[9,10], Aline C Tregnago[4], Stephania M Bezerra[11], Christopher VandenBussche[4], Kazutoshi Fujita[12], Dilek Ertoy[13], Isabela W Cunha[11], Lijia Yu[5], Trinity J Bivalacqua[14], Arthur P Grollman[15,16], Luis A Diaz[17], Rachel Karchin[7,9], Ludmila Danilova[10,13], Chao-Yuan Huang[3], Chia-Tung Shun[18], Robert J Turesky[19,20], Byeong Hwa Yun[19,20], Thomas A Rosenquist[15], Yeong-Shiau Pu[3], Ralph H Hruban[4], Cristian Tomasetti[6,10], Nickolas Papadopoulos[1,2], Ken W Kinzler[1,2], Bert Vogelstein[1,2*], Kathleen G Dickman[15,16*], George J Netto[4,5*]

Springer et al. eLife 2018

PANIC !!!

THE END OF MICROSCOPY !!!

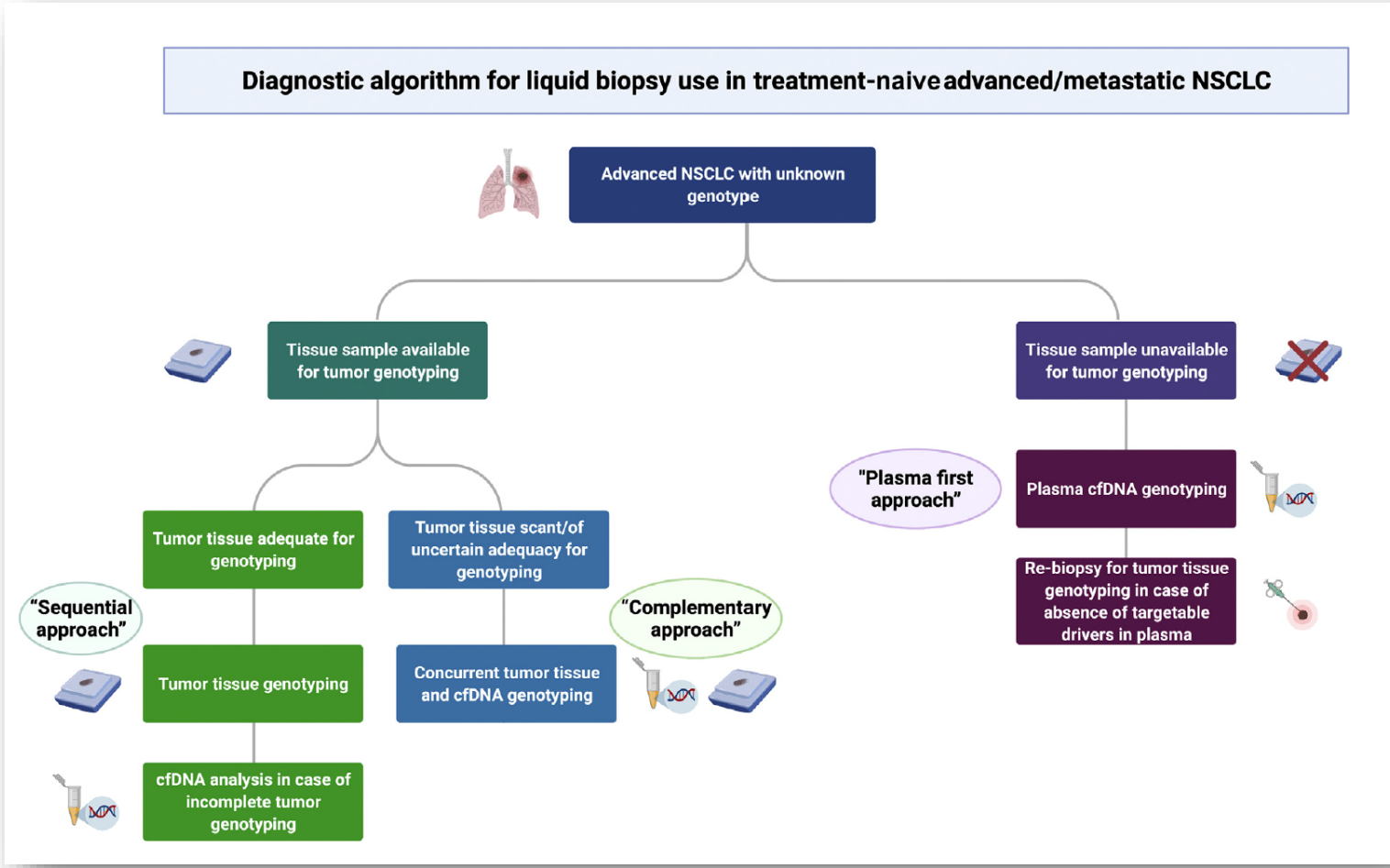
NOT EXACTLY, YET !!

Company	Liquid biopsy	Use	Status in US	Company notes
Guardant Health	Guardant360	Helps assign targeted therapy	Approved Aug 7, 2020, price approx $6,800	$550m VC funding; floated in 2018
Foundation Medicine (Roche)	FoundationOne Liquid CDx	Helps assign targeted therapy	Approved Aug 27, 2020, price $5,800	$115m VC funding; bought by Roche for $2.5bn in 2015
Grail	Galleri	Screening for early detection and identification of tumour origin	Launched as LDT Jun 4, 2021, price $949	$2.1bn VC funding; bought by Illumina for $8bn in 2020
Thrive Earlier Detection (Exact Sciences)	CancerSeek	Early detection	FDA breakthrough device status	$367m VC funding; bought by Exact Sciences in 2020 for $1.7bn
Natera	Signatera	Postsurgical, detects disease recurrence	FDA breakthrough device status	$152m in VC funding; floated in 2015
Archer DX (Invitae)	Stratafide	Helps assign targeted therapy	FDA breakthrough device status	$150m VC funding; bought by Invitae in 2020 for $1.4bn

IASLC

Liquid Biopsy for Advanced NSCLC: A Consensus Statement From the International Association for the Study of Lung Cancer

Check for updates

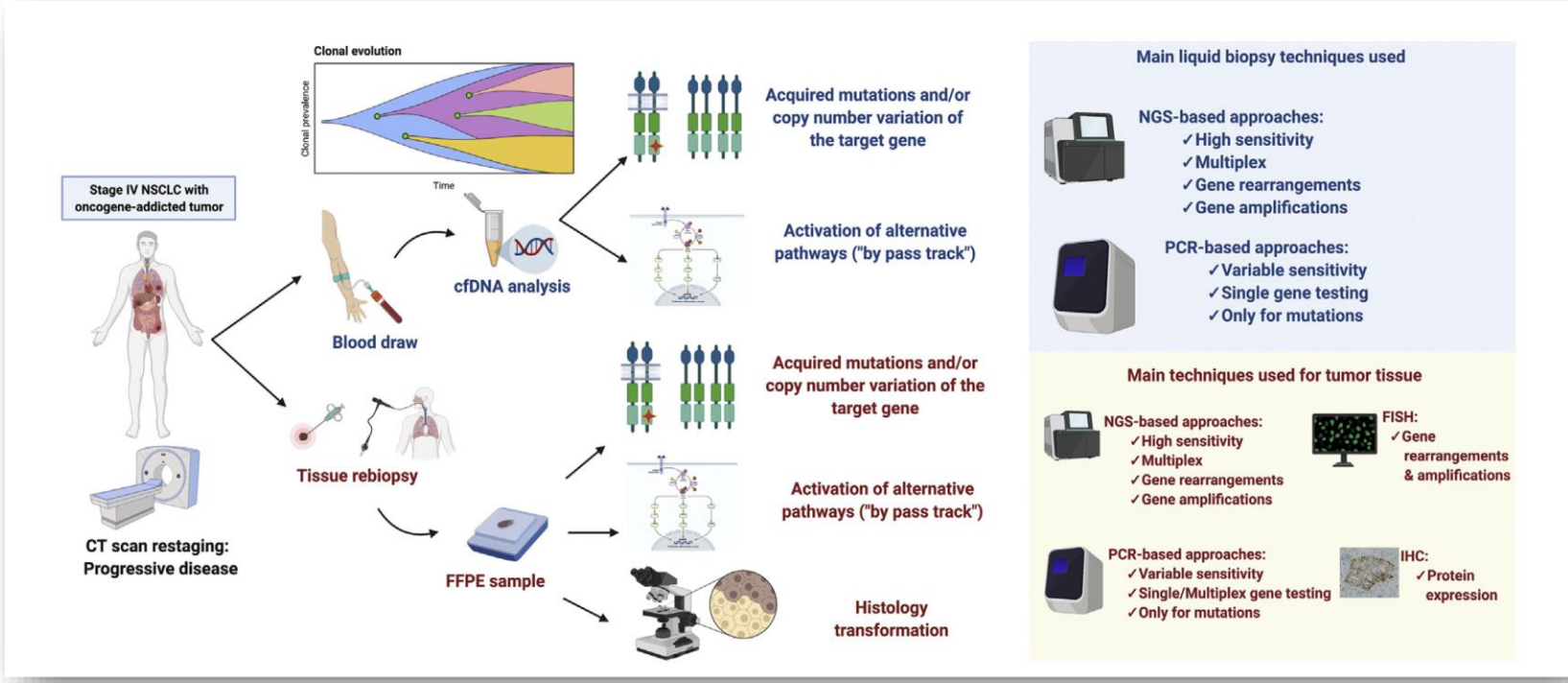


Rolfo C et al , J Thoracic Oncol October 2021

IASLC

Liquid Biopsy for Advanced NSCLC: A Consensus Statement From the International Association for the Study of Lung Cancer

Check for updates



Rolfo C et al , J Thoracic Oncol October 2021

Genomic Technology

&

Bioinformatics

NEXT FRONTIERS

Single Cell Spatial “Omics”

Cell Rx: **CAR-T, TCR**

CellPress
OPEN ACCESS

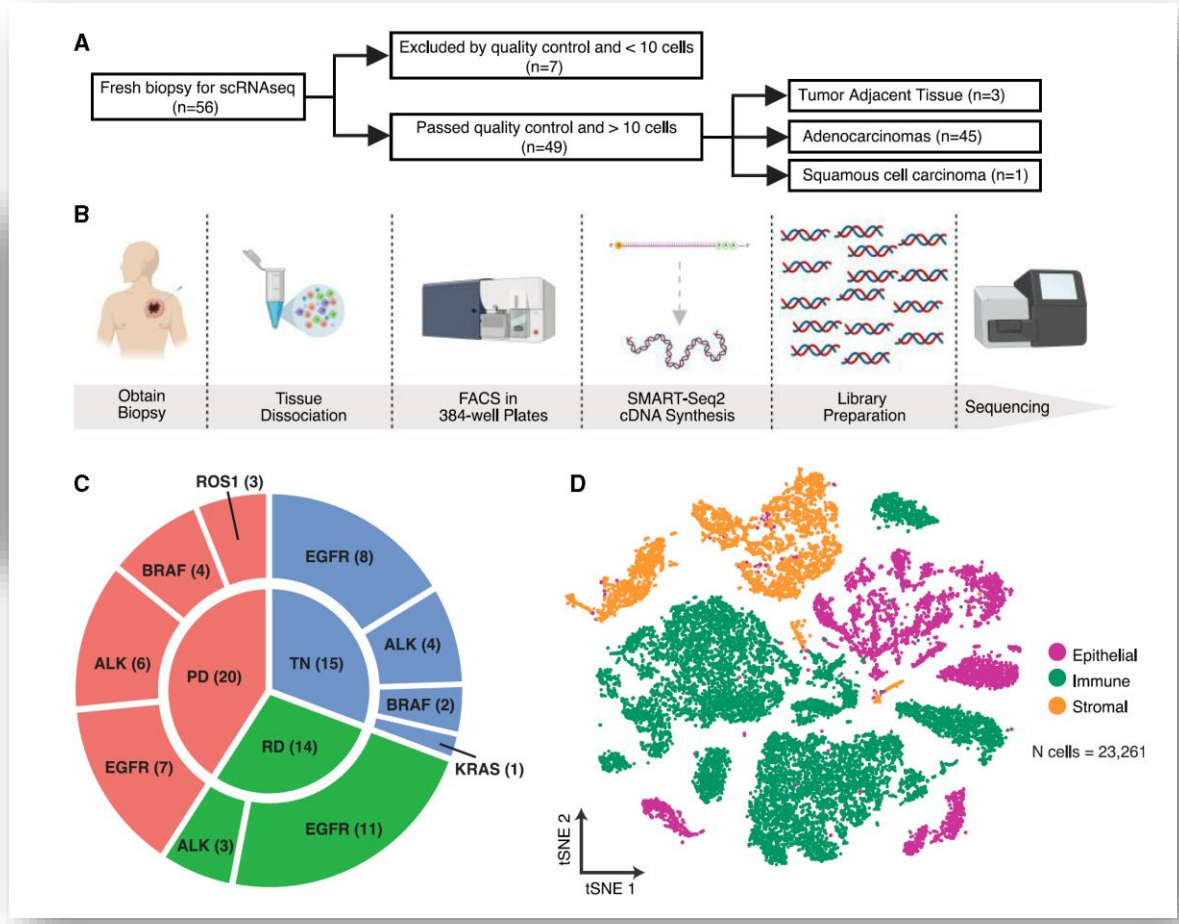
Cell

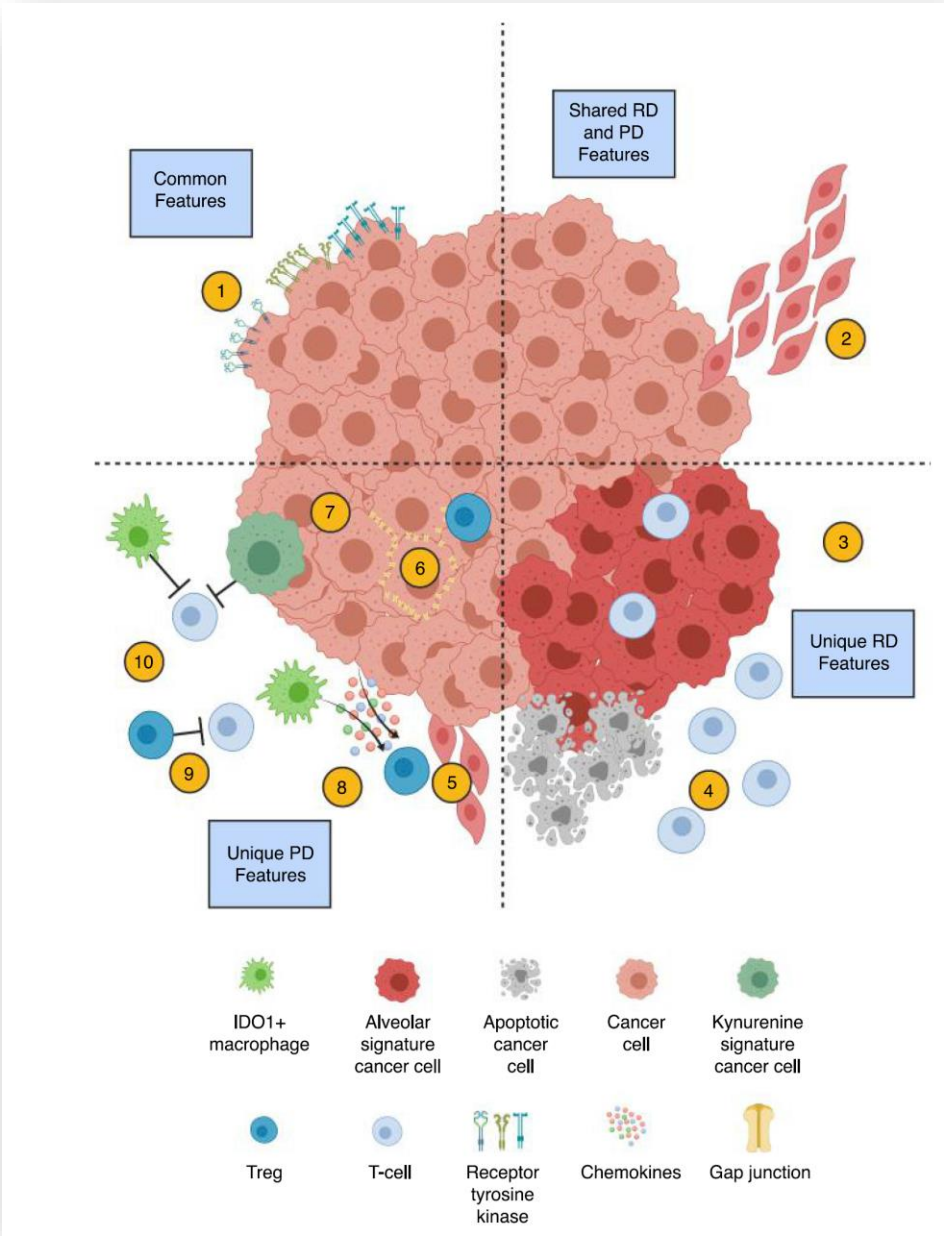
Article

Therapy-Induced Evolution of Human Lung Cancer Revealed by Single-Cell RNA Sequencing

Ashley Maynard,[1,15] Caroline E. McCoach,[2,3,15] Julia K. Rotow,[4,16] Lincoln Harris,[1,16] Franziska Haderk,[2,3,5,16] D. Lucas Kerr,[2,16] Elizabeth A. Yu,[2] Erin L. Schenk,[6] Weilun Tan,[1] Alexander Zee,[1,7] Michelle Tan,[1] Philippe Gui,[2,3] Tasha Lea,[3] Wei Wu,[2] Anatoly Urisman,[8] Kirk Jones,[8] Rene Sit,[1] Pallav K. Kolli,[9] Eric Seeley,[2] Yaron Gesthalter,[2] Daniel D. Le,[1] Kevin A. Yamauchi,[1] David M. Naeger,[10,11] Sourav Bandyopadhyay,[3,12] Khyati Shah,[12] Lauren Cech,[2] Nicholas J. Thomas,[2] Anshal Gupta,[2] Mayra Gonzalez,[2] Hien Do,[2] Lisa Tan,[2] Bianca Bacaltos,[2] Rafael Gomez-Sjoberg,[1] Matthew Gubens,[2,3] Thierry Jahan,[2,3] Johannes R. Kratz,[13] David Jablons,[13] Norma Neff,[1] Robert C. Doebele,[6] Jonathan Weissman,[5,14] Collin M. Blakely,[2,3,*] Spyros Darmanis,[1,*] and Trever G. Bivona[2,3,5,17,*]

Ashley Maynard et al. Cell 2020

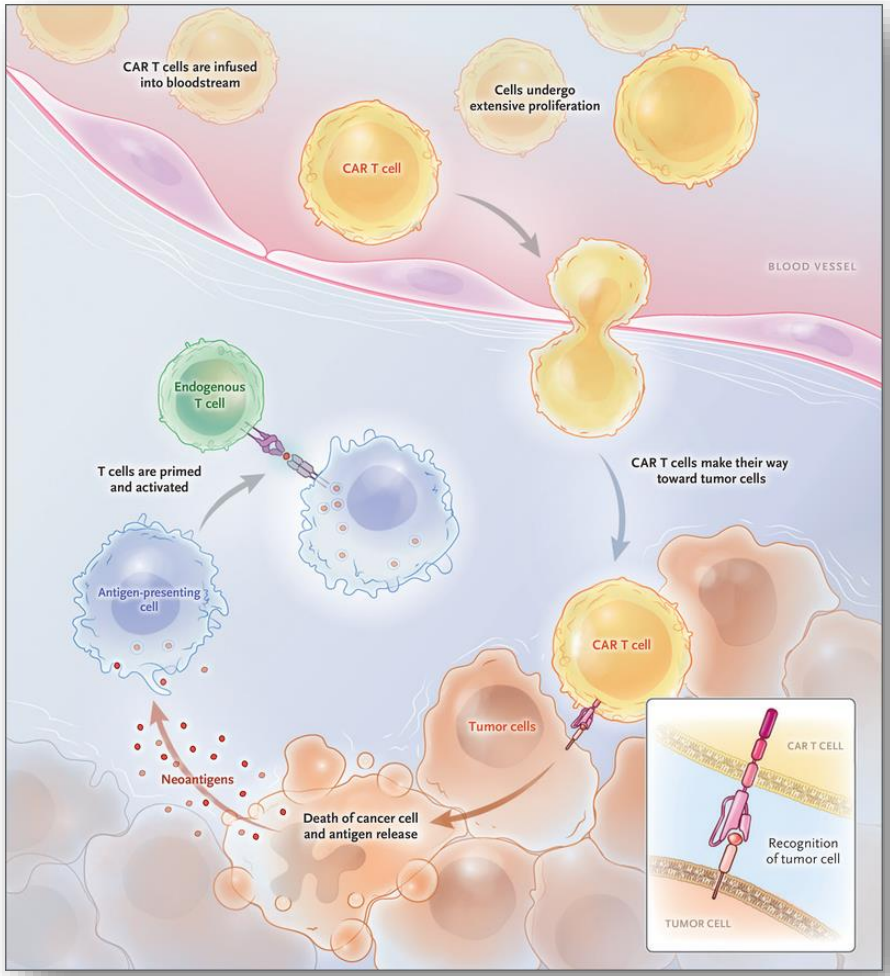




Ashley Maynard et al. Cell 2020

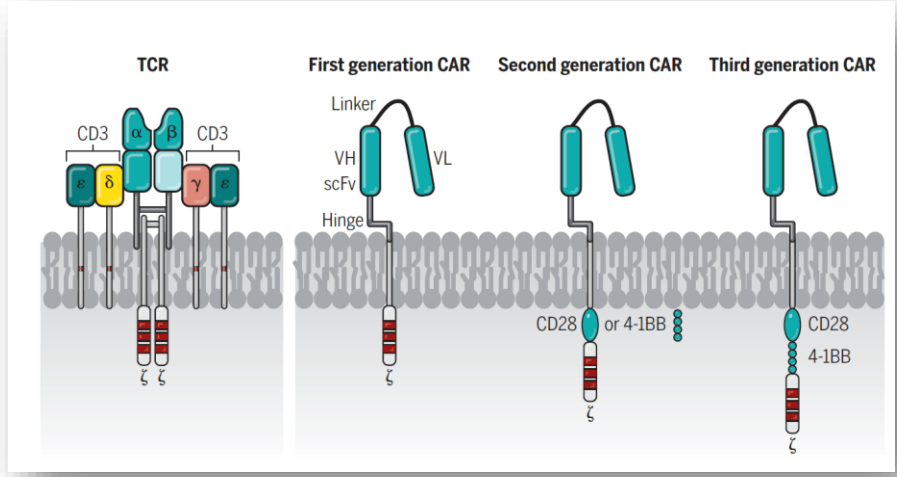
- Over **20,000** cancer and TME **cells** scRNA-seq profiles
- Cancer and TME exhibit marked Rx-induced **plasticity (rich and dynamic ecosystem)**
- **New opportunities** to improve clinical outcome

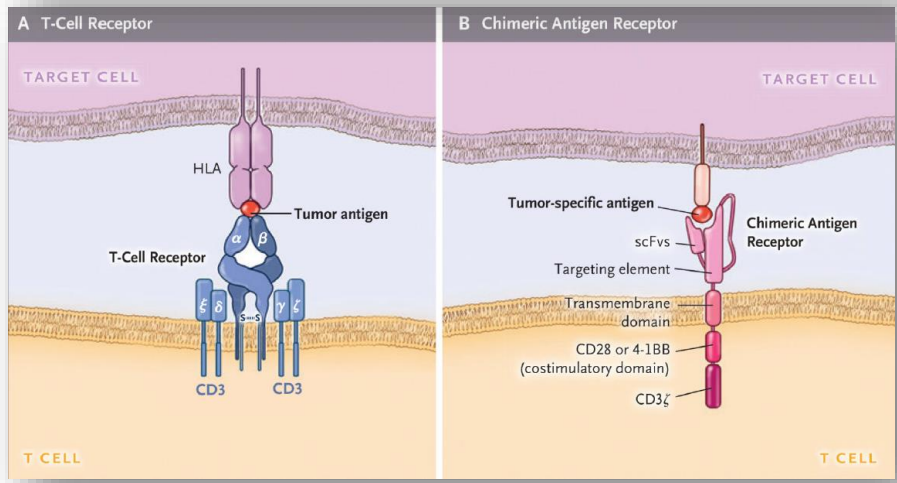
Cell Therapy



CAR-T

Carl H June & Michel Sadelain M.
N Engl J Med. 2018



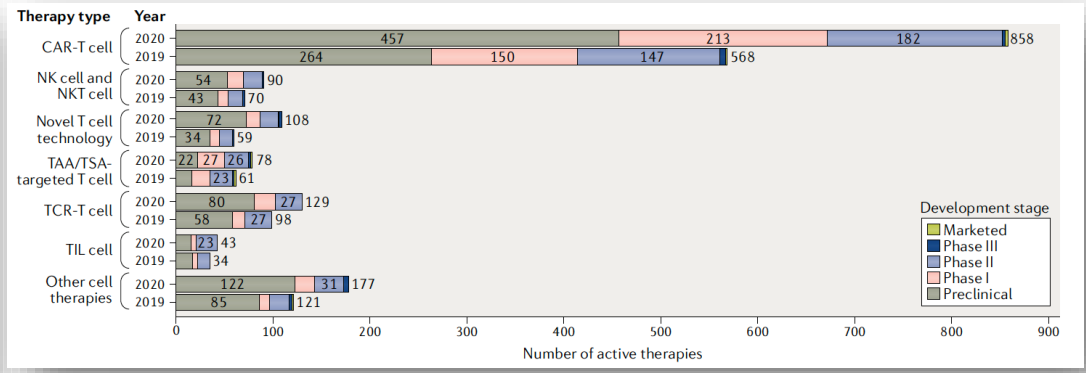


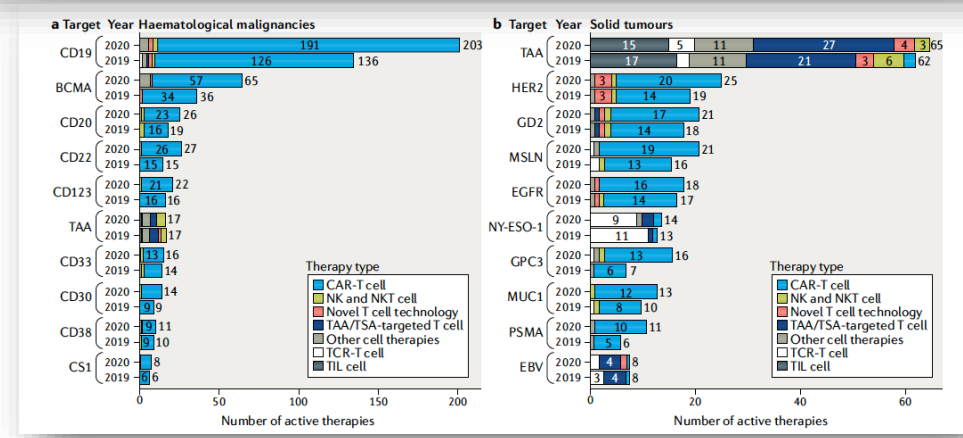
TCR **CAR-T**

June et al., Science 2018

Cancer immunotherapy comes of age and looks for maturity

Amanda Finck[1], Saar I. Gill[1] & Carl H. June[1,2]✉





Fink A et al., Nat. Comm. 2020

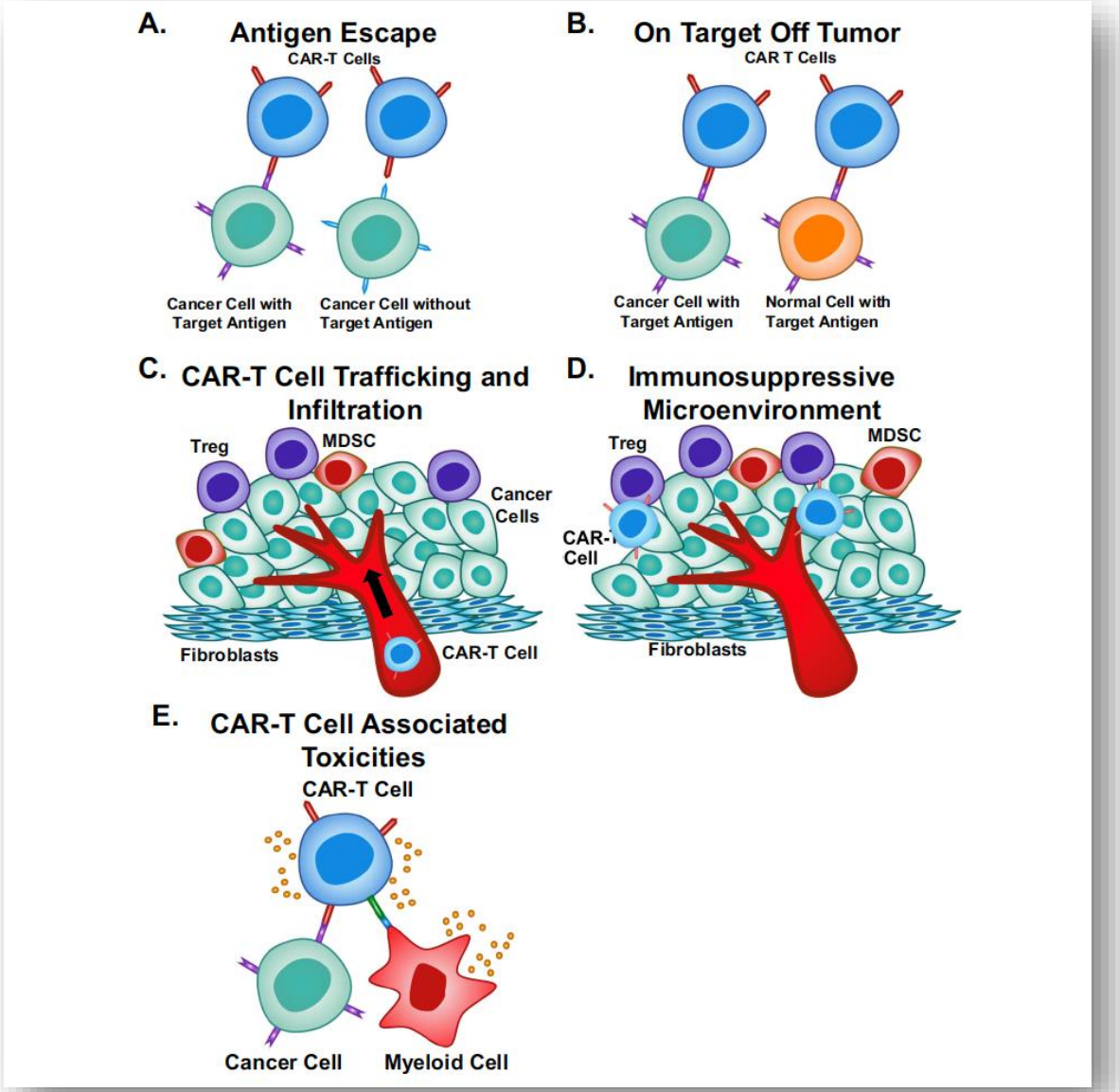
Nat. Rev. Drug Discov. 2018

Limitations and challenges of CAR-T cell Therapy

Perelman School of Medicine
University of Pennsylvania

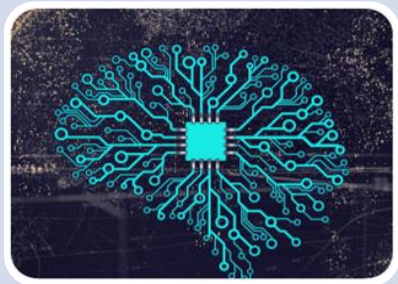
Michael C. Milone

Bruce L. Levine



Sterner and Sterner, Blood Cancer Journal 2021

Advances in Digital and Computational Pathology



Digital Pathology

&

Computational Pathology

Pathology and Lab Med Opportunities

- Precision AP diagnostics
- Operational workflow efficiencies

- Precision biomarkers assessment
- **Multispectral and spatial resolution**

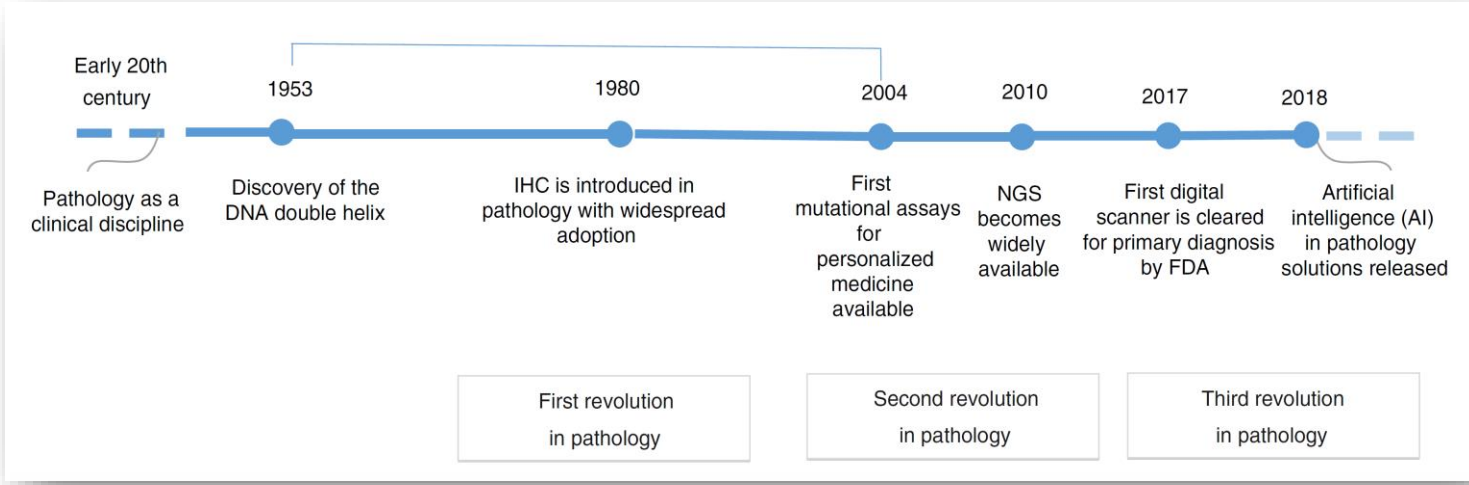
Histopathology

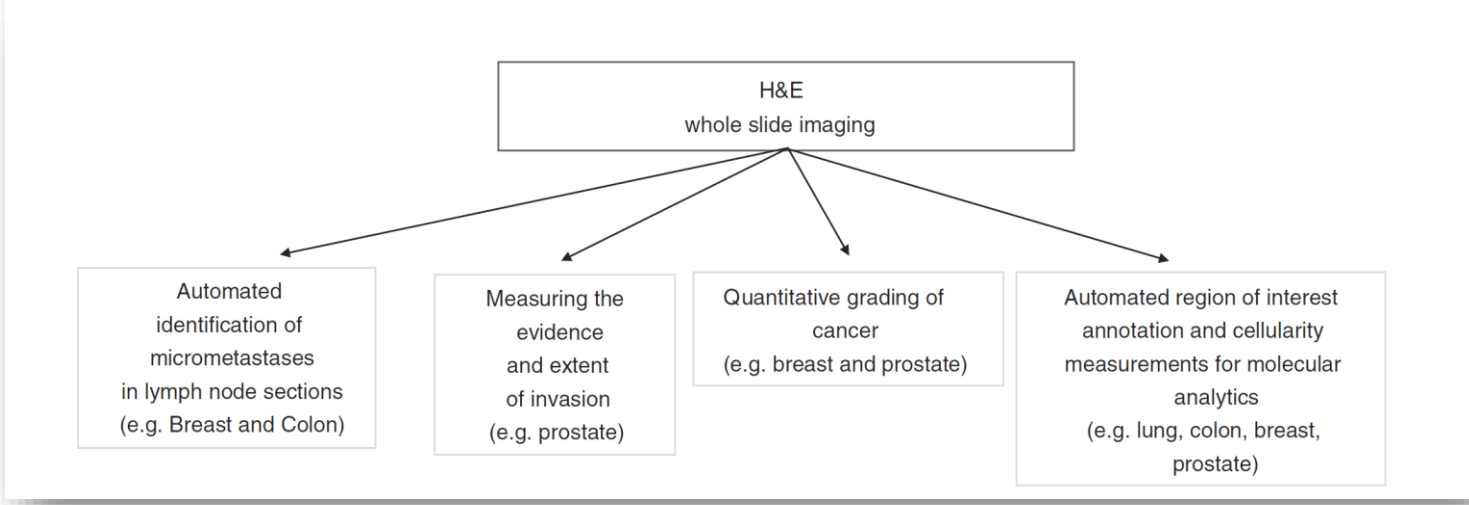
Histopathology 2019, **74**, 372–376.

Artificial intelligence—the third revolution in pathology

Manuel Salto-Tellez[1,2,3]
Perry Maxwell[1,2]
Peter Hamilton[4]

[1]*Precision Medicine Centre of Excellence,* [2]*Centre for Cancer Research and Cell Biology, Queen's University Belfast,* [3]*Tissue Pathology, Belfast Health and Social Care Trust, and* [4]*Philips Digital Pathology, Belfast, UK*



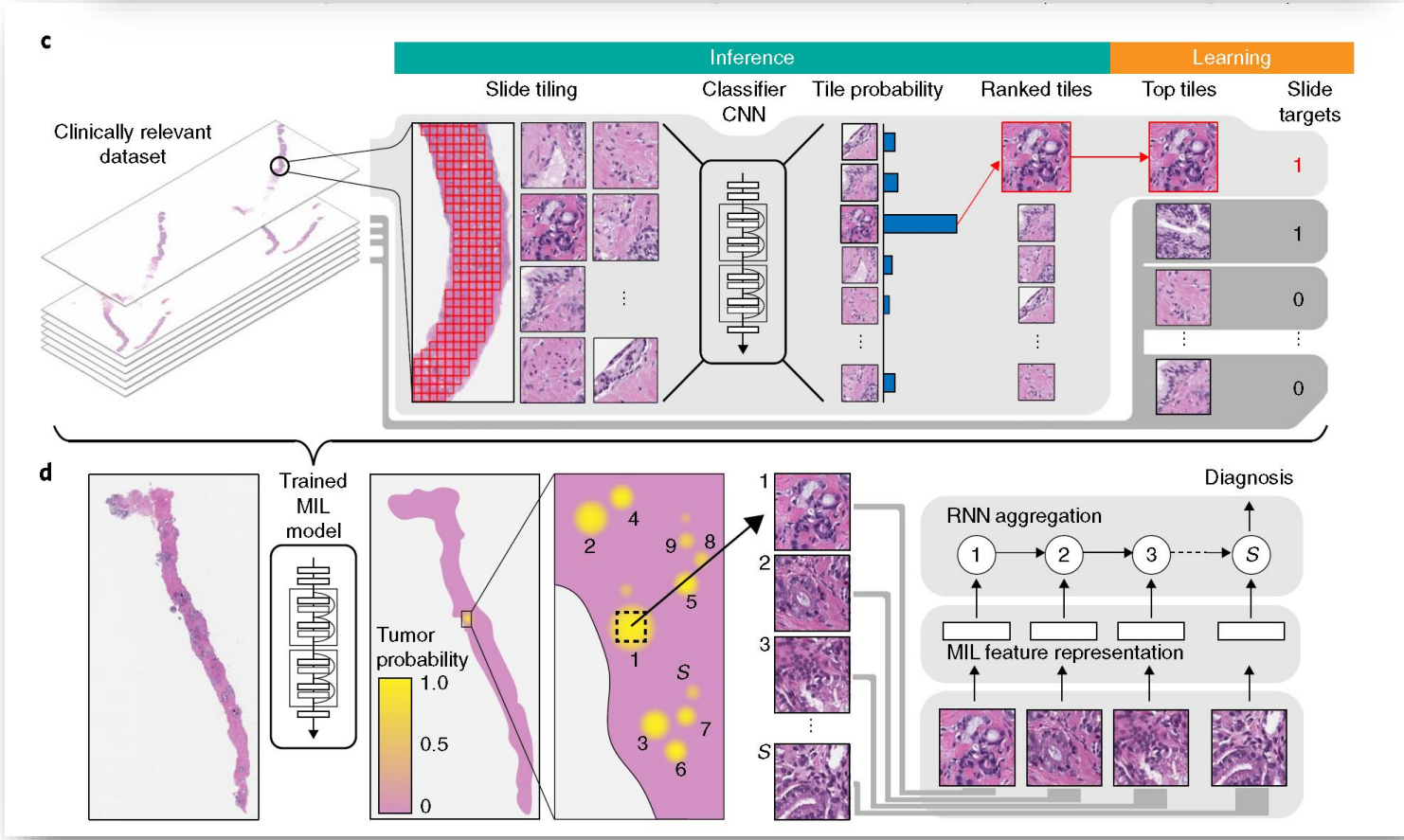


Clinical-grade computational pathology using weakly supervised deep learning on whole slide images

Gabriele Campanella[1,2], Matthew G. Hanna[1], Luke Geneslaw[1], Allen Miraflor[1], Vitor Werneck Krauss Silva[1], Klaus J. Busam[1], Edi Brogi[1], Victor E. Reuter[1], David S. Klimstra[1] and Thomas J. Fuchs[1,2]*

nature medicine

44,732 WSI
from 15,187

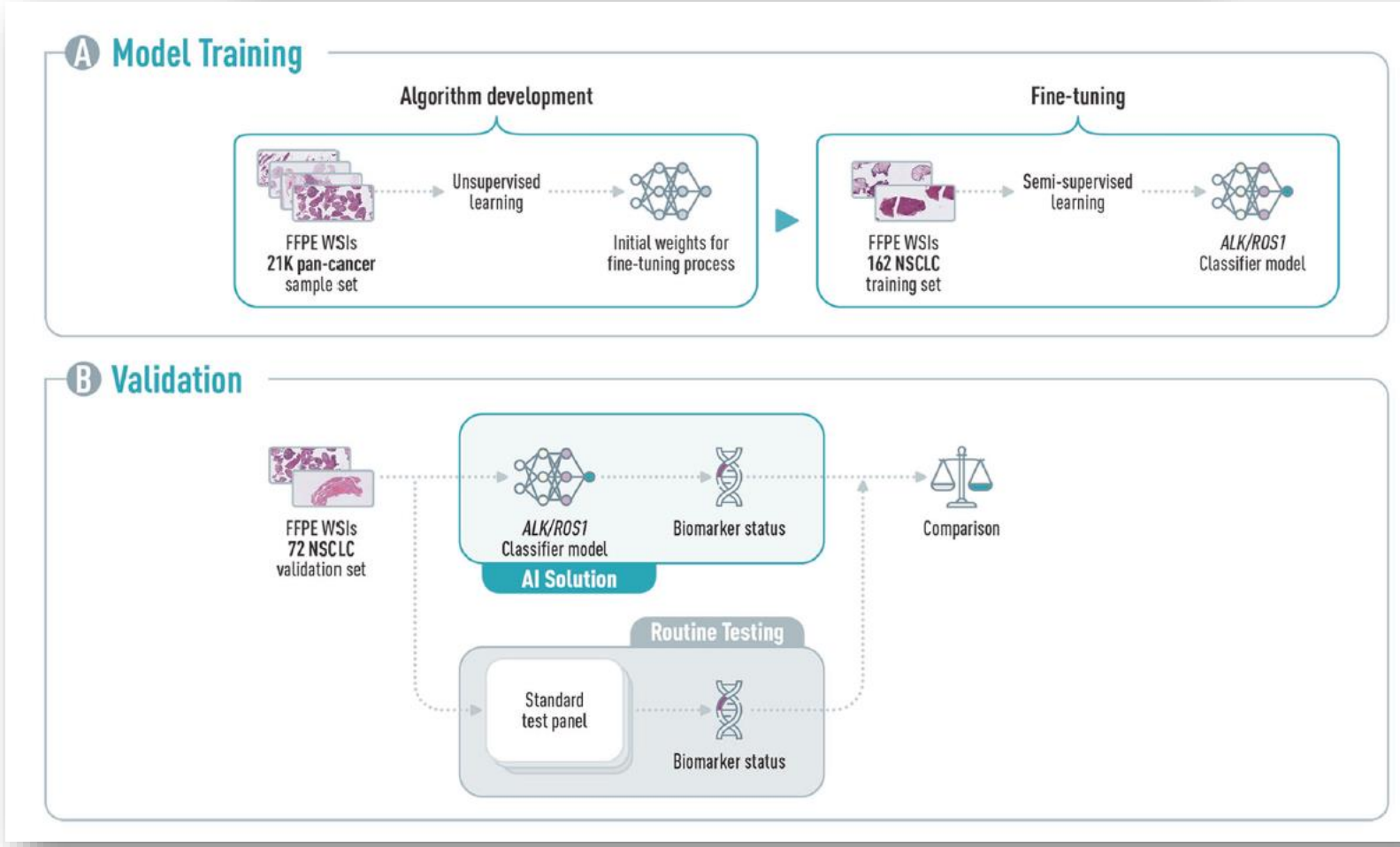


ARTICLE OPEN

Check for updates

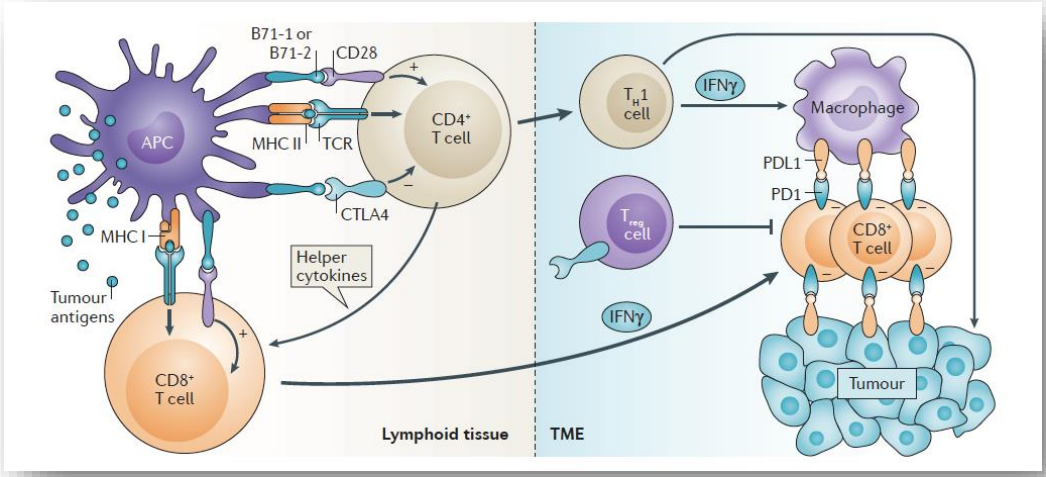
Direct identification of *ALK* and *ROS1* fusions in non-small cell lung cancer from hematoxylin and eosin-stained slides using deep learning algorithms

Chen Mayer[1,4], Efrat Ofek[1,4], Danielle Even Fridrich[1], Yossef Molchanov[1], Rinat Yacobi[1], Inbal Gazy[2], Ido Hayun[2], Jonathan Zalach[2], Nurit Paz-Yaacov[2] and Iris Barshack[1,3]

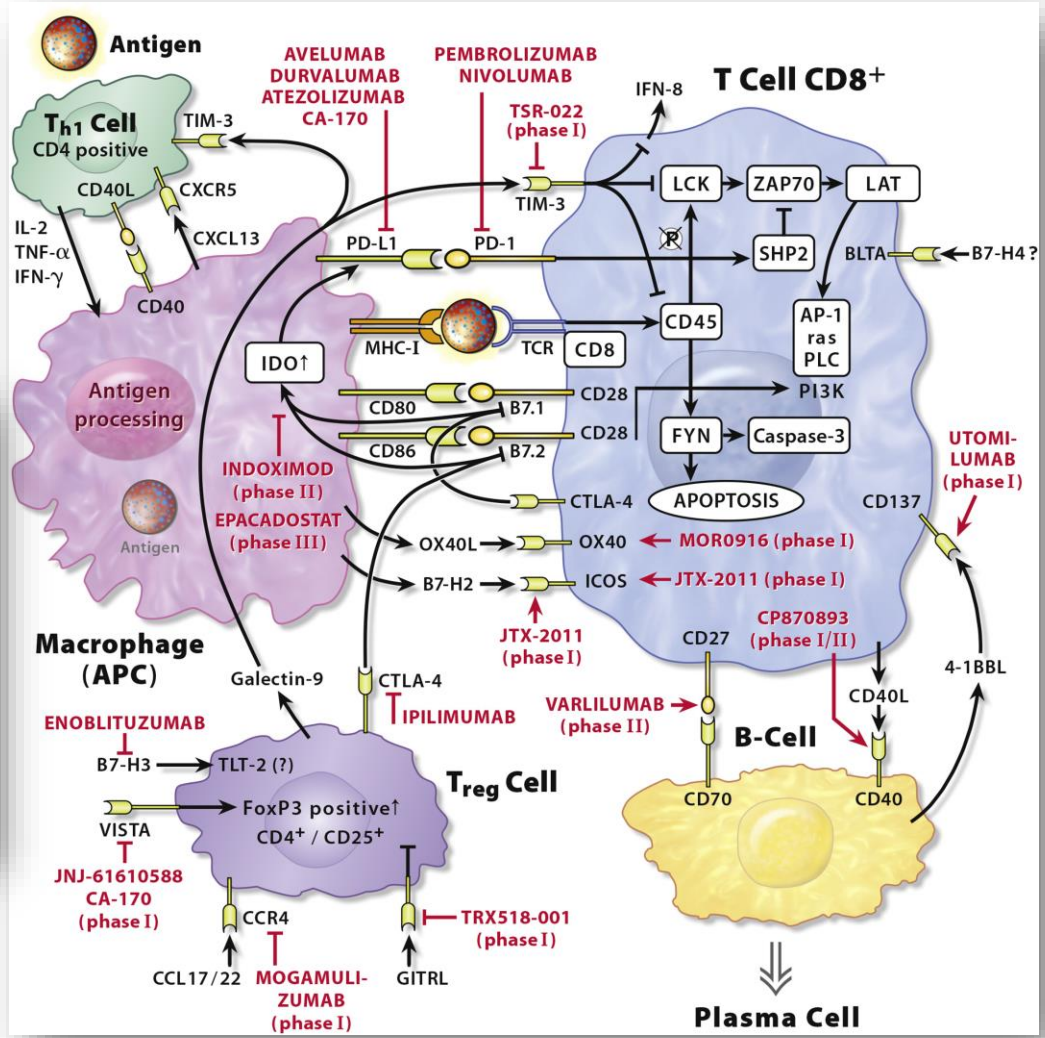


Modern Pathology Sept 2022

Immune Checkpoint Pathways

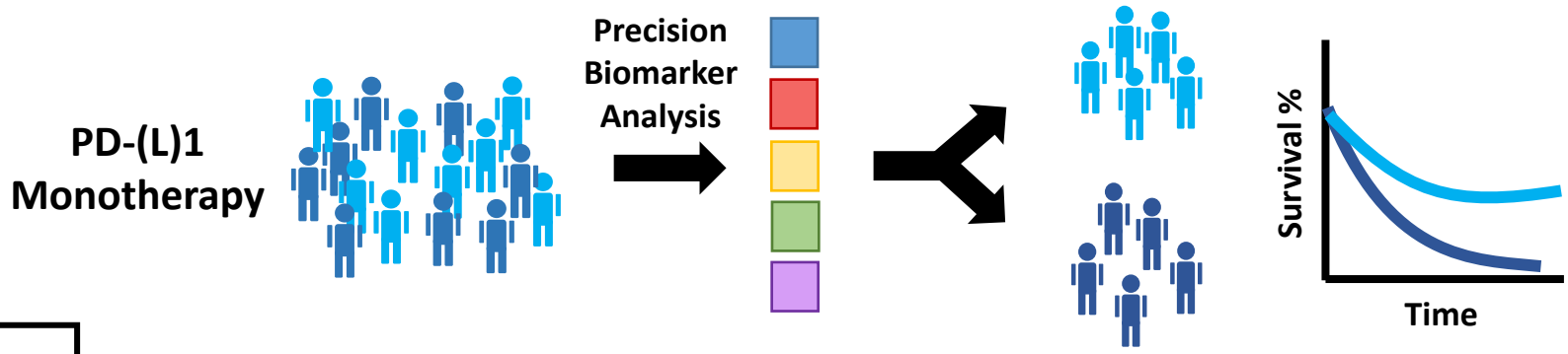


Nature Reviews CANCER 2016



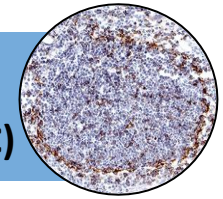
European Journal of Cancer 2017

Evaluating Predictive Biomarkers for Immunotherapies

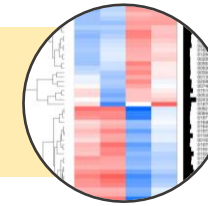


Biomarker Strategies/
Assay Modalities

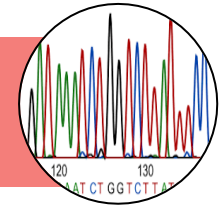
PD-L1
Immunohistochemistry (IHC)



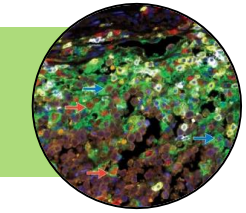
Gene Expression
Profiling (GEP)



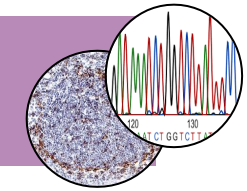
Tumor Mutation
Burden (TMB)



Multiplex IF/IHC



Multimodality

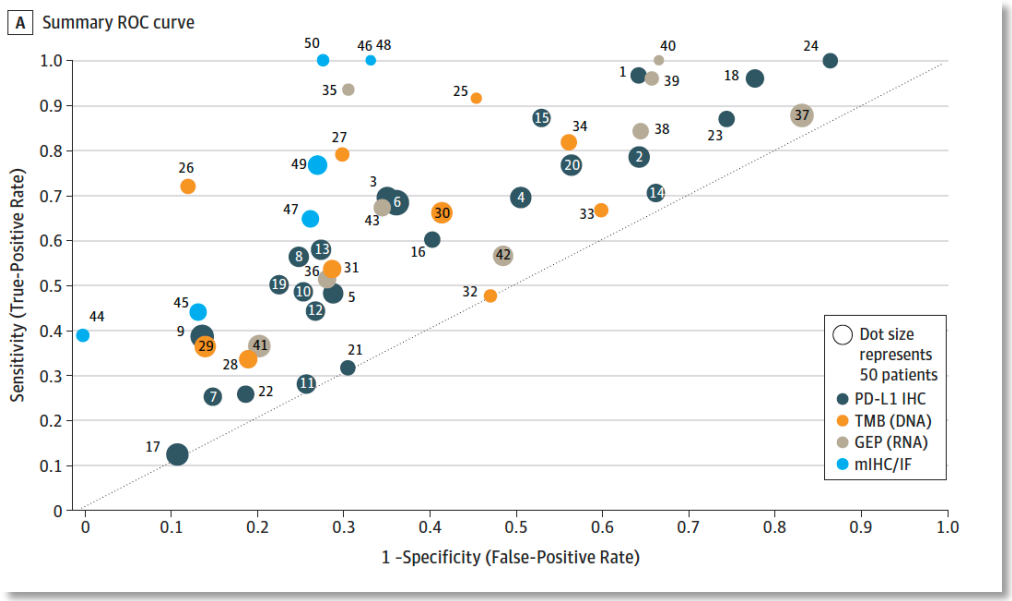


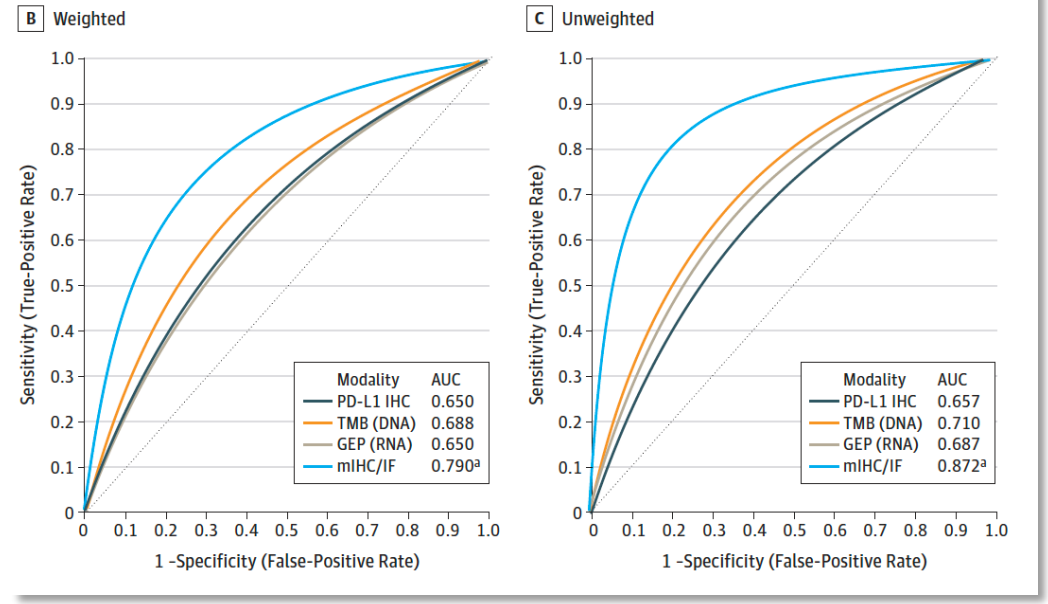
Courtesy of Dr. Janis Taube

JAMA Oncology | Original Investigation

Comparison of Biomarker Modalities for Predicting Response to PD-1/PD-L1 Checkpoint Blockade
A Systematic Review and Meta-analysis

Steve Lu; Julie E. Stein, MD; David L. Rimm, MD, PhD; Daphne W. Wang, MS; J. Michael Bell; Douglas B. Johnson, MD; Jeffrey A. Sosman, MD; Kurt A. Schalper, MD, PhD; Robert A. Anders, MD, PhD; Hao Wang, PhD; Clifford Hoyt, MS; Drew M. Pardoll, MD, PhD; Ludmila Danilova, PhD; Janis M. Taube, MD



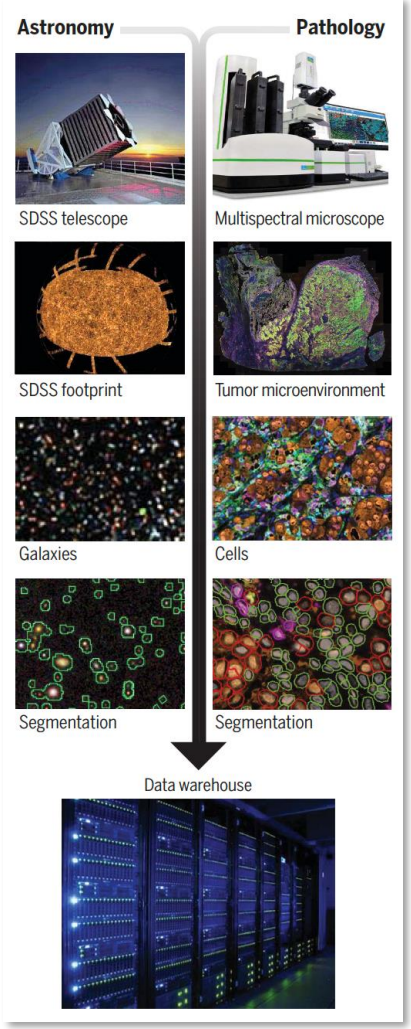


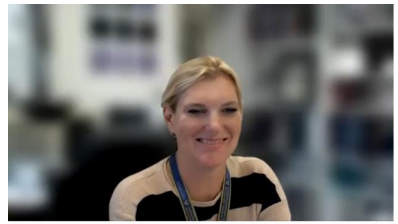
10 solid tumor types in 8135 patients

Analysis of multispectral imaging with the AstroPath platform informs efficacy of PD-1 blockade

Sneha Berry†, Nicolas A. Giraldo†, Benjamin F. Green†, Tricia R. Cottrell, Julie E. Stein, Elizabeth L. Engle, Haiying Xu, Aleksandra Ogurtsova, Charles Roberts, Daphne Wang, Peter Nguyen, Qingfeng Zhu, Sigfredo Soto-Diaz, Jose Loyola, Inbal B. Sander, Pok Fai Wong, Shlomit Jessel, Joshua Doyle, Danielle Signer, Richard Wilton, Jeffrey S. Roskes, Margaret Eminizer, Seyoun Park, Joel C. Sunshine, Elizabeth M. Jaffee, Alexander Baras, Angelo M. De Marzo, Suzanne L. Topalian, Harriet Kluger, Leslie Cope, Evan J. Lipson, Ludmila Danilova, Robert A. Anders, David L. Rimm, Drew M. Pardoll, Alexander S. Szalay†, Janis M. Taube*†

Sloan Digital Sky Survey





The Economist

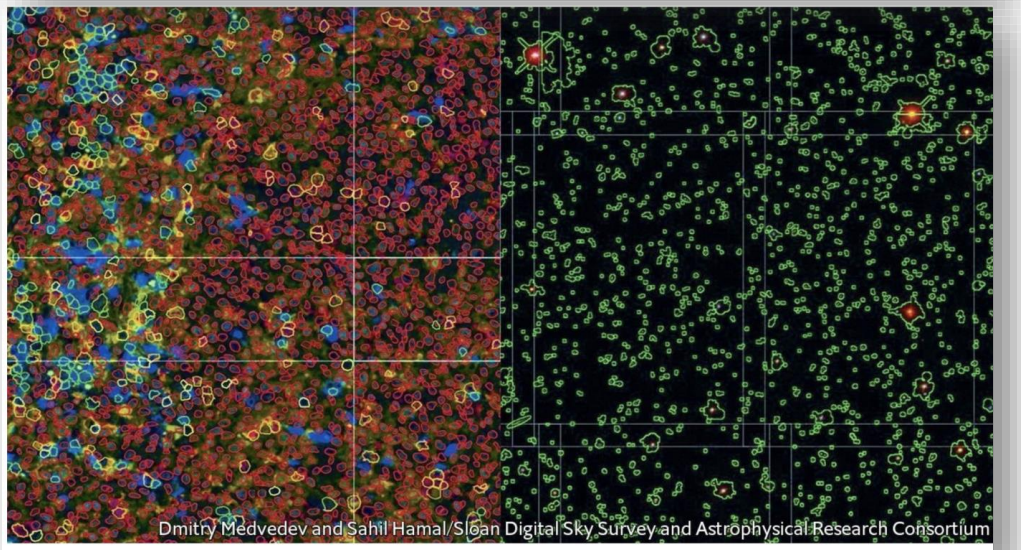
Science & technology

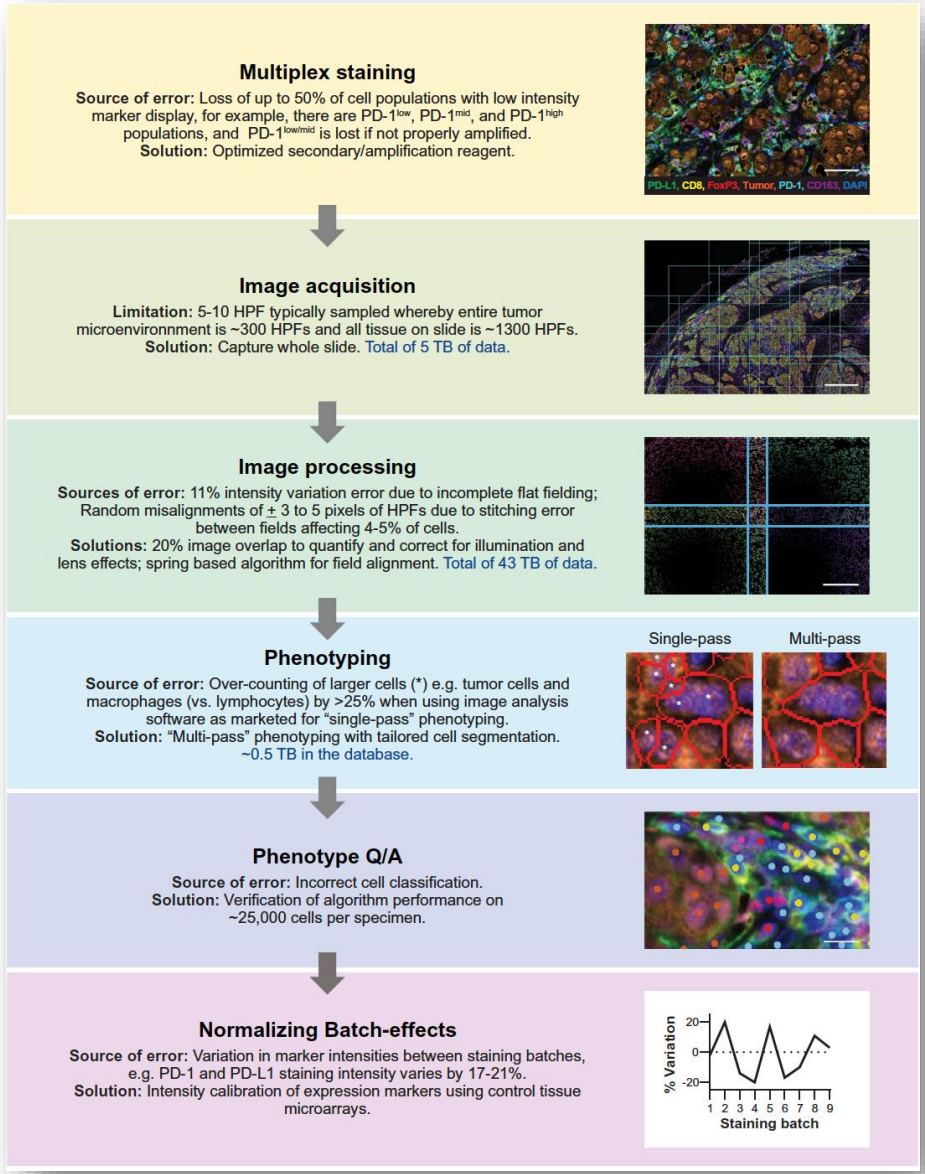
Apr 24th 2021 edition ›

Cancer research

Mapping cancer as if it were the universe

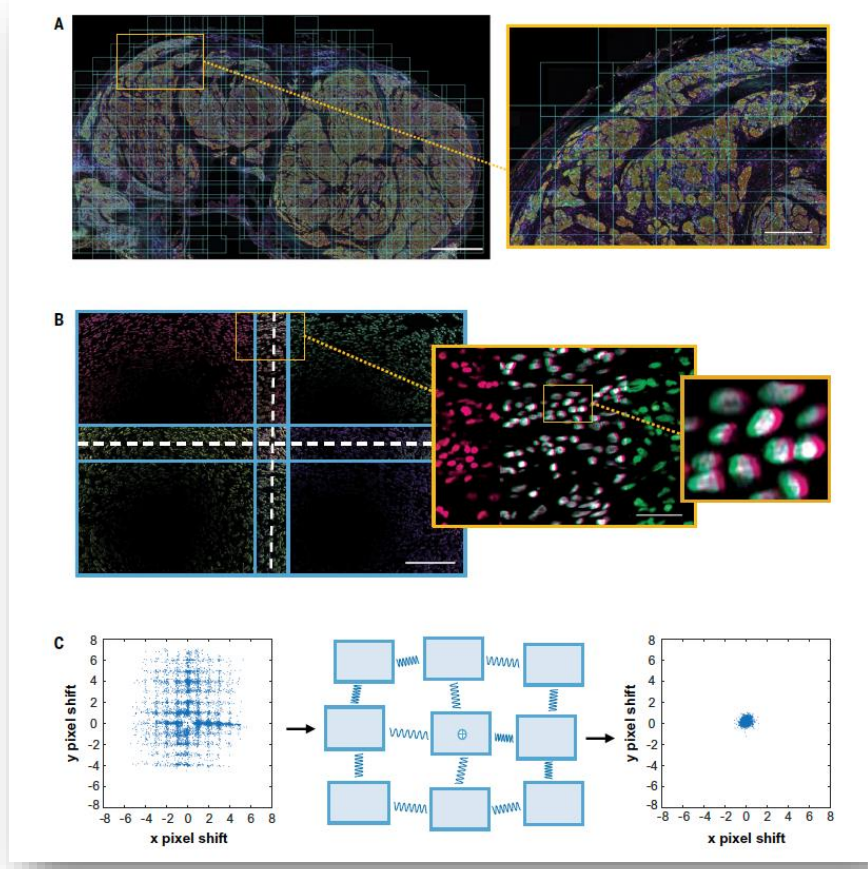
Techniques from astronomy are being applied to medicine



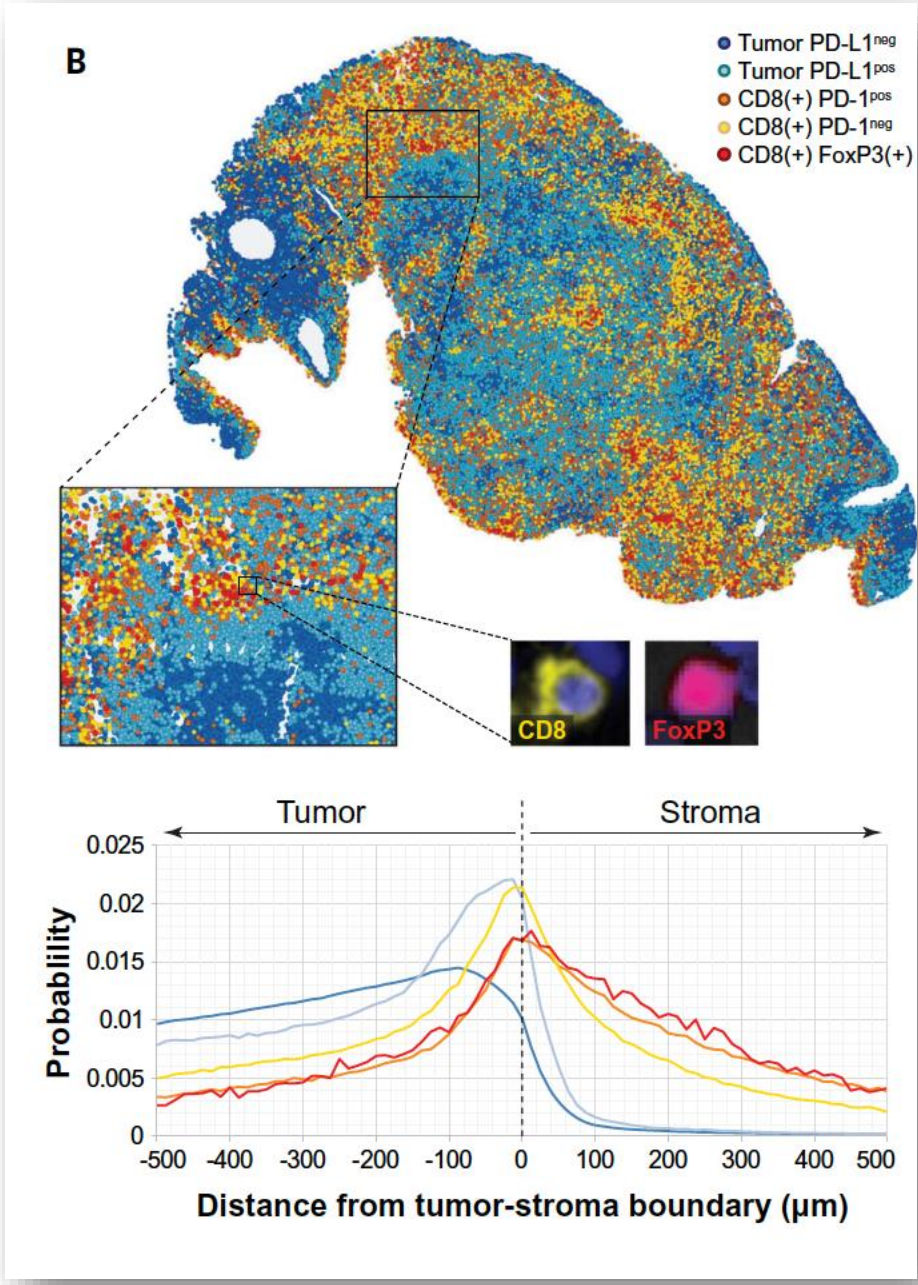


Berry S… Szalay AS and Taube JM; Science 2021

*Minimizing **instrument errors** during field **acquisition and stitching** of whole slide using lessons from astronomy*



Six PLEX
127,400 image mosaics
100 million single cells



Melanoma Anti PD1 Rx prediction:
CD163+PD-L1– myeloid cells
& **CD8+FoxP3+PD-1low/mid** T cells

CHALLENGES
Impact on Pathology and Lab Medicine

1) Unprecedented demands on **Expertise** and **Capital**
   - *Evolution and adaptation of pathology work force*
   - *$$ Investment*

2) **Financial viability** in constrained healthcare economics

Evolution of Pathology Work Force

- **Education** of the pathologist of the future
  Residency *curriculum adjustment*
  Fellowship *modifications*
  Multichannel Learning

https://www.nature.com/collections/fbdjhcfiia

- Pathologist **Physician Scientist**
  *Training Pipelines (**MSTP**, **Integrated Residency Track**)*
  Junior faculty mentorship
  Enhance integration in clinical & ***translational research teams***

Conclusions & Open Discussion

- **The future is ours to claim** if we embrace the unstoppable change in our profession

- Precision medicine opens **new doors** for pathologists to be on the **frontlines of patient care** delivery

- Tough economic challenges are not insurmountable but will require operational and Business Models adjustments

THANK YOU !.....

Acknowledgements

George J. Netto Lab

- Marie-Lisa Eich
- Maria del Carmen Rodriguez Peña
- Aline C. Tregnago
- Diana Taheri
- Stephania M. Bezerra
- Enrico Munari
- Sheila F. Faraj

Bert Vogelstein Lab: Howard Hughes Medical Institute, Ludwig Center

- Simeon U. Springer
- Isaac Kinde
- Cristian Tomasetti
- Luis A. Diaz
- Christopher Douville
- Yuxuan Wang
- Nickolas Papadopoulos
- Kenneth W. Kinzler

Johns Hopkins University

- Trinity J. Bivalacqua
- Christopher VandenBussche
- Ralph H. Hruban

AC Camargo Cancer Center, Brasil

- Stephania M. Bezerra
- Isabela W. Cunha

Osaka University, Japan

- Kazutoshi Fujita

Hacettepe University, Turkey

- Dilek Ertoy

Stony Brook University

- Kathleen G Dickman
- Arthur P Grollman

National Taiwan University Hospital

- Chao-Yuan Huang
- Yeong-Shiau Pu
- Chung-Hsin Chen

Funding

- NIH (Grants CA-77598, CA 06973, GM 07309, and ES019564).
- National Science Council, Taiwan to CHC (104-2314-B-002-132) and to YSP (104-2314-B-002-121-MY3)
- Henry and Marsha Laufer
- Virginia and DK Ludwig Fund for Cancer Research
- Commonwealth Foundation
- John Templeton Foundation
- Conrad R Hilton Foundation.

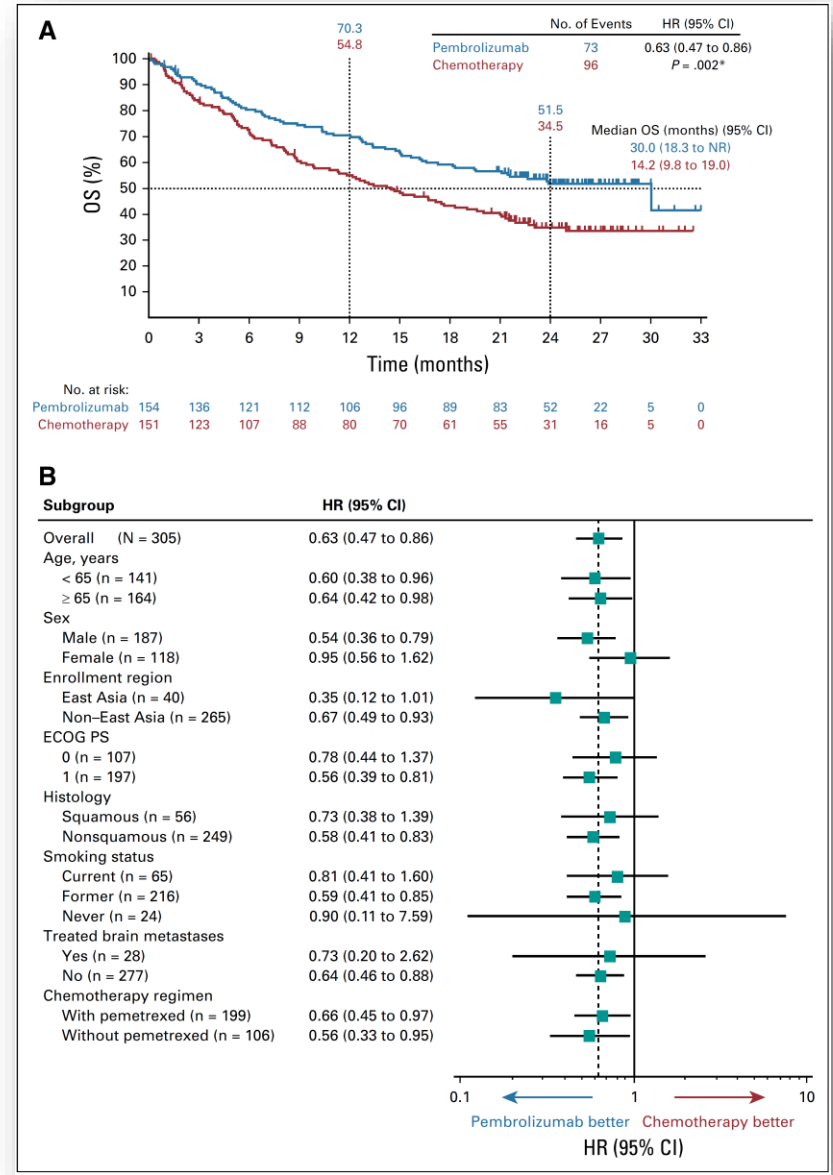
UAB MEDICINE

Knowledge that will change your world

Updated Analysis of KEYNOTE-024: Pembrolizumab Versus Platinum-Based Chemotherapy for Advanced Non–Small-Cell Lung Cancer With PD-L1 Tumor Proportion Score of 50% or Greater

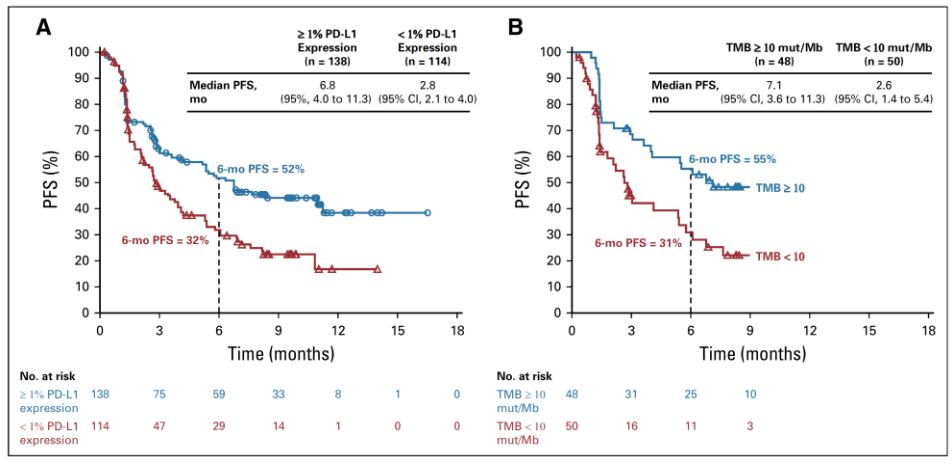
Martin Reck, MD, PhD[1]; Delvys Rodríguez-Abreu, MD[2]; Andrew G. Robinson, MD[3]; Rina Hui, MBBS, PhD[4]; Tibor Csőszi, MD[5]; Andrea Fülöp, MD[6]; Maya Gottfried, MD[7]; Nir Peled, MD, PhD[8]; Ali Tafreshi, MD[9]; Sinead Cuffe, MD[10]; Mary O'Brien, MD[11]; Suman Rao, MD[12]; Katsuyuki Hotta, MD, PhD[13]; Kristel Vandormael, MSc[14]; Antonio Riccio, PhD[15]; Jing Yang, PhD[15]; M. Catherine Pietanza, MD[15]; and Julie R. Brahmer, MD[16]

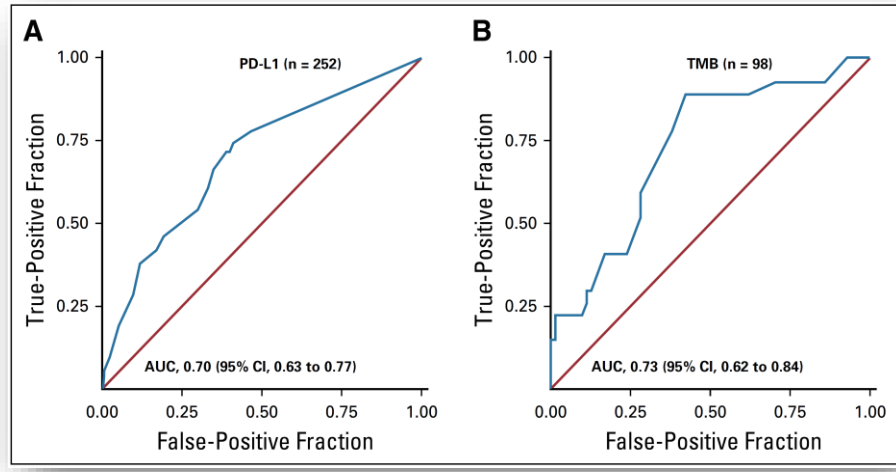
Reck M et al JCO 2019



First-Line Nivolumab Plus Ipilimumab in Advanced Non–Small-Cell Lung Cancer (CheckMate 568): Outcomes by Programmed Death Ligand 1 and Tumor Mutational Burden as Biomarkers

Neal Ready, MD, PhD[1]; Matthew D. Hellmann, MD[2]; Mark M. Awad, MD, PhD[3]; Gregory A. Otterson, MD[4]; Martin Gutierrez, MD[5]; Justin F. Gainor, MD[6]; Hossein Borghaei, DO[7]; Jacques Jolivet, MD[8]; Leora Horn, MD[9]; Mihaela Mates, MD[10]; Julie Brahmer, MD[11]; Ian Rabinowitz, MD[12]; Pavan S. Reddy, MD[13]; Jason Chesney, MD, PhD[14]; James Orcutt, MD[15]; David R. Spigel, MD[16]; Martin Reck, PhD[17]; Kenneth John O'Byrne, MD[18]; Luis Paz-Ares, MD, PhD[19]; Wenhua Hu, PhD[20]; Kim Zerba, PhD[20]; Xuemei Li, MD[20]; Brian Lestini, MD, PhD[20]; William J. Geese, PhD[20]; Joseph D. Szustakowski, PhD[20]; George Green, PhD[20]; Han Chang, PhD[20]; and Suresh S. Ramalingam, MD[21]





Ready N et al JCO 2019

Laboratory Informatics, Data Analytics and Big Data

Laboratory Informatics

&

Big Data

Pathology and Lab Med Opportunities

- **Big Data:** 2/3 of EMR data is Lab Med data
  Clinical Laboratory scientists are positioned to be the "Rock Stars" of Big Data ☺

- Clinical **decision support**
- Judicial **test utilization**
- Patient **outcome optimization**
- Phenotype/Genotype datasets $$$

https://health.usf.edu
https://www.datanami.com
https://theconversation.com

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- Pathologist **Physician Scientist**
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  Junior faculty mentorship
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Financial Viability
“Precision” Pathology Service

“Precision” Pathology Service

- **Value Based Product**
- **Quality** that **impacts** patient **outcome**
  Downstream cost savings
- **Judicial test utilization**
  Evidence based/Guidelines driven utilization (NCCN, AMP/CAP/ASCO)
- **Pathologist of the future** is a **vital** player in patient management team
  Molecular multidisciplinary tumor boards
  Diagnostic Management Teams (DMT)
  Cell Therapy (CAR-T Cell)

Financial Viability of Pathology Services

New Revenue Stream

- **Expanding Services Portfolio**
  Community Network Services
  Monetize Knowledge/ Processes transfer (National and International)
  Anatomic Pathology Consultations Services ***(Digital Path/Telehealth)****

- **Discovery and Innovation**
  *Entrepreneurial opportunities of Translational Pathology**
  Academic/Industry/NFP partnerships

Growth of Pathology Research Enterprise

Research Funding

- **NIH**
  2022: Biden admin proposes $51.9 billion **(21% increase)**

- Other Governmental
  DOD/ VA

- Non-Governmental Foundations
- **Philanthropy**
- **Industry Grants**

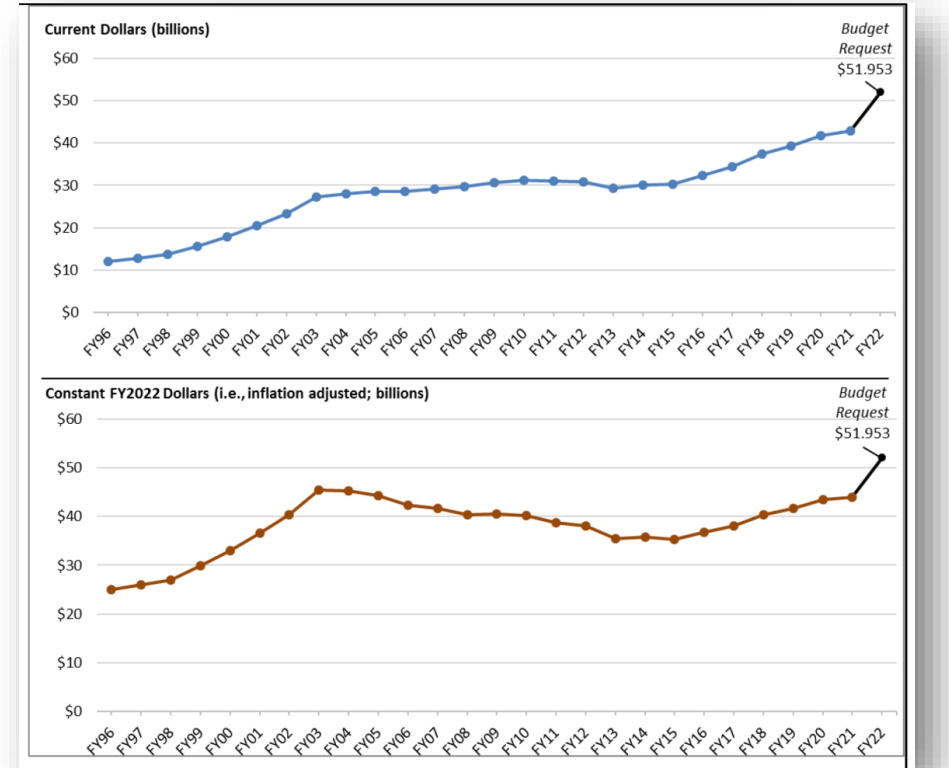

Figure 1. National Institutes of Health (NIH) Funding, FY1996-FY2022
Program Level Funding in Current and Projected Constant (FY2022) Dollars.

Growth of Pathology Research Enterprise

FOLLOW THE MONEY !!

- “Late” translational research
- Aging
- Health Disparity/Population health
- Tissue/Biospecimen Repositories
- URiM

Conclusions & Open Discussion

- **The future is ours to claim** if we embrace the unstoppable change in our profession

- Precision medicine opens **new doors** for pathologists to be on the **frontlines of patient care** delivery

- Tough economic challenges are not insurmountable but will require operational and Business Models adjustments

THANK YOU !.....

Open Discussion

Personal Research Contributions

Personal Research Contributions

- TMPRSS2-ERG Fusion in Prostate Ca
- MTOR Pathway Alterations in GU Malignancies
- Molecular Assays for Early Detection of Bladder Ca & UTUC
- Tumor Immune Microenvironment and Molecular Classification (Basal/Luminal) in MIBC and NMIBC

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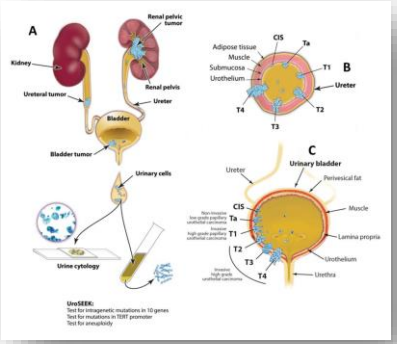
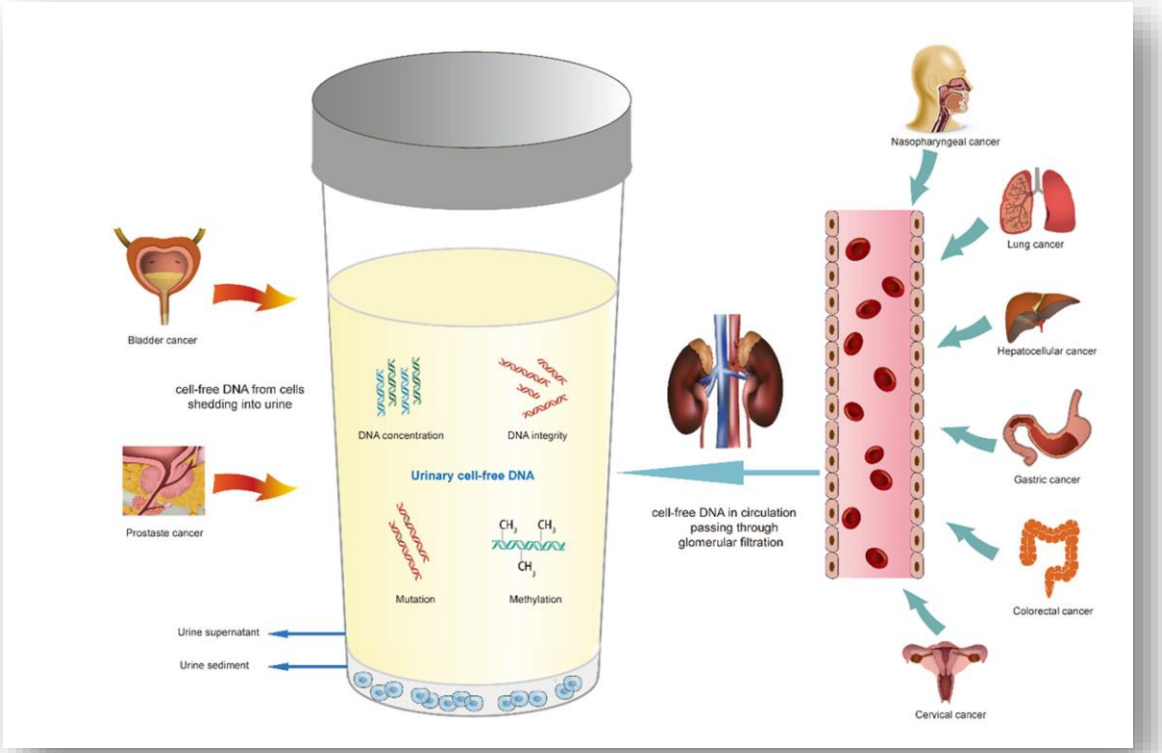


UroSEEK

Urine: The “other” Liquid Biopsy

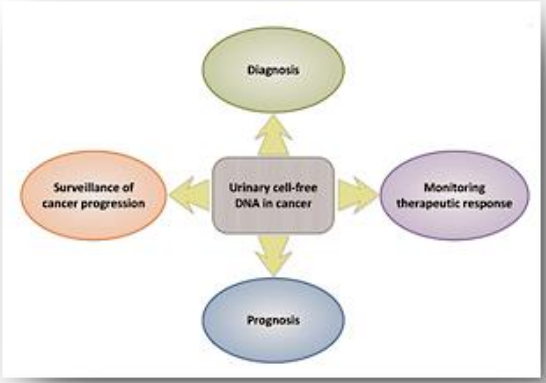
Urine Liquid Biopsy Analytes

- **Exfoliated cellular NA** (3x10^6 cells daily)
- **ucfDNA**
  - HMW (1K bp): Necrotic cells (shed)
  - LMW (**150**-250 bp)
    - Apoptotic cells (shed)
    - Transrenal DNA (**trDNA**)
  - ucfDNA of fetal origin (29-45bp)
- **ucfRNA** (miRNA)
- **EV**



Lu T, Li J.. Am J Cancer Res. 2017

Urine
Liquid Biopsy Applications



Lu T, Li J.. Am J Cancer Res. 2017

Table 1. Summary of potential clinical applications of ucfDNA in cancer

Clinical application	Markers	Types of cancer	Detection methods	References
Detection/Diagnosis	UcfDNA concentration	Bladder cancer	GeneQuant Pro	Zancan et al. [54]
			Quant-iT DNA high-sensitivity assay kit	
			Real-time PCR	
			NanoDrop 1000	
	UcfDNA/UCr concentration and ucfDNA integrity	Bladder cancer	PicoGreen 400-bp real-time PCR	Chang et al. [25]
	UcfDNA quantification	Bladder cancer	Real-time PCR	Brisuda et al. [55]
	TopoIIA levels	NMIBC	Real-time PCR	Kim et al. [60]
	UcfDNA integrity	Bladder cancer	Real-time PCR using IQ SYBR Green	Casadio et al. [38]
	Six microsatellite markers on chromosomes 4, 9, and 17	Bladder cancer	PCR	Utting et al. [66]
	Twelve microsatellite markers on 6 chromosomes	Bladder cancer	PCR	Szarvas et al. [13]
	TSPAN13-to-S100A9 ratio	Prostate cancer	Real-time PCR	Yan et al. [68]
	UcfDNA integrity (c-Myc, BCAS1, and HER2)	Prostate cancer	Real-time PCR	Casadio et al. [39]
	UcfDNA integrity (c-MYC, HER2, and AR)	Prostate cancer	Real-time PCR	Salvi et al. [69]
	GSTP1 gene promoter hypermethylation	Prostate cancer	Methylation-specific PCR	Bryzgunova et al. [72]
	KRAS mutations	Advanced colorectal adenocarcinoma and advanced pancreatic cancer	PCR	Botezatu et al. [18]
	KRAS mutations	Colorectal cancer	Restriction-enriched PCR	Su et al. [17, 33, 35]
	mVIM	Colorectal cancer	Quantitative MethyLight PCR-based assay	Song et al. [73]
	TP53 mutation	Hepatocellular carcinoma	Locked nucleic acid clamp-mediated PCR assay	Lin et al. [74]
	HCC-associated HBV mutation	HBV-associated hepatocellular carcinoma	Real-time PCR	Lin et al. [75]
	HPV DNA	Cervical cancer	NGS	Guerrero-Preston et al. [80]
Surveillance of cancer progression	Somatic variants	Bladder cancer	ddPCR	Birkenkamp-Demtröder et al. [81]
	Somatic variants	UBC	OncoScan assay	Togneri et al. [82]
	FGFR3 and *PIK3CA* mutations	Bladder cancer	ddPCR	Christensen et al. [83]
	EGFR mutations	NSCLC	ddPCR	Li et al. [88]
	KRAS mutations	NSCLC	ddPCR	Wang et al. [85]
Monitoring treatment response	Copy number variations	Prostate cancer	Whole genome sequencing	Xia et al. [86]
	EGFR mutations	NSCLC	Short footprint mutation enrichment NGS	Reckamp et al. [40]
	EGFR mutations	NSCLC	ddPCR	Li et al. [84]
				Chen et al. [89]
				Husain et al. [96]
				Tchekmedyian et al. [91]
	EGFR mutations	Gastric cancer	ddPCR	Shi et al. [36]
	CAD-ALK gene rearrangement	Colorectal cancer	NGS	Siravegna et al. [92]
	BRAF V600E mutations	Colorectal neuroendocrine cancer	PCR	Klempner et al. [93]
	KRAS G12/G13 mutations	Advanced cancers	Mutation-enrichment NGS	Fujii et al. [41]
Prognosis	EBV DNA	Nasopharyngeal carcinoma	Real-time PCR	Chan et al. [94]
				Sengar et al. [95]
	EGFR mutations	NSCLC	ddPCR	Li et al. [84]
	KRAS mutations	NSCLC	ddPCR	Wang et al. [85]

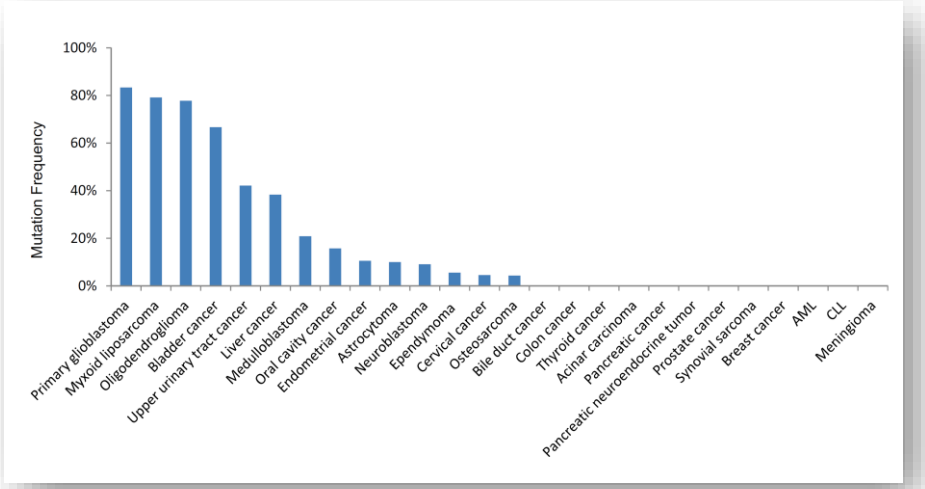
Abbreviations: ucfDNA, urinary cell-free DNA; NMIBC, non-muscle-invasive bladder cancer; GSTP1, glutathione S-transferase P1 gene; mVIM, hypermethylated vimentin gene; NGS, next-generation sequencing; ddPCR, droplet digital PCR; UBC, urothelial bladder cancer; NSCLC, non-small cell lung cancer.

TERT promoter mutations occur frequently in gliomas and a subset of tumors derived from cells with low rates of self-renewal

Patrick J. Killela[a,1], Zachary J. Reitman[a,1], Yuchen Jiao[b,1], Chetan Bettegowda[b,c,1], Nishant Agrawal[b,d], Luis A. Diaz, Jr.[b], Allan H. Friedman[a], Henry Friedman[a], Gary L. Gallia[c,d], Beppino C. Giovanella[e], Arthur P. Grollman[f], Tong-Chuan He[g], Yiping He[a], Ralph H. Hruban[h], George I. Jallo[c], Nils Mandahl[i], Alan K. Meeker[h,m], Fredrik Mertens[i], George J. Netto[h,l], B. Ahmed Rasheed[a], Gregory J. Riggins[c], Thomas A. Rosenquist[f], Mark Schiffman[j], Ie-Ming Shih[h], Dan Theodorescu[k], Michael S. Torbenson[h], Victor E. Velculescu[b], Tian-Li Wang[h], Nicolas Wentzensen[j], Laura D. Wood[h], Ming Zhang[b], Roger E. McLendon[a], Darell D. Bigner[a], Kenneth W. Kinzler[b], Bert Vogelstein[b,2], Nickolas Papadopoulos[b], and Hai Yan[a,2]

Killela PJ et al. PNAS 2013

- ***TERT*** promoter mutations in **1,230** tumor
- Identified **TERT** mutations in 231 **(18.8%)** tumors
  - **C228T** (77.5%)
  - **C250T** (20.8%)
  - Rare C228A and C229A mutation
- ***TERT*** & ***ATRX*** mutations mutually exclusive



Priority Report

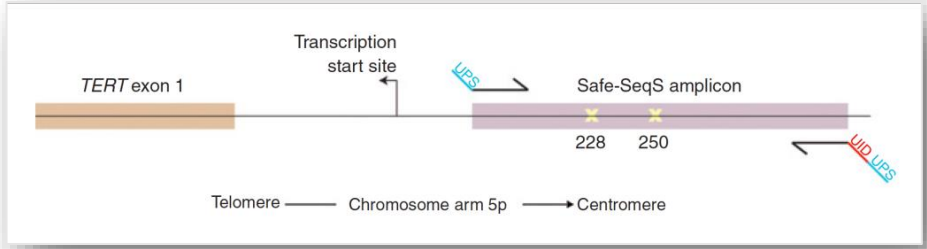
Cancer Research

TERT Promoter Mutations Occur Early in Urothelial Neoplasia and Are Biomarkers of Early Disease and Disease Recurrence in Urine

Isaac Kinde[1], Enrico Munari[2], Sheila F. Faraj[2], Ralph H. Hruban[2,3], Mark Schoenberg[4], Trinity Bivalacqua[4], Mohamad Allaf[4], Simeon Springer[1], Yuxuan Wang[1], Luis A. DiazJr[1], Kenneth W. Kinzler[1], Bert Vogelstein[1], Nickolas Papadopoulos[1], and George J. Netto[2,3,4]

Kinde I et al Cancer Research 2013

- 76 noninvasive urothelial carcinomas
  - 28 pTa LG
  - 31 pTa HG
  - 17 pTis CIS



- 14 early bladder neoplasms and matched follow-up urine

Priority Report

Cancer Research

TERT Promoter Mutations Occur Early in Urothelial Neoplasia and Are Biomarkers of Early Disease and Disease Recurrence in Urine

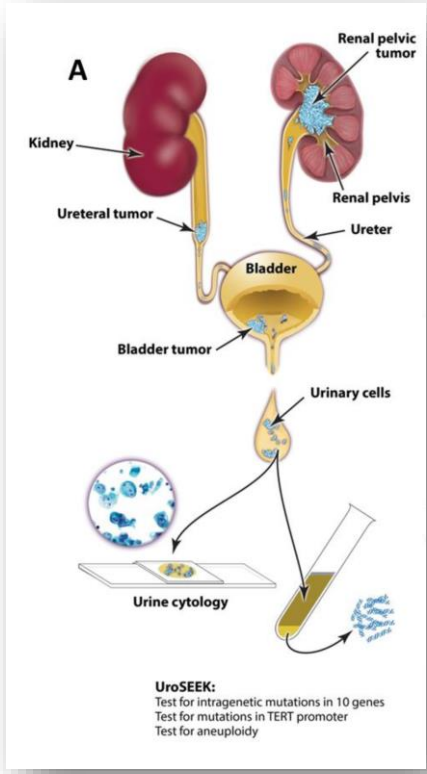
Isaac Kinde[1], Enrico Munari[2], Sheila F. Faraj[2], Ralph H. Hruban[2,3], Mark Schoenberg[4], Trinity Bivalacqua[4], Mohamad Allaf[4], Simeon Springer[1], Yuxuan Wang[1], Luis A. DiazJr[1], Kenneth W. Kinzler[1], Bert Vogelstein[1], Nickolas Papadopoulos[1], and George J. Netto[2,3,4]

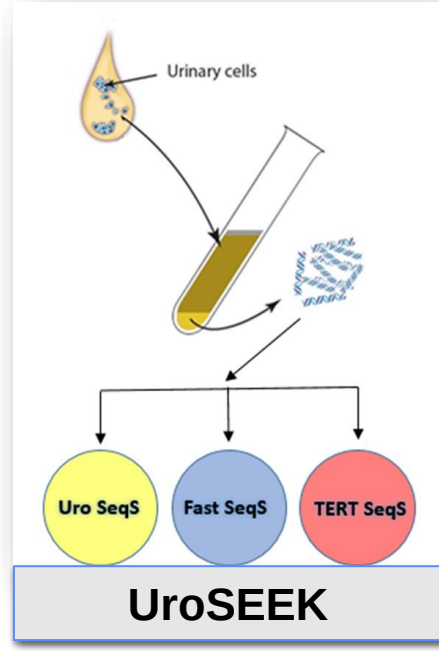
TERT promoter mutation	pTa LG ($N = 28$)	pTa HG ($N = 31$)	CIS ($N = 17$)	*P*
Present (%)	24/28 (86%)	21/31 (68%)	11/17 (65%)	0.18

Abbreviations: HG, high-grade noninvasive urothelial carcinoma; LG, low-grade noninvasive urothelial carcinoma.

TERT mutation in follow-up urine	Number of patients	Recurred	Did not recur	*P*
Present	8	8/8 (100%)	0/8 (0%)	<0.001
Absent	7	1/7 (11%)	6/7 (89%)	($r = 0.87$)[a]

[a]Pearson coefficient of correlation.





UroSeqS
(10 genes)

- *FGFR3*
- *PIK3CA*
- *HRAS*
- *KRAS*
- *TP53*
- *CDKN2A*
- *ERBB2*
- *MET*
- *MLL*
- *VHL*

Ludwig Cancer Research
JHU Pathology
JHU Brady Institute

- Two Application Settings
  - Surveillance
  - ED: Primary Screen (Hematuria no prior TCC)

- International Collaborators
  - Osaka University, Japan
  - AC CAMARGO Cancer Ctr, Brazil
  - Hacettepe University, Turkey
  - **Taiwan UTUC**

- >2800 Urine and > 600 FFPE Sequenced

UroSEEK in Bladder Cancer Tissue

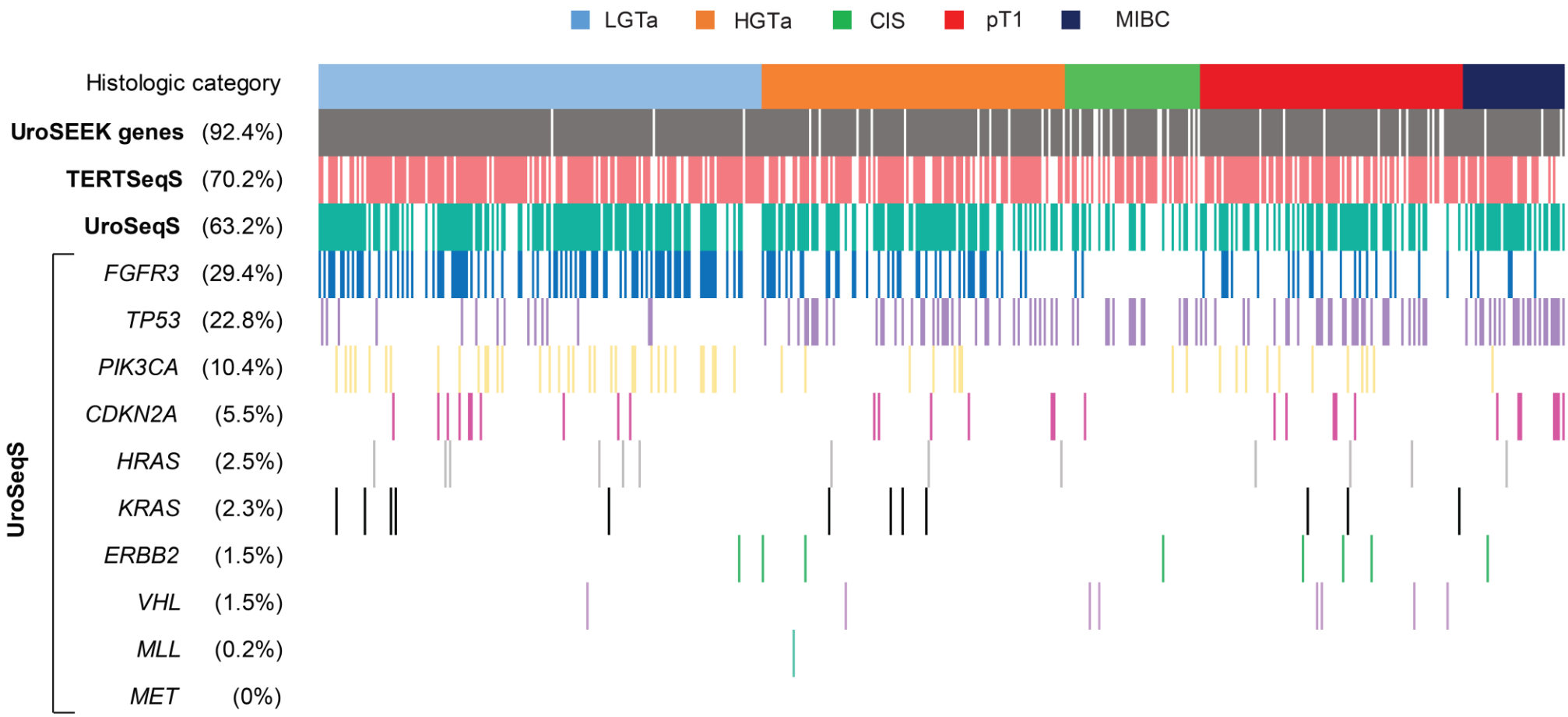
Incidence and Distribution of UroSEEK Gene Panel in a Multi-institutional Cohort of Bladder Urothelial Carcinoma

Marie-Lisa Eich[1], Maria Del Carmen Rodriguez Pena[1], Simeon Springer[2,3], Diana Taheri[4,5], Aline C. Tregnago[4], Daniela C. Salles[4], Stephania Martins Bezerra[6,7], Isabela W. Cunha[6], Kazutoshi Fujita[8], Dilek Ertoy[9], Trinity J. Bivalacqua[10], Cristian Tomasetti[11,12], Nickolas Papadopoulos[2,3], Ken W. Kinzler[2,3], Bert Vogelstein[2,3], George J. Netto[1]

- **527** tumors from 484 patients
  - 188 LGTa
  - 129 HGTa
  - 56 CIS
  - 111 pT1 tumors
  - 43 MIBC
- 36 patients with more than one tumor analyzed

Eich et al. Mod Pathol 2019

UroSEEK in Bladder Cancer Tissue



Eich et al. Mod Pathol 2019

Targeted sequencing of plasmacytoid urothelial carcinoma reveals frequent *TERT* promoter mutations☆,☆☆

Doreen N. Palsgrove MD[a], Diana Taheri MD[a,b], Simeon U. Springer PhD[c,d], Morgan Cowan MD[a], Gunes Guner MD[a], Maria A. Mendoza Rodriguez MD[a], Maria Del Carmen Rodriguez Pena MD[a,e], Yuxuan Wang BS[d], Isaac Kinde MD, PhD[d], Bernardo F.P. Ricardo MD[a], Isabela Cunha MD, PhD[f], Kazutoshi Fujita MD, PhD[g], Dilek Ertoy MD[h], Kenneth W. Kinzler PhD[c,d], Trinity J. Bivalacqua MD, PhD[i], Nickolas Papadopoulos PhD[c,d], Bert Vogelstein MD[c,d], George J. Netto MD[a,e,*]

Human Pathology (2019) **85**, 1–9

Detection of *TERT* promoter mutations in primary adenocarcinoma of the urinary bladder☆,☆☆

Morgan L. Cowan MD[a], Simeon Springer PhD[b,c], Doreen Nguyen MD[a], Diana Taheri MD[a], Gunes Guner MD[a], Maria Angelica Mendoza Rodriguez MD[a], Yuxuan Wang BS[c], Isaac Kinde MD, PhD[c], Maria Del Carmen Rodriguez Pena MD[a], Christopher J. VandenBussche MD, PhD[a], Mathew T. Olson MD, PhD[a], Isabela Cunha MD, PhD[d], Kazutoshi Fujita MD, PhD[e], Dilek Ertoy MD[f], Kenneth Kinzler PhD[b,c], Trinity Bivalacqua MD, PhD[g], Nickolas Papadopoulos PhD[b,c], Bert Vogelstein MD[b,c], George J. Netto MD[a,g,*]

Human Pathology (2016) **53**, 8–13

High prevalence of *TERT* promoter mutations in micropapillary urothelial carcinoma

Doreen Nguyen[1] · Diana Taheri[1,5] · Simeon Springer[3,4] · Morgan Cowan[1] · Gunes Guner[1] · Maria Angelica Mendoza Rodriguez[1] · Yuxuan Wang[4] · Isaac Kinde[4] · Christopher J. VandenBussche[1] · Matthew T. Olson[1] · Bernardo F. P. Ricardo[1] · Isabela Cunha[6] · Kazutoshi Fujita[7] · Dilek Ertoy[8] · Kenneth W. Kinzler[3,4] · Trinity J. Bivalacqua[2] · Nickolas Papadopoulos[3,4] · Bert Vogelstein[3,4] · George J. Netto[1,2,9]

Virchows Arch (2016) 469:427–434

High prevalence of *TERT* promoter mutations in primary squamous cell carcinoma of the urinary bladder

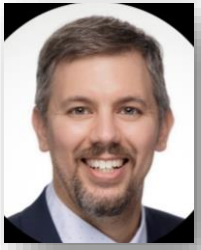
Morgan Cowan[1], Simeon Springer[2,3], Doreen Nguyen[1], Diana Taheri[1], Gunes Guner[1], Maria Angelica Mendoza Rodriguez[1], Yuxuan Wang[3], Isaac Kinde[3], Christopher J VandenBussche[1], Matthew T Olson[1], Isabela Cunha[4], Kazutoshi Fujita[5], Dilek Ertoy[6], Trinity J Bivalacqua[7], Kenneth Kinzler[2,3], Bert Vogelstein[2,3], George J Netto[1,7] and Nickolas Papadopoulos[2,3]

MODERN PATHOLOGY (2016) 29, 511–515

Spectrum of genetic mutations in de novo PUNLMP of the urinary bladder

Maria Del Carmen Rodriguez Pena[1] · Aline C. Tregnago[1] · Marie-Lisa Eich[1] · Simeon Springer[2] · Yuxuan Wang[2] · Diana Taheri[1] · Dilek Ertoy[3] · Kazutoshi Fujita[4] · Stephania M. Bezerra[5] · Isabela W. Cunha[5] · Maria Rosaria Raspollini[6] · Lijia Yu[7] · Trinity J. Bivalacqua[8] · Nickolas Papadopoulos[2] · Kenneth W. Kinzler[2] · Bert Vogelstein[2] · George J. Netto[1,7,9]

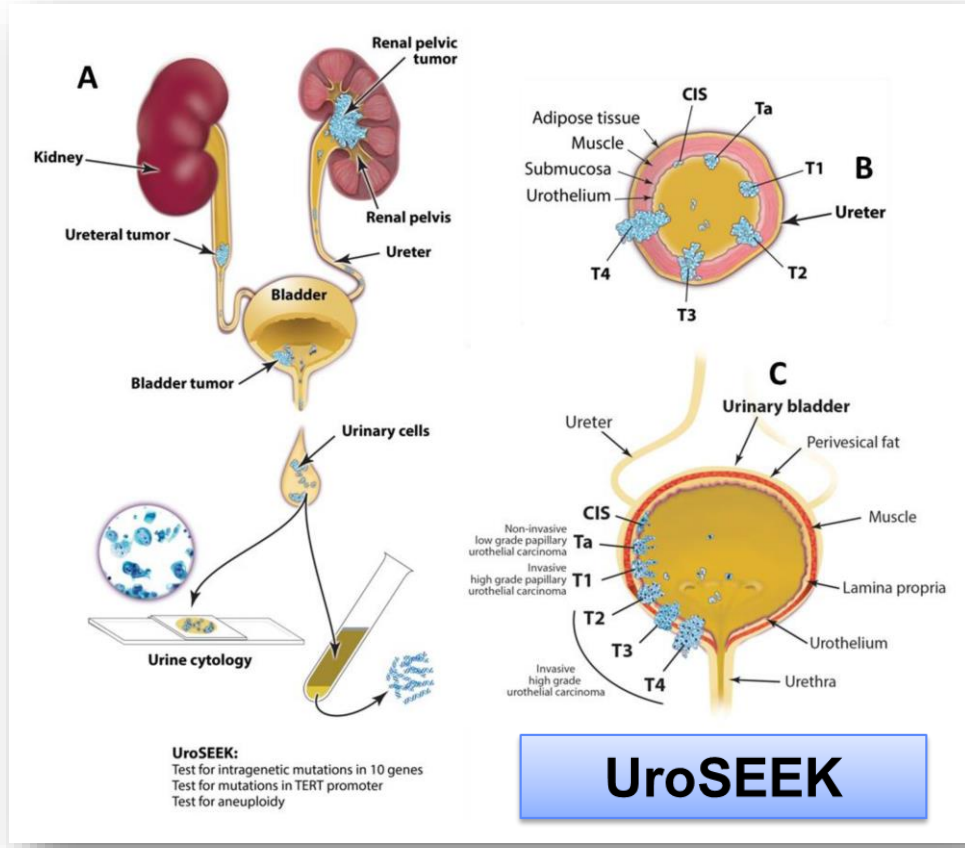
Virchows Arch (2017) 471:761–767



Non-invasive detection of urothelial cancer through the analysis of driver gene mutations and aneuploidy

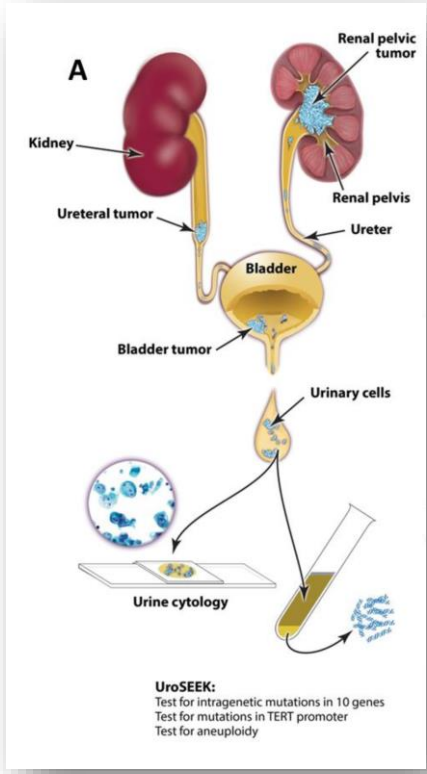
Simeon U Springer[1,2†], Chung-Hsin Chen[3†], Maria Del Carmen Rodriguez Pena[4,5†], Lu Li[6], Christopher Douville[7], Yuxuan Wang[1,2], Joshua David Cohen[1,2], Diana Taheri[4,8], Natalie Silliman[1,2], Joy Schaefer[1,2], Janine Ptak[1,2], Lisa Dobbyn[1,2], Maria Papoli[1,2], Isaac Kinde[1,2], Bahman Afsari[9,10], Aline C Tregnago[4], Stephania M Bezerra[11], Christopher VandenBussche[4], Kazutoshi Fujita[12], Dilek Ertoy[13], Isabela W Cunha[11], Lijia Yu[5], Trinity J Bivalacqua[14], Arthur P Grollman[15,16], Luis A Diaz[17], Rachel Karchin[7,9], Ludmila Danilova[10,13], Chao-Yuan Huang[3], Chia-Tung Shun[18], Robert J Turesky[19,20], Byeong Hwa Yun[19,20], Thomas A Rosenquist[15], Yeong-Shiau Pu[3], Ralph H Hruban[4], Cristian Tomasetti[6,10], Nickolas Papadopoulos[1,2], Ken W Kinzler[1,2], Bert Vogelstein[1,2*], Kathleen G Dickman[15,16*], George J Netto[4,5*]

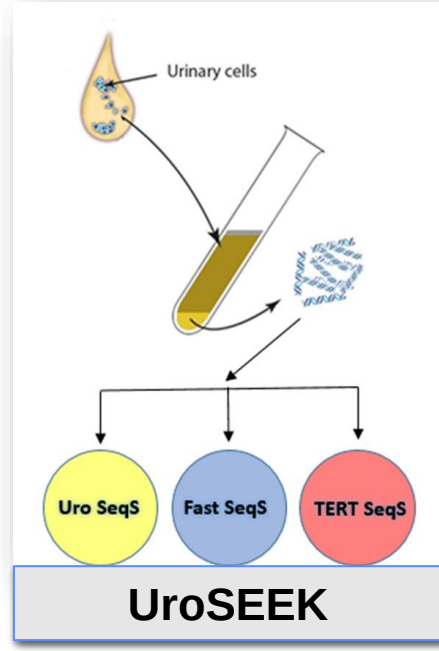
Springer et al. eLife 2018



UroSEEK:
Test for intragenetic mutations in 10 genes
Test for mutations in TERT promoter
Test for aneuploidy

UroSEEK





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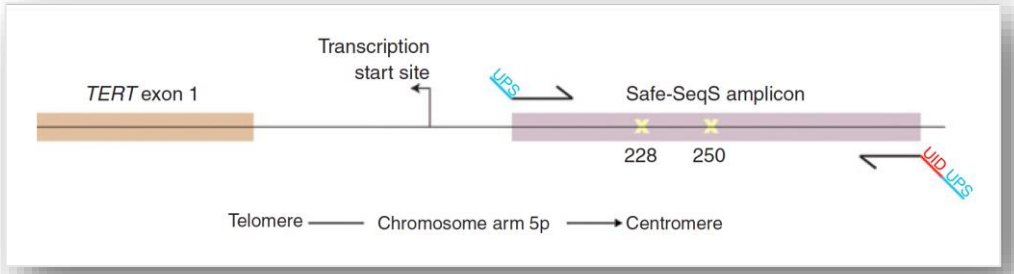
- *ERBB2*
- *MET*
- *MLL*
- *VHL*

TERTSeqS and UroSeqS

Safe SeqS (Safe-Sequencing System)

- **Cellular DNA**
- Massively parallel sequencing



- Error reducing approach
  - Unique Identifier for family of template
  - **Supermutant** (95%)

- Applicable for identifying mutations in a small fraction of DNA templates (0.03%)

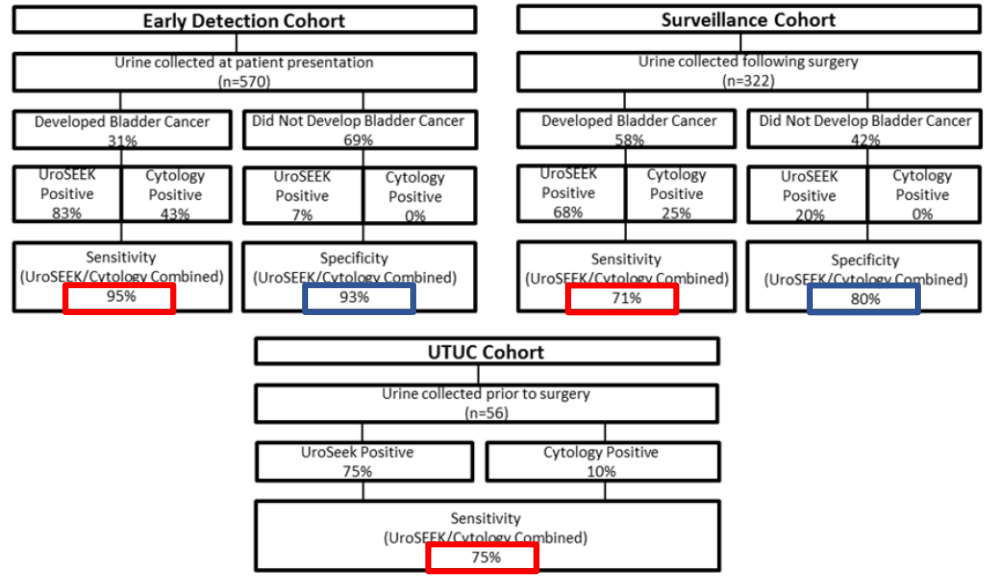
FastSeqS

- Aneuploidy Analysis
- Massively parallel sequencing

- **Single primer pair** to amplify about **38,000 loci** scattered throughout the genome

- Gains and losses in **39 chromosome arms** can be detected

UroSEEK


Early Detection Cohort
Urine collected at patient presentation
(n=570)
Developed Bladder Cancer
31%
Did Not Develop Bladder Cancer
69%
UroSEEK Positive
83%
Cytology Positive
43%
UroSEEK Positive
7%
Cytology Positive
0%
Sensitivity
(UroSEEK/Cytology Combined)
95%
Specificity
(UroSEEK/Cytology Combined)
93%
Surveillance Cohort
Urine collected following surgery
(n=322)
Developed Bladder Cancer
58%
Did Not Develop Bladder Cancer
42%
UroSEEK Positive
68%
Cytology Positive
25%
UroSEEK Positive
20%
Cytology Positive
0%
Sensitivity
(UroSEEK/Cytology Combined)
71%
Specificity
(UroSEEK/Cytology Combined)
80%
UTUC Cohort
Urine collected prior to surgery
(n=56)
UroSeek Positive
75%
Cytology Positive
10%
Sensitivity
(UroSEEK/Cytology Combined)
75%

UroSEEK in Equivocal Urine Cytology

Performance of Novel Non-Invasive Urine Assay UroSEEK in a Cohort of Atypical Cytology

Maria Del Carmen Rodriguez Pena[1], Simeon U. Springer[2], Diana Taheri[4], Marie-Lisa Eich[1], Aline C. Tregnago[3], Christopher J. VandenBussche[3], Isam-Eldin A. Eltoum[1], Nickolas Papadopoulos[2], Kenneth W. Kinzler[2], Bert Vogelstein[2], George J. Netto[1,3]

Paris System: significant proportion of equivocal dx “atypical” or “suspicious” categories

ED:

- 375 urine samples (348 patients)
- 114/375 (**30%)** ATYP

Surveillance:

- 717 urine samples (496 patients)
- 332/717 (**46%)** ATYP

UroSEEK in Equivocal Urine Cytology: Early Detection

	UroSEEK	TERTSeqS	UROSeqS	FastSeqS
Sensitivity	96%	63%	88%	54%
Specificity	87%	90%	96%	99%
NPV	99%	90%	97%	89%
PPV	66%	63%	84%	93%

Rodriguez Pena et al. Virchow Pathol 2020

UroSEEK in Equivocal Urine Cytology: Surveillance

	UroSEEK	TERTSeqS	UROSeqS	FastSeqS
Sensitivity	74%	65%	54%	59%
Specificity	72%	77%	89%	80%
NPV	53%	47%	44%	45%
PPV	87%	87%	92%	88%

Rodriguez Pena et al. Virchow Pathol 2020

UroSEEK/CancerSEEK/PapSEEK

CANCER

Detection and localization of surgically resectable cancers with a multi-analyte blood test

Joshua D. Cohen,[1,2,3,4,5] Lu Li,[6] Yuxuan Wang,[1,2,3,4] Christopher Thoburn,[3] Bahman Afsari,[7] Ludmila Danilova,[7] Christopher Douville,[1,2,3,4] Ammar A. Javed,[8] Fay Wong,[1,3,4] Austin Mattox,[1,2,3,4] Ralph. H. Hruban,[3,4,9] Christopher L. Wolfgang,[8] Michael G. Goggins,[3,4,9,10,11] Marco Dal Molin,[4] Tian-Li Wang,[3,9] Richard Roden,[3,9] Alison P. Klein,[3,4,12] Janine Ptak,[1,2,3,4] Lisa Dobbyn,[1,3,4] Joy Schaefer,[1,3,4] Natalie Silliman,[1,2,3,4] Maria Popoli,[1,3,4] Joshua T. Vogelstein,[13] James D. Browne,[14] Robert E. Schoen,[15,16] Randall E. Brand,[15] Jeanne Tie,[17,18,19,20] Peter Gibbs,[17,18,19,20] Hui-Li Wong,[17] Aaron S. Mansfield,[21] Jin Jen,[22] Samir M. Hanash,[23] Massimo Falconi,[24] Peter J. Allen,[25] Shibin Zhou,[1,3,4] Chetan Bettegowda,[1,3,4] Luis A. Diaz Jr.,[1,3,4*] Cristian Tomasetti,[3,6,7†] Kenneth W. Kinzler,[1,3,4†] Bert Vogelstein,[1,2,3,4†] Anne Marie Lennon,[3,4,8,10,11†] Nickolas Papadopoulos[1,3,4†]

Cohen, J.D., et al. Science, 2018

SCIENCE TRANSLATIONAL MEDICINE | RESEARCH ARTICLE

CANCER

Evaluation of liquid from the Papanicolaou test and other liquid biopsies for the detection of endometrial and ovarian cancers

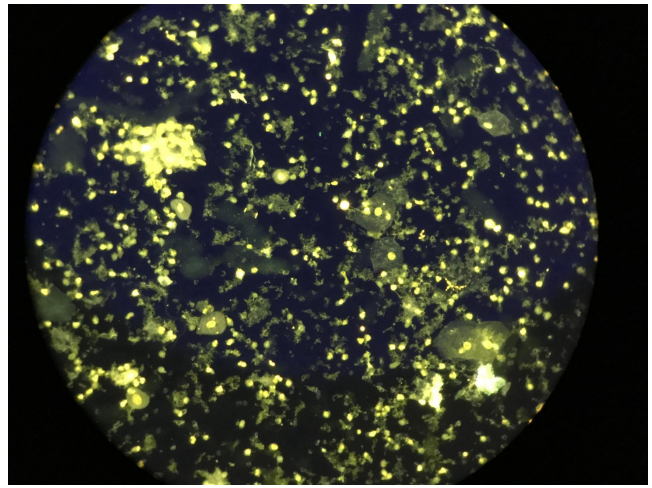
Yuxuan Wang,[1] Lu Li,[2] Christopher Douville,[1] Joshua D. Cohen,[1,3] Ting-Tai Yen,[4] Isaac Kinde,[5] Karin Sundfelt,[6] Susanne K. Kjær,[7,8] Ralph H. Hruban,[9] Ie-Ming Shih,[9] Tian-Li Wang,[9] Robert J. Kurman,[9] Simeon Springer,[1] Janine Ptak,[1] Maria Popoli,[1] Joy Schaefer,[1] Natalie Silliman,[1] Lisa Dobbyn,[1] Edward J. Tanner,[4] Ana Angarita,[4] Maria Lycke,[6] Kirsten Jochumsen,[10] Bahman Afsari,[2] Ludmila Danilova,[2] Douglas A. Levine,[11] Kris Jardon,[12] Xing Zeng,[12] Jocelyne Arseneau,[12] Lili Fu,[12] Luis A. Diaz Jr.,[1] Rachel Karchin,[13] Cristian Tomasetti,[2*] Kenneth W. Kinzler,[1*] Bert Vogelstein,[1,14*] Amanda N. Fader,[4*] Lucy Gilbert,[12*] Nickolas Papadopoulos[1*]

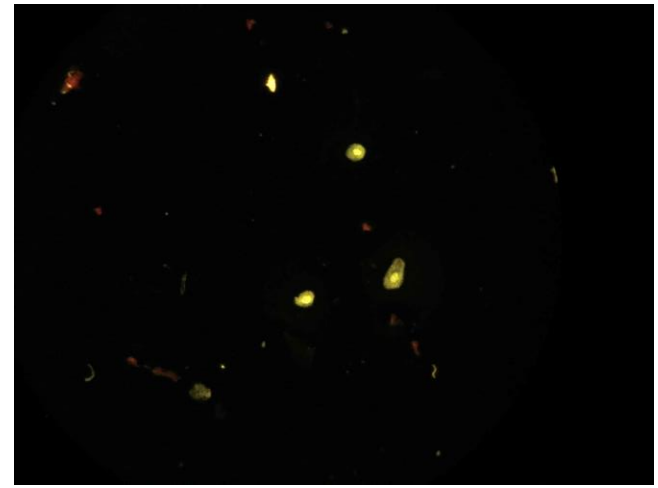
Wang Y., et al. Sci Trans Med, 2018

UroSEEK
Next Steps

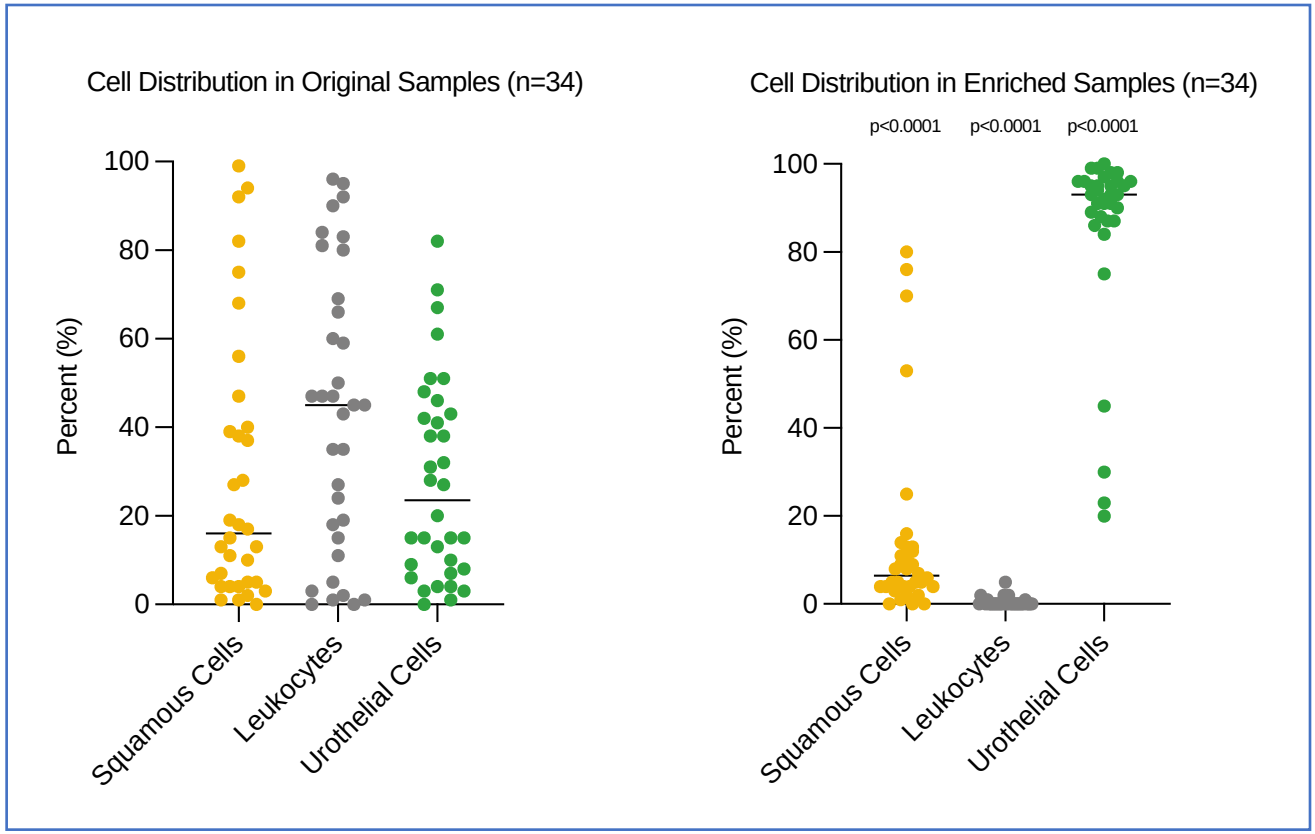
- Bring down **cost** per test
- Secure funding for **CLIA** grade test development and **FDA** approval
- Head to head **prospective study** with *UroVysion*
  (Non-inferiority approval)
- Commercialization

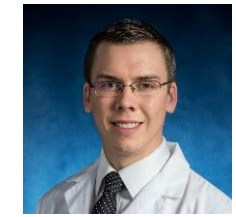
Voided Urine Sample
99% WBCs
1% Squamous cells





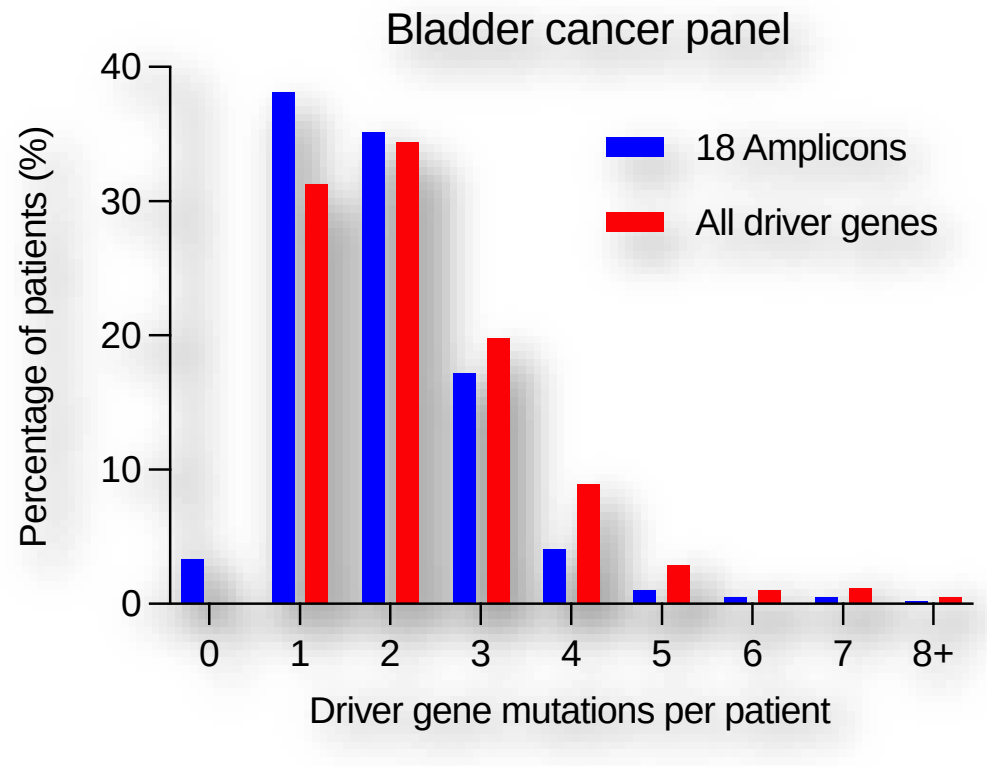
Enriched Sample
3% WBCs
41% Squamous cells
57% Urothelial cells





Jonathan Dudley

- **SaferSeq** sequencing panel
- Panel designed based on
  UroSEEK cohort
  MSK-IMPACT cohort
- 18-amplicon covers at least 1 driver mutation in 97% (median 2 per patient)



Conclusions & Open Discussion

- **The future is ours to claim** if we embrace the unstoppable change in our profession

- Precision medicine opens **new doors** for pathologists to be on the **frontlines of patient care** delivery

- Tough economic challenges are not insurmountable but will require operational and Business Models adjustments

THANK YOU !.....

Acknowledgements

George J. Netto Lab

- Marie-Lisa Eich
- Maria del Carmen Rodriguez Peña
- Aline C. Tregnago
- Diana Taheri
- Stephania M. Bezerra
- Enrico Munari
- Sheila F. Faraj

Bert Vogelstein Lab: Howard Hughes Medical Institute, Ludwig Center

- Simeon U. Springer
- Isaac Kinde
- Cristian Tomasetti
- Luis A. Diaz
- Christopher Douville
- Yuxuan Wang
- Nickolas Papadopoulos
- Kenneth W. Kinzler

Johns Hopkins University

- Trinity J. Bivalacqua
- Christopher VandenBussche
- Ralph H. Hruban

AC Camargo Cancer Center, Brasil

- Stephania M. Bezerra
- Isabela W. Cunha

Osaka University, Japan

- Kazutoshi Fujita

Hacettepe University, Turkey

- Dilek Ertoy

Stony Brook University

- Kathleen G Dickman
- Arthur P Grollman

National Taiwan University Hospital

- Chao-Yuan Huang
- Yeong-Shiau Pu
- Chung-Hsin Chen

Funding

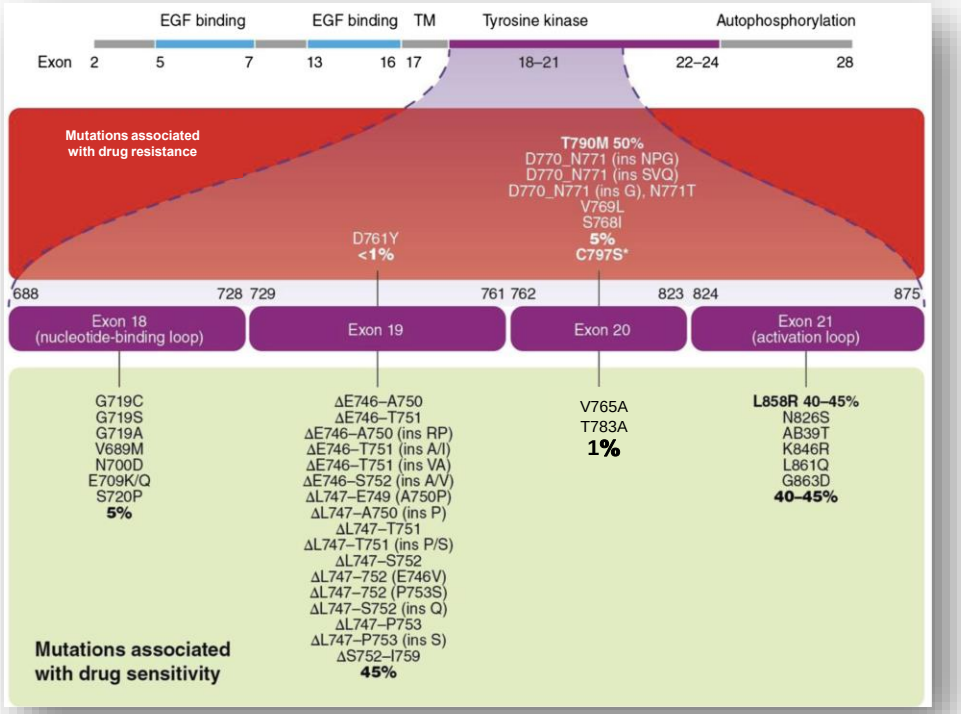
- NIH (Grants CA-77598, CA 06973, GM 07309, and ES019564).
- National Science Council, Taiwan to CHC (104-2314-B-002-132) and to YSP (104-2314-B-002-121-MY3)
- Henry and Marsha Laufer
- Virginia and DK Ludwig Fund for Cancer Research
- Commonwealth Foundation
- John Templeton Foundation
- Conrad R Hilton Foundation.

Open Discussion

EGFR Mutations in NSCLC

	EGFR mutation	EGRF wild type	K-ras mutation	K-ras wild type
AdenoCA*	20%	80%	22%	78%
Non-AdenoCA	13%	87%	5%	95%
Female	18%	82%	14%	86%
Male	16%	84%	15%	85%
Smokers#	14%	86%	16%	84%
Never smoker	28%	72%	11%	89%
Asian	38%	62%	0%	100%
Non-Asian	15%	85%	16%	84%

NCICC Trials Group study BR.21 J Clin Oncol 2008



Ghafoor Q et al. Pathol & Oncol Res, 2018

Omics: Coming Together…

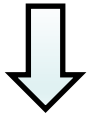
- Genomic advances paved the way to Precision Medicine

- Multiparametric Analyses (e.g. TCGA studies)
  - DNA
  - RNA
  - Protein
  - Epigenetics

- Robust Molecular Classifications
  - Functional role of molecular alterations across tumor types
  - Druggable targets

Omics: Coming Together…

- Genomic advances paved the way to Precision Medicine



- Multiparametric Analyses (e.g. TCGA studies)
  - DNA
  - RNA
  - Protein
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- Robust Molecular Classifications
  - Functional role of molecular alterations across tumor types
  - Druggable targets

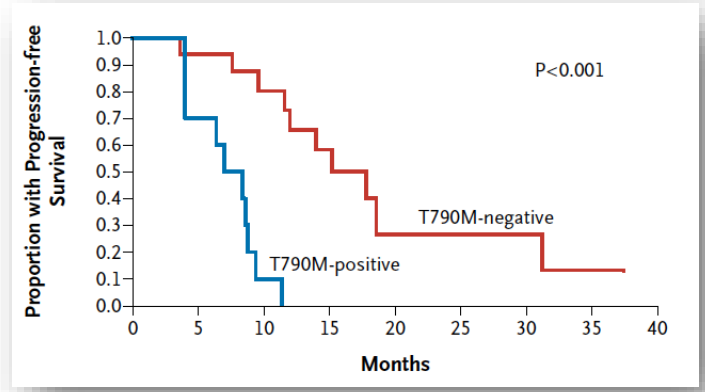
Acquired EGFR Rx Resistance

- **Mutation in exon 20 (T790M)**

  Kobayashi S et al. N Engl J Med 2005

  Maheswaran et al N Engl J Med 2008

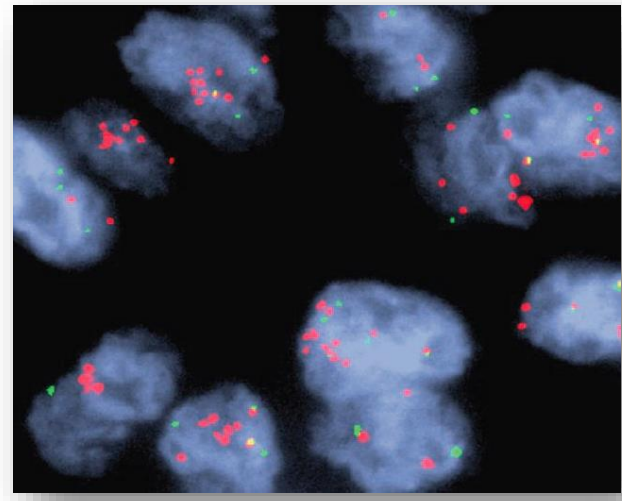
  Pao W et al. PlosMed 2005

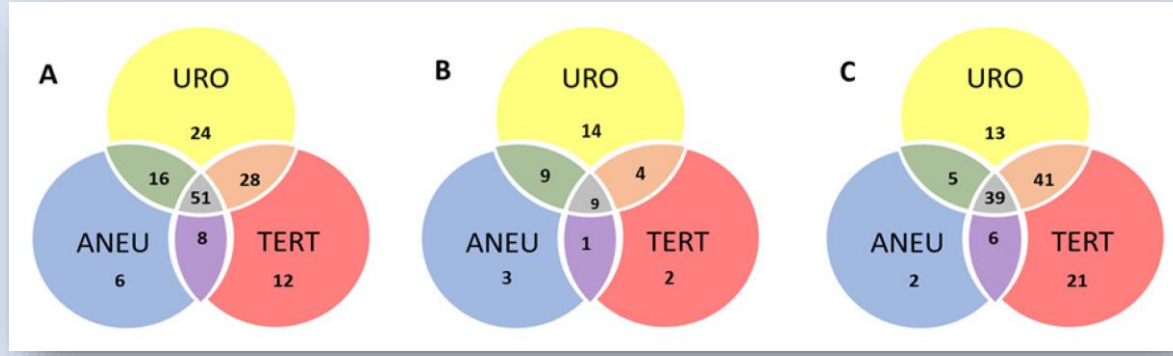


- **Amplification of MET gene (7q31)**

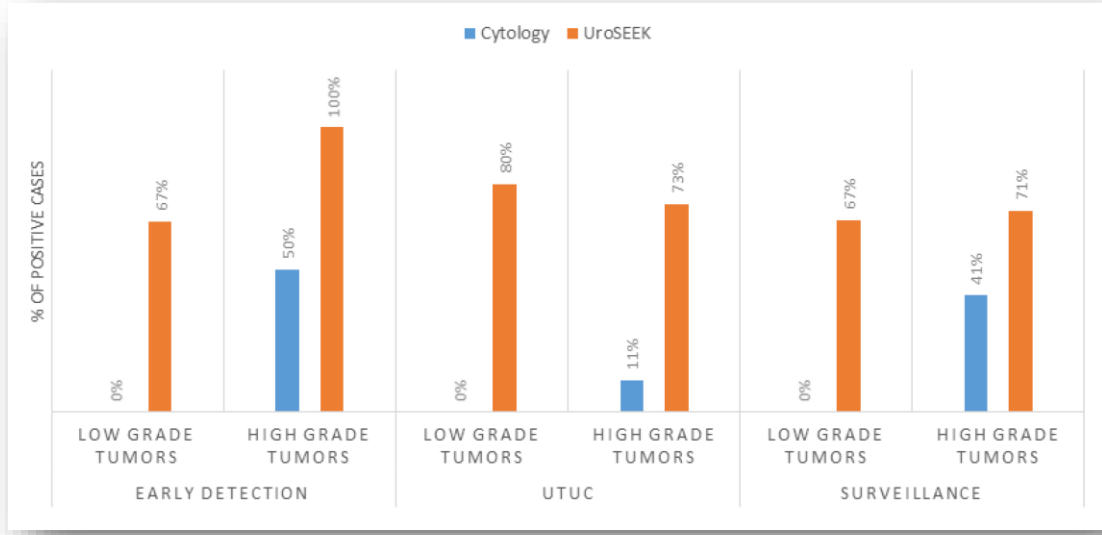
  Engelman JA. Science 2007; 316(5827);1039-43

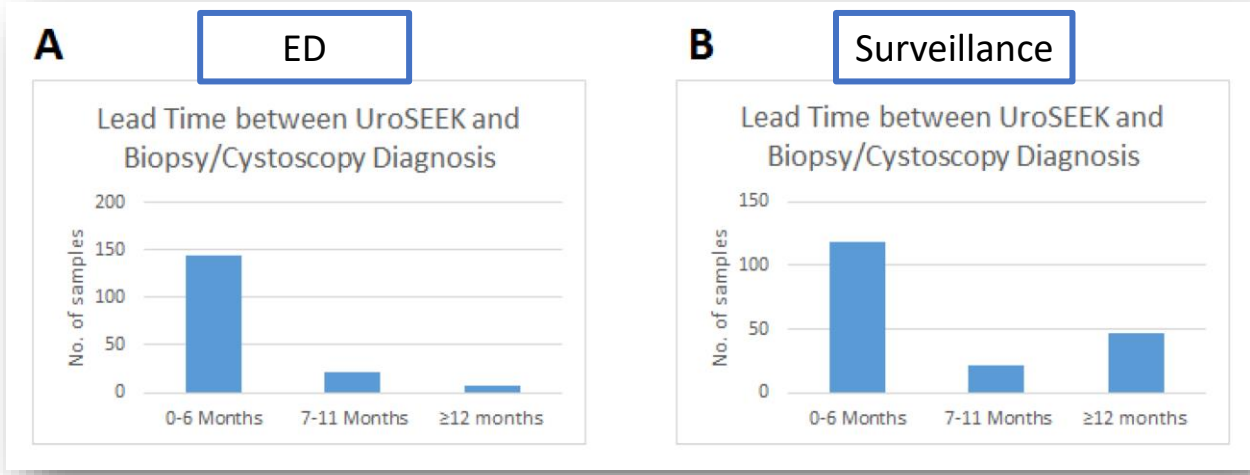
  Sequist et al 2008 JCO




A
URO
24
16
51
28
ANEU
6
8
TERT
12
B
URO
14
9
9
4
ANEU
3
1
TERT
2
C
URO
13
5
39
41
ANEU
2
6
TERT
21

UroSEEK


Cytology
UroSEEK
% OF POSITIVE CASES
0%
67%
50%
100%
0%
80%
11%
73%
0%
67%
41%
71%
LOW GRADE TUMORS
HIGH GRADE TUMORS
LOW GRADE TUMORS
HIGH GRADE TUMORS
LOW GRADE TUMORS
HIGH GRADE TUMORS
EARLY DETECTION
UTUC
SURVEILLANCE


A
ED
Lead Time between UroSEEK and Biopsy/Cystoscopy Diagnosis
No. of samples
200
150
100
50
0
0-6 Months
7-11 Months
≥12 months
B
Surveillance
Lead Time between UroSEEK and Biopsy/Cystoscopy Diagnosis
No. of samples
150
100
50
0
0-6 Months
7-11 Months
≥12 months

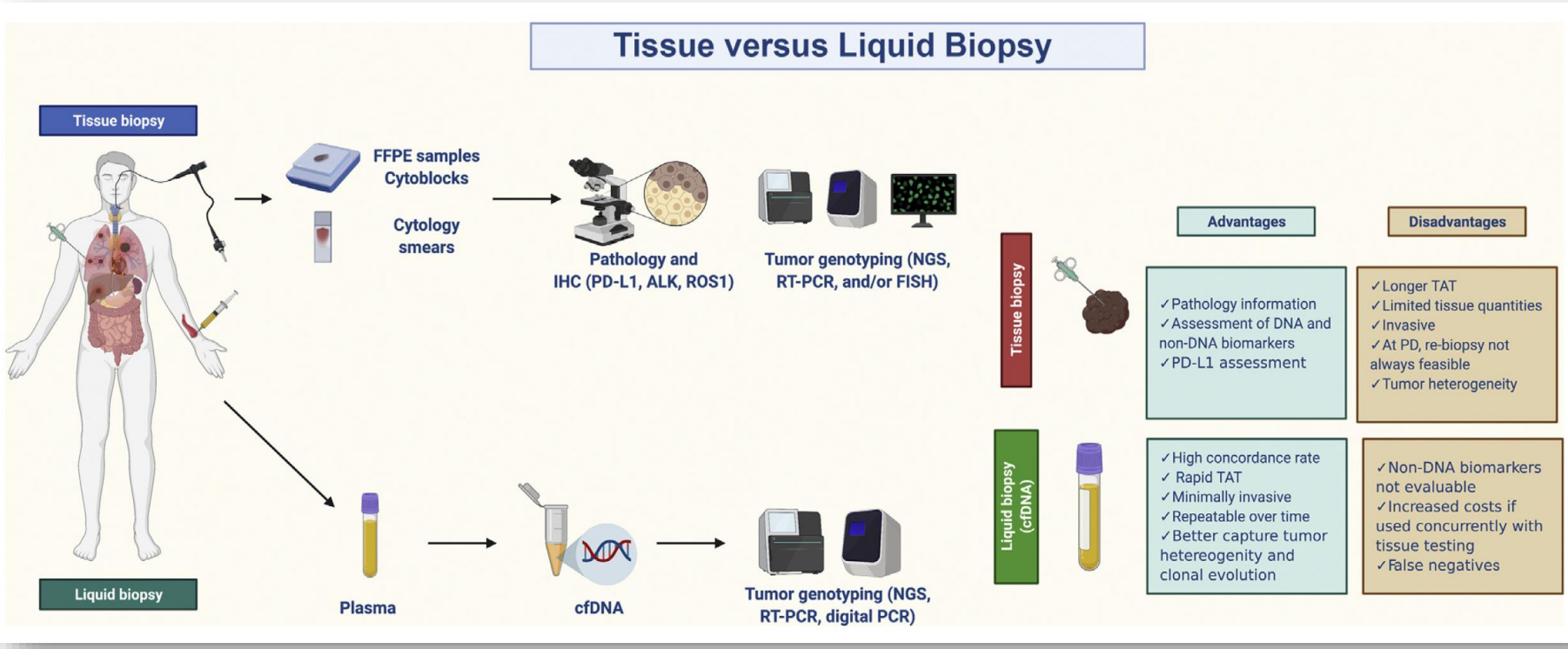
FDA - Approved Liquid Biopsy Assays

- **The CellSearch system** (Menarini Silicon Biosystems)
  - Metastatic breast, prostate or CRCa
  - CTC platform
- **Cobas EGFR Mutation Test v2** (Roche Molecular Diagnostics)
  - NSCLC
  - Detects EGFR mutations in plasma cfDNA
- **Epi proColon** (Epigenomics AG)
  - CRCa screening assay
  - Methylation status of *SEPT9* promoter in plasma cfDNA

IASLC

Liquid Biopsy for Advanced NSCLC: A Consensus Statement From the International Association for the Study of Lung Cancer

Check for updates



Rolfo C et al , J Thoracic Oncol October 2021

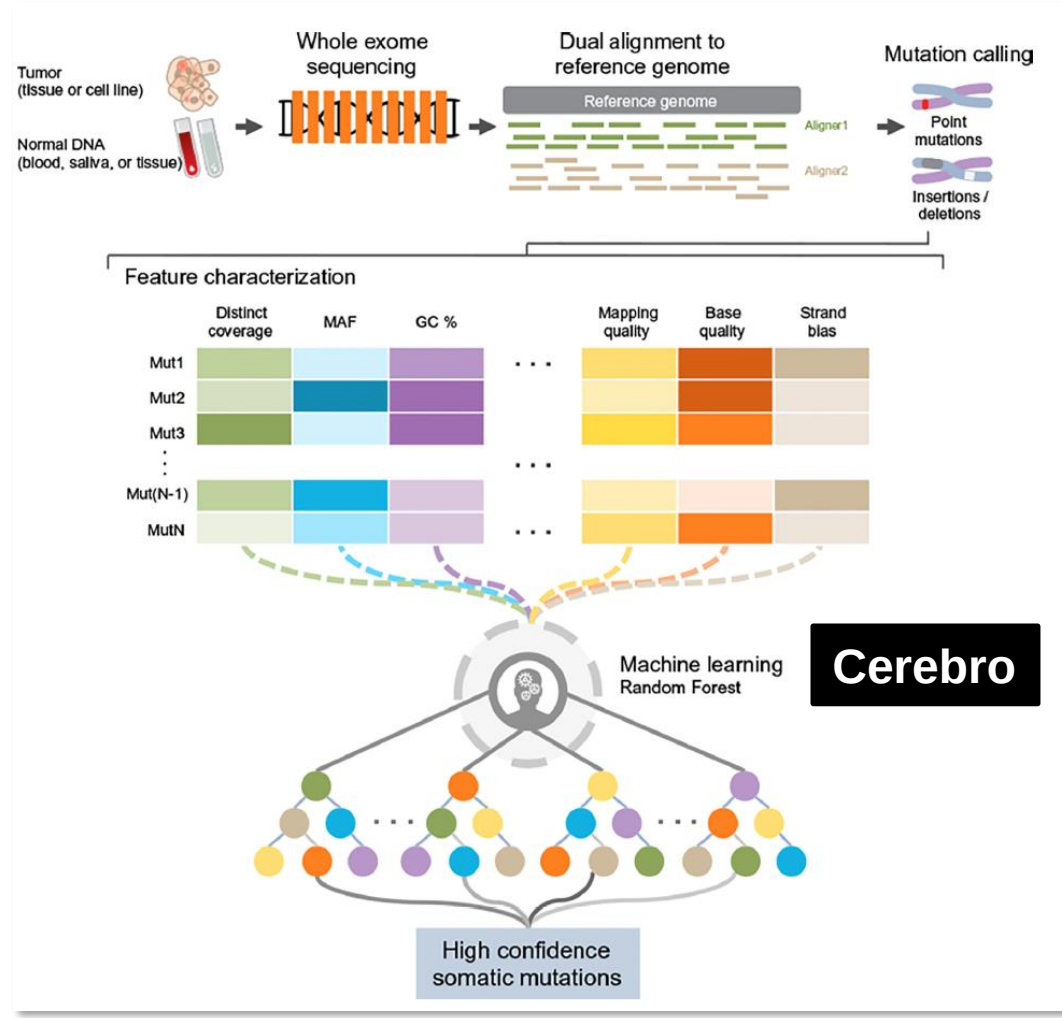
A machine learning approach for somatic mutation discovery

Derrick E. Wood[1], **James R. White**[1], **Andrew Georgiadis**[1], **Beth Van Emburgh**[1], **Sonya Parpart-Li**[1], **Jason Mitchell**[1], **Valsamo Anagnostou**[2], **Noushin Niknafs**[2], **Rachel Karchin**[2,3], **Eniko Papp**[1], **Christine McCord**[1], **Peter LoVerso**[1], **David Riley**[1], **Luis A. Diaz Jr.**[4], **Siân Jones**[1], **Mark Sausen**[1], **Victor E. Velculescu**[2,*], and **Samuel V. Angiuoli**[1,*]

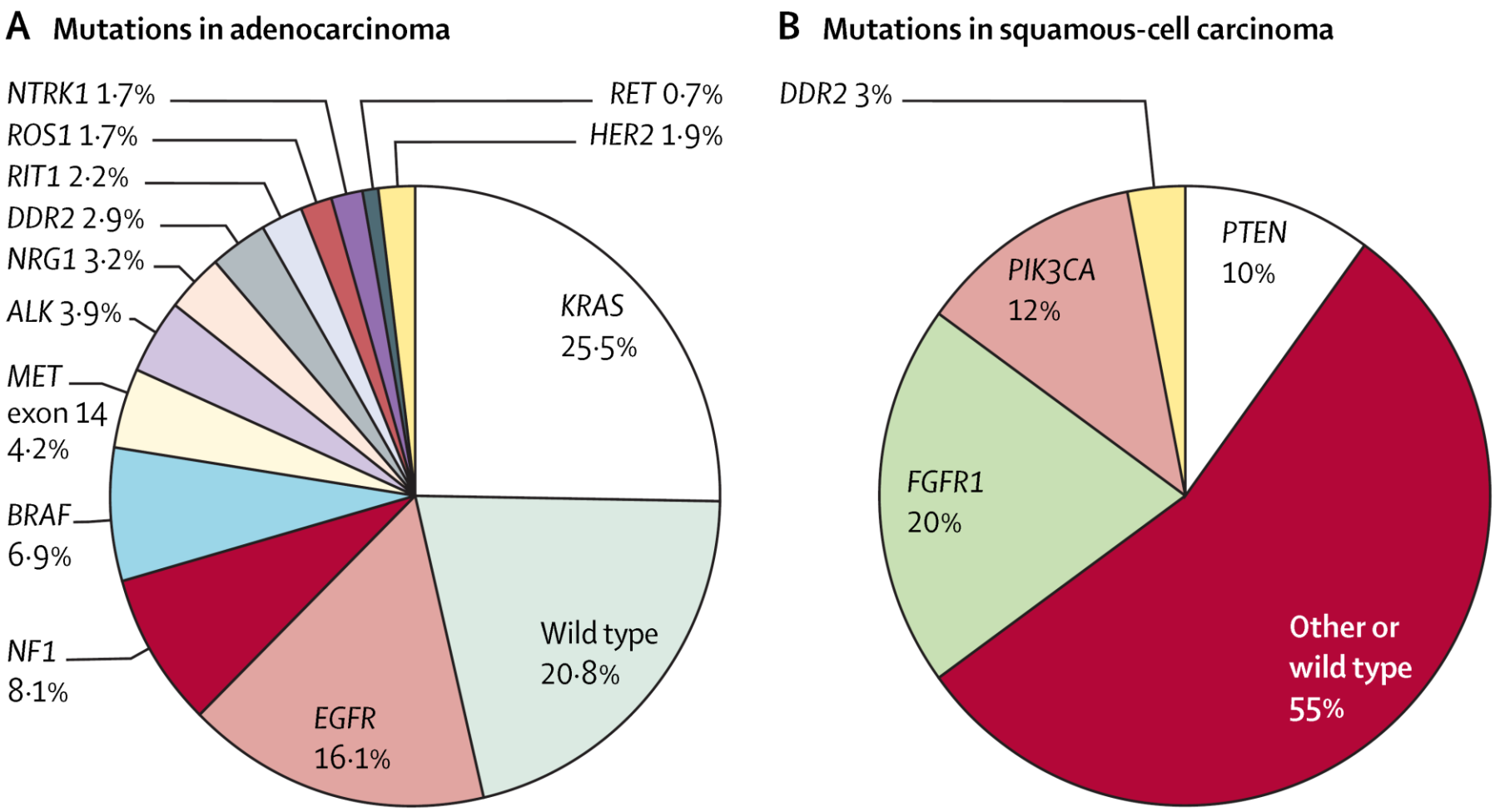
[1]Personal Genome Diagnostics, Baltimore, MD 21224, USA.

[2]The Sidney Kimmel Comprehensive Cancer Center, Johns Hopkins University School of Medicine, Baltimore, MD 21287, USA.

Sci Transl Med. 2018 September 05



Genetic Alterations in Lung Adenocarcinoma



Rafael Rosell, Niki Karachaliou, Lancet 2016

Genetic Alterations in Lung Adenocarcinoma

EGFR exon 19 and 21
Nazartinib
BPI-7711
Lazertinib
HS-10296

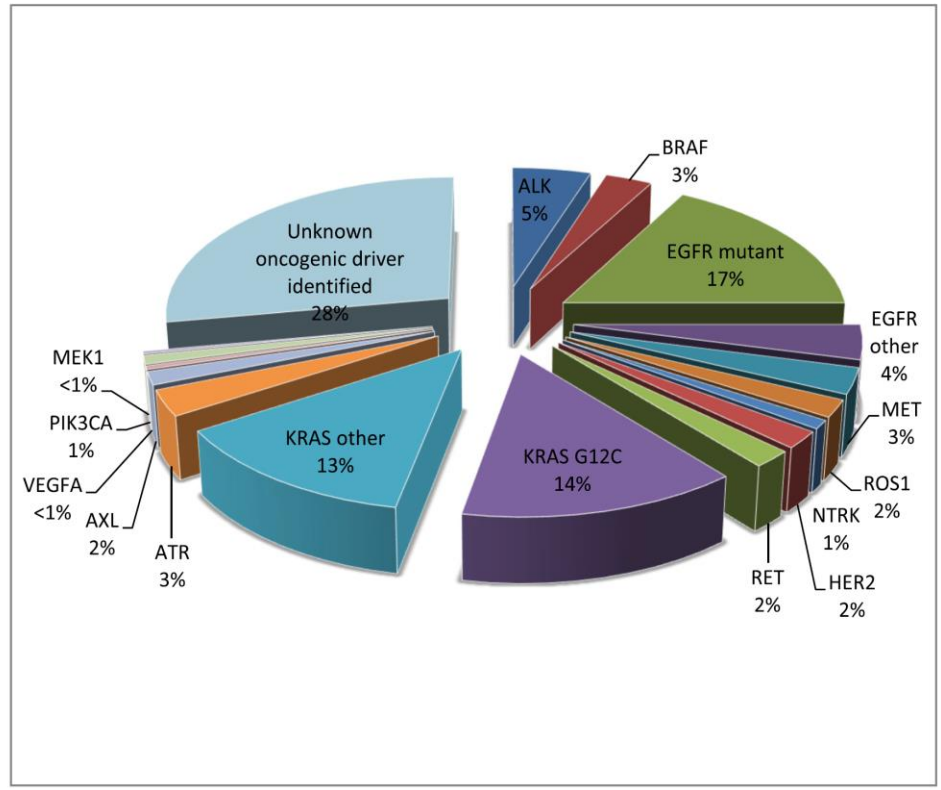
EGFR exon 20
TAK-788
Poziotinib

ALK
Ensartinib

ROS1
Ceritinib
Lolartinib
Repotrectinib

NTRK
DS-6051b
Repotrectinib

MET
Capmatinib
Tepotinib



RET
RXDX-105
BLU-667
LOXO-292

HER2
DS-8201a
TDM1
XMT-1522
Pyrotinib
Poziotinib

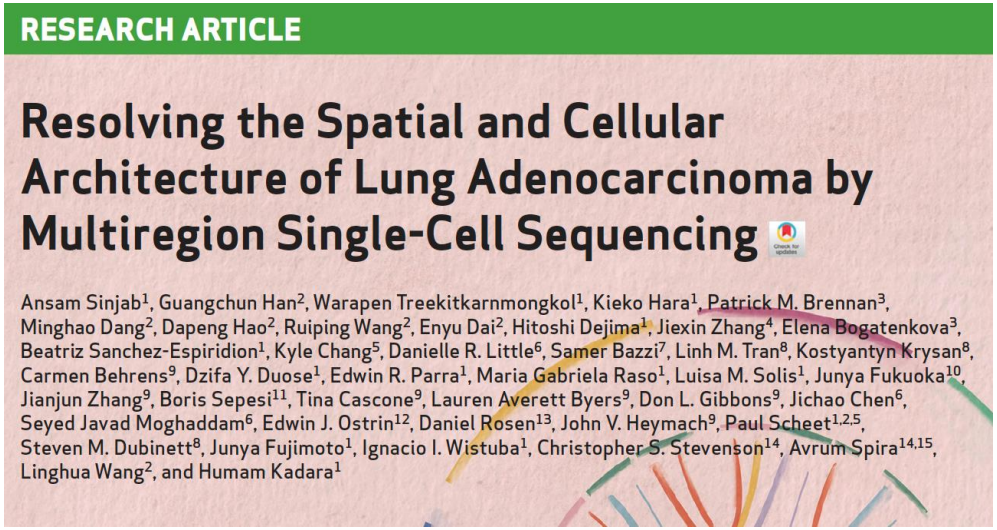
KRAS G12C
AMG510
MRTX849

ATR
M6620

AXL
TP0903
Bemcentinib

VEGF/VEGFR
MP0250

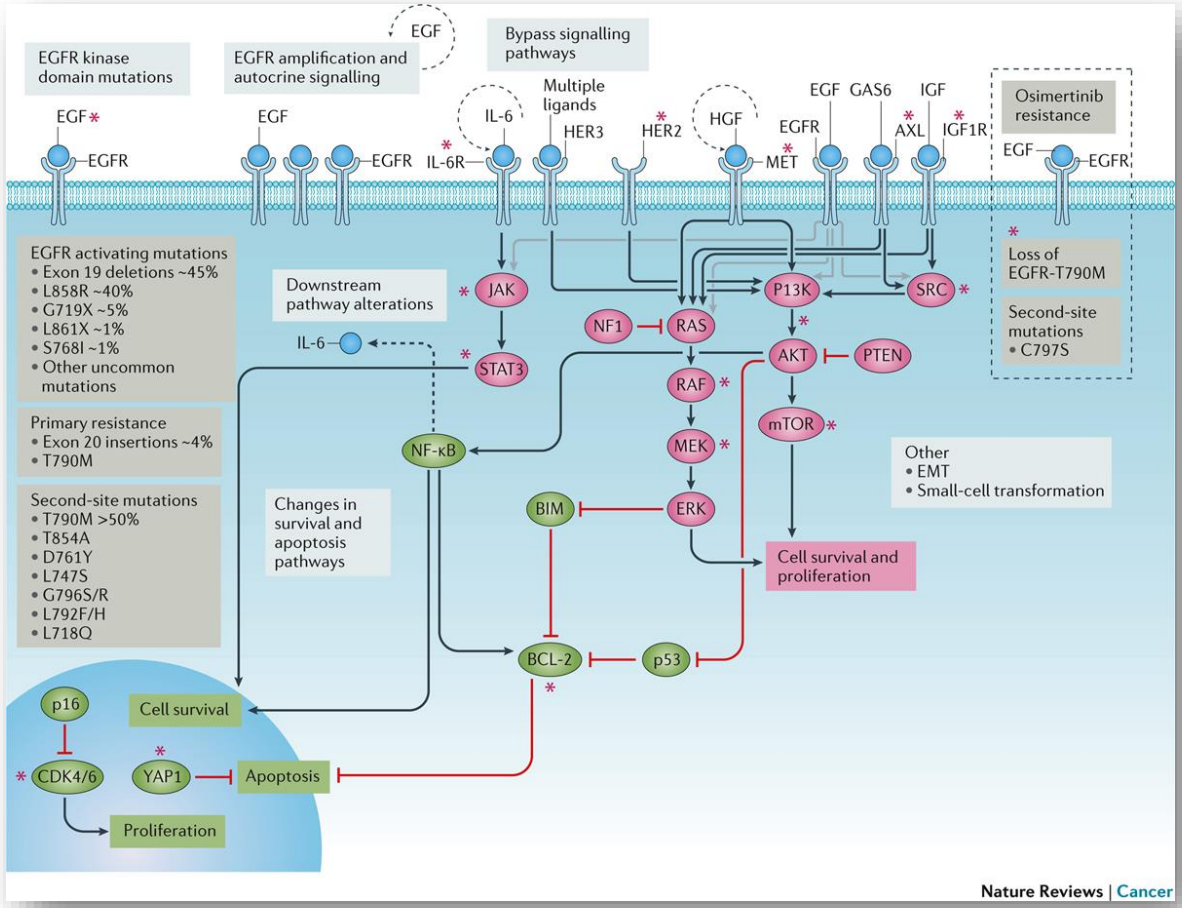
Chen et al. Journal of Hematology & Oncology (2020)

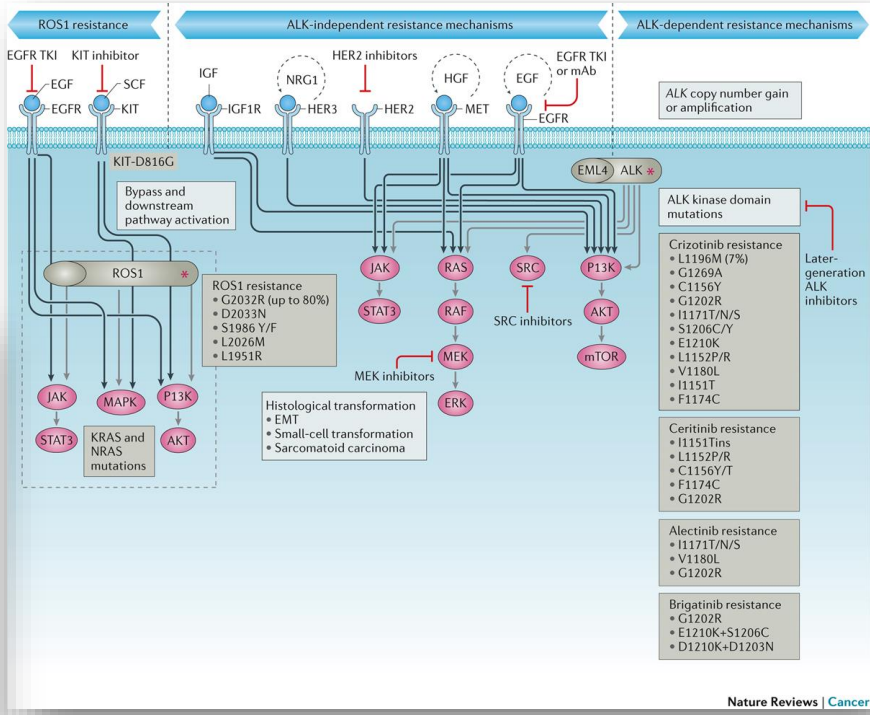


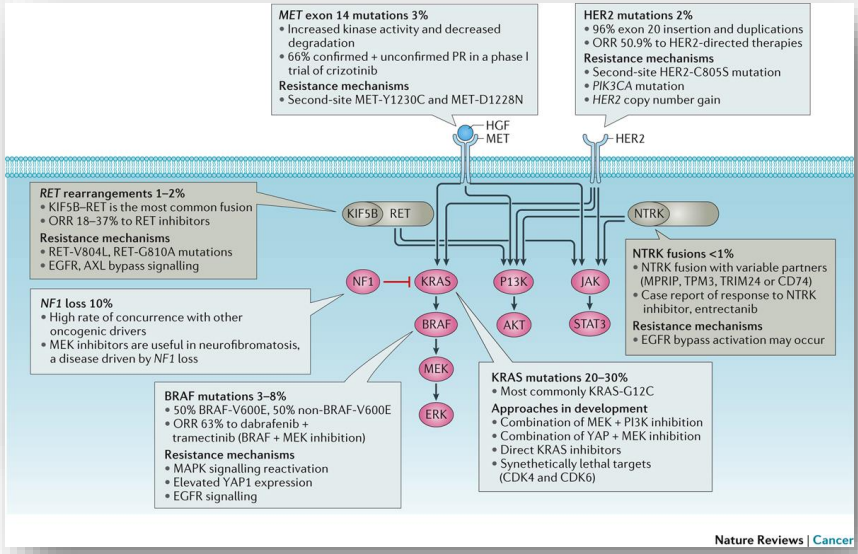
Sinjab A et al; Cancer Discovery 2021

perform single-cell RNA sequencing
of 186,916 cells from five early-stage LUADs and 14 multiregion normal lung tissues of defined spatial
proximities from the tumors. We show that cellular lineages, states, and transcriptomic features
geospatially evolve across normal regions to LUADs. LUADs also exhibit pronounced intratumor cell
heterogeneity within single sites and transcriptional lineage-plasticity programs. T regulatory cell phenotypes
are increased in normal tissues with proximity to LUAD, in contrast to diminished signatures and fractions of cytotoxic CD8+ T cells, antigen-presenting macrophages, and inflammatory dendritic
cells. We further find that the LUAD ligand–receptor interactome harbors increased expression of
epithelial CD24, which mediates protumor phenotypes. These data provide a spatial atlas of LUAD
evolution, and a resource for identification of targets for its treatment.
Significanc e: The geospatial ecosystem of the peripheral lung and early-stage LUAD is not

Mechanisms of Acquired Resistance to NSCLC TKI



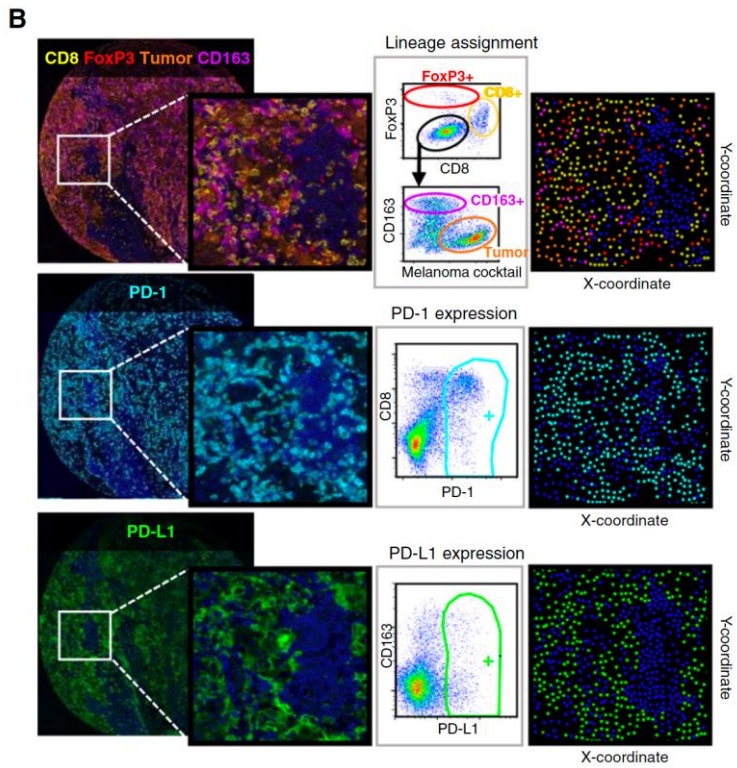


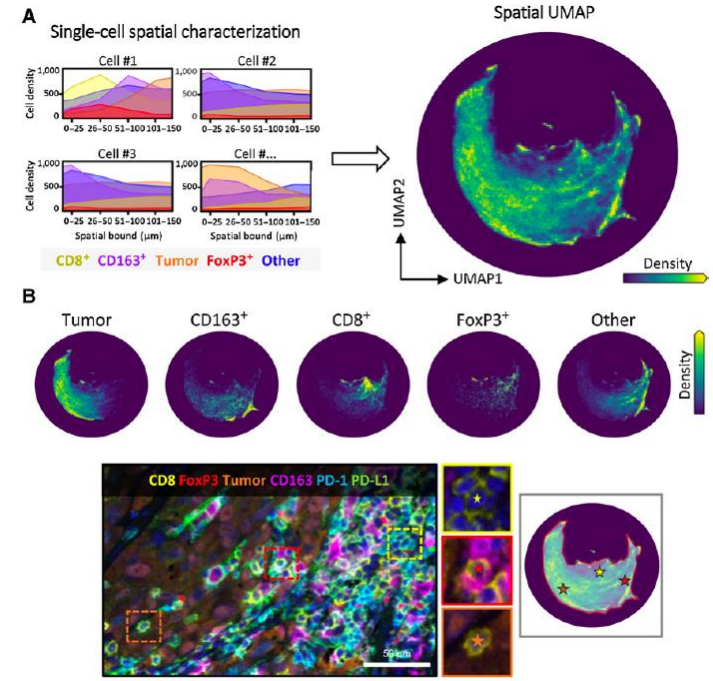


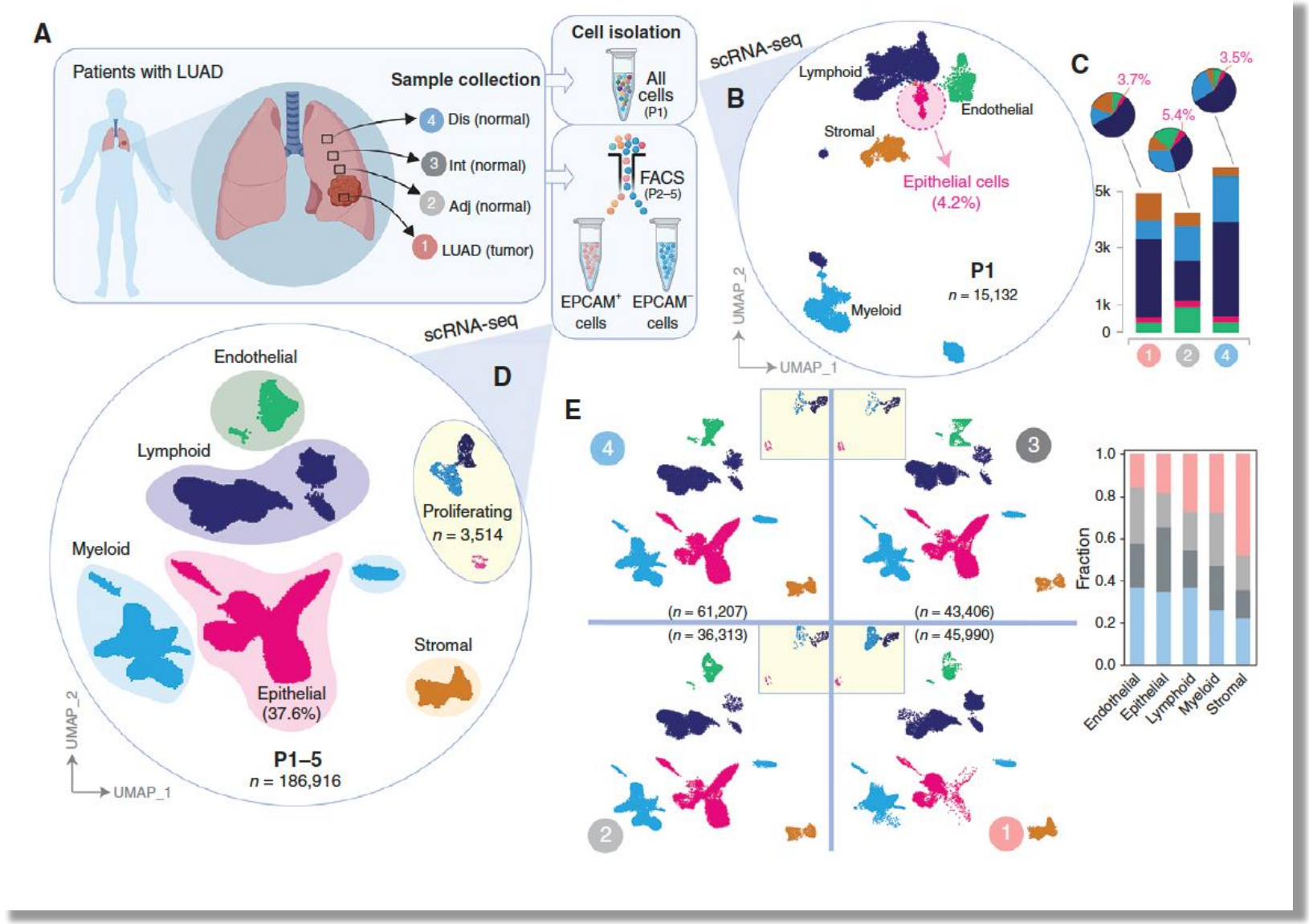
Rotow, J., Bivona, T. Nat Rev Cancer 2017

Spatial UMAP and Image Cytometry for Topographic Immuno-oncology Biomarker Discovery

Nicolas A. Giraldo[1], Sneha Berry[2], Etienne Becht[3], Deniz Ates[4], Kara M. Schenk[2], Elizabeth L. Engle[5], Benjamin Green[2], Peter Nguyen[5], Abha Soni[5], Julie E. Stein[5], Farah Succaria[5], Aleksandra Ogurtsova[5], Haiying Xu[5], Raphael Gottardo[3], Robert A. Anders[1], Evan J. Lipson[2], Ludmila Danilova[2], Alexander S. Baras[1], and Janis M. Taube[1,2,5]







Sinjab A et al; Cancer Discovery 2021

The Economist

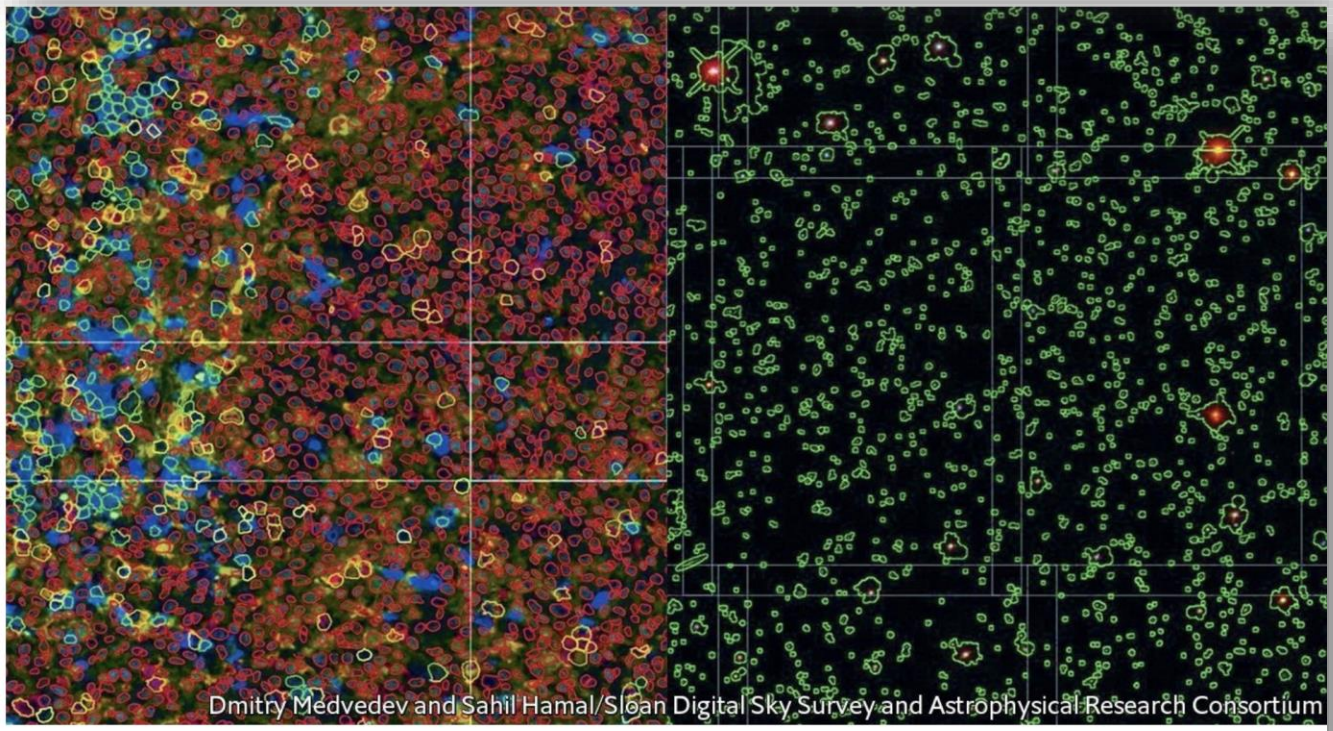
Science & technology

Apr 24th 2021 edition ›

Cancer research

Mapping cancer as if it were the universe

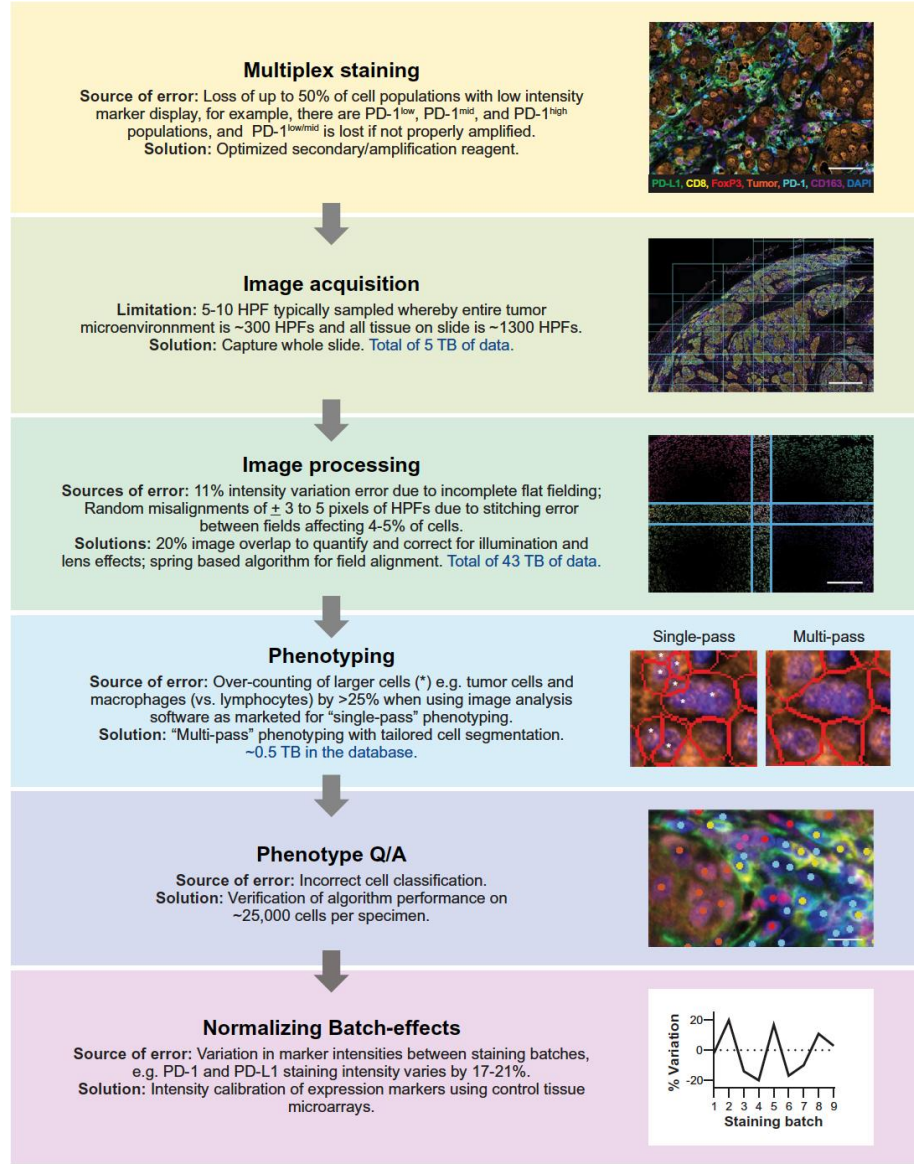
Techniques from astronomy are being applied to medicine

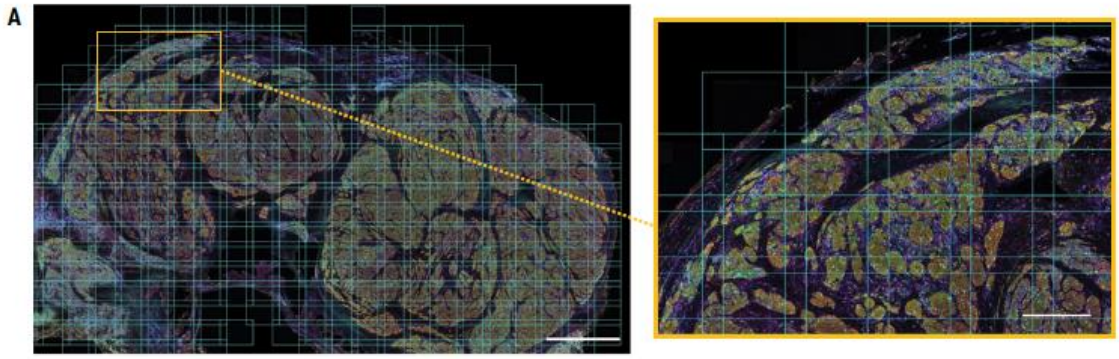


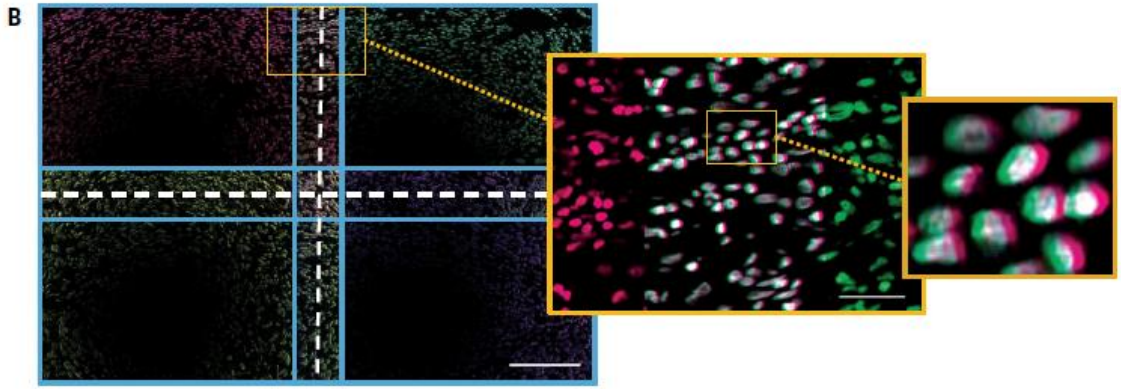
Analysis of multispectral imaging with the AstroPath platform informs efficacy of PD-1 blockade

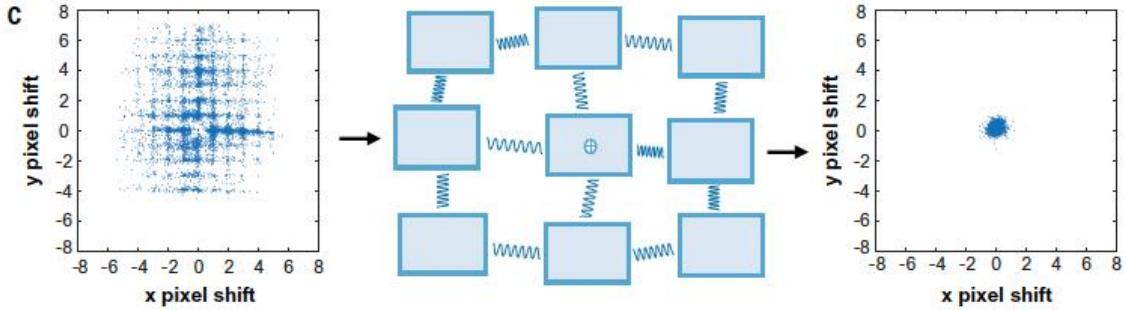
Sneha Berry†, Nicolas A. Giraldo†, Benjamin F. Green†, Tricia R. Cottrell, Julie E. Stein, Elizabeth L. Engle, Haiying Xu, Aleksandra Ogurtsova, Charles Roberts, Daphne Wang, Peter Nguyen, Qingfeng Zhu, Sigfredo Soto-Diaz, Jose Loyola, Inbal B. Sander, Pok Fai Wong, Shlomit Jessel, Joshua Doyle, Danielle Signer, Richard Wilton, Jeffrey S. Roskes, Margaret Eminizer, Seyoun Park, Joel C. Sunshine, Elizabeth M. Jaffee, Alexander Baras, Angelo M. De Marzo, Suzanne L. Topalian, Harriet Kluger, Leslie Cope, Evan J. Lipson, Ludmila Danilova, Robert A. Anders, David L. Rimm, Drew M. Pardoll, Alexander S. Szalay†, Janis M. Taube*†

Berry S… Szalay AS and Taube JM; Science 2021

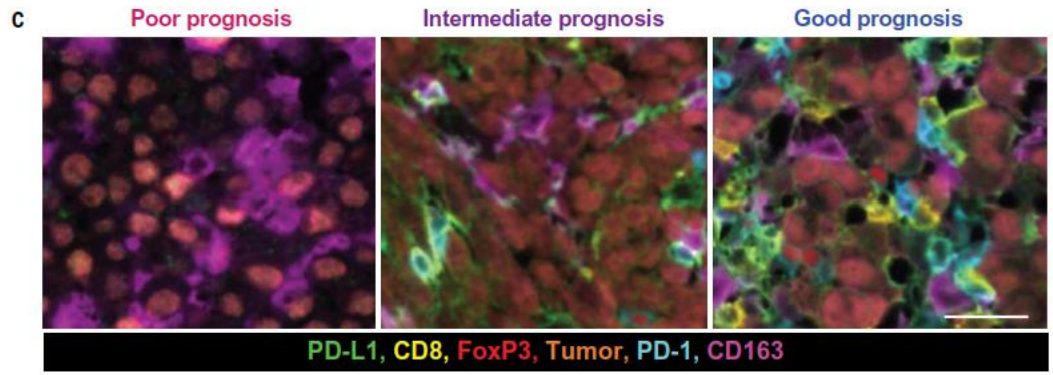


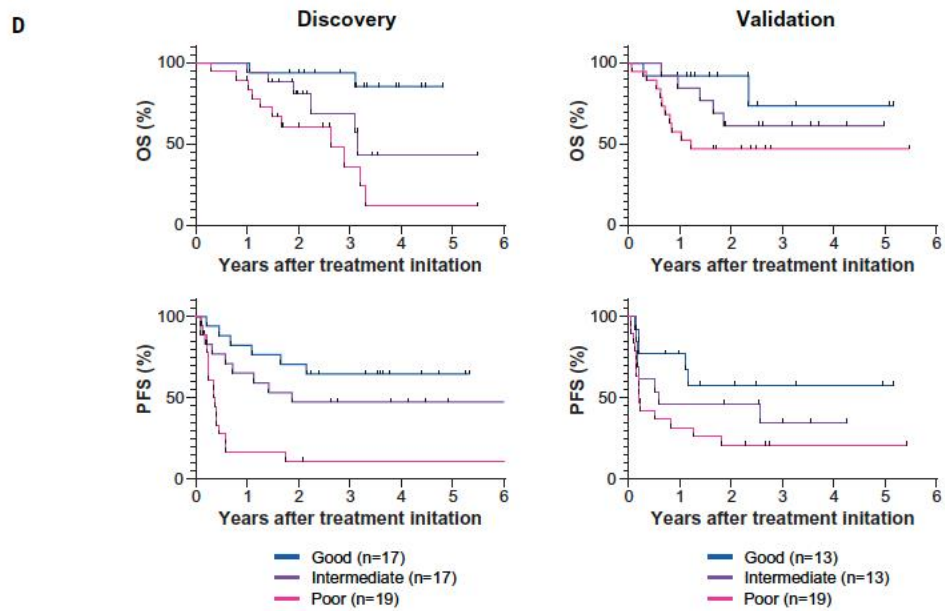


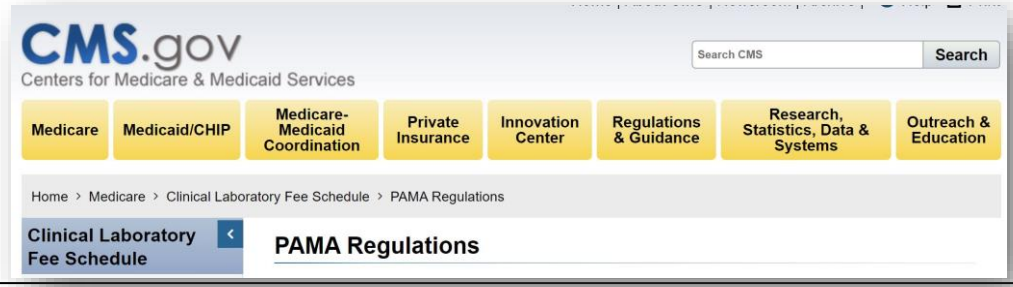




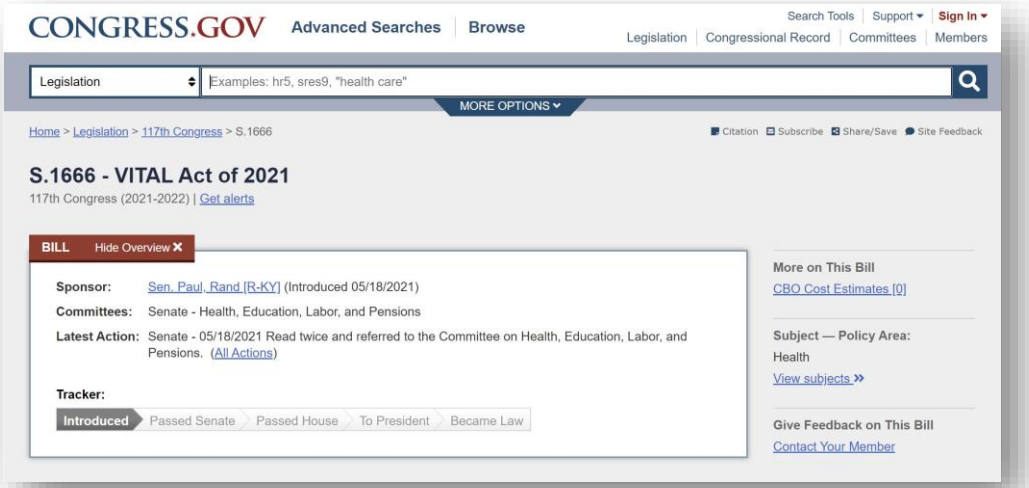
Minimizing instrumental errors during field **acquisition and stitching** of whole slide by using lessons from astronomy

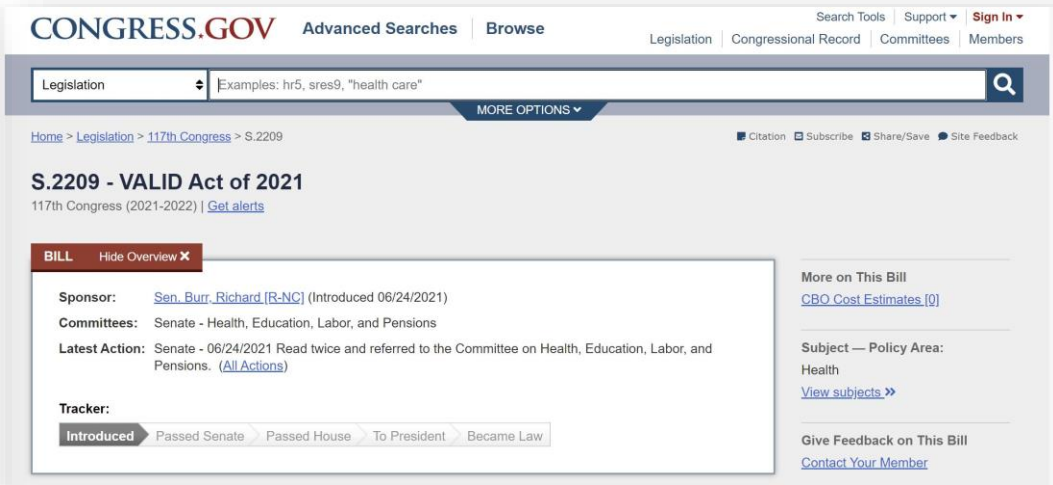

C
Poor prognosis
Intermediate prognosis
Good prognosis
PD-L1, CD8, FoxP3, Tumor, PD-1, CD163


D
Discovery
Validation
OS (%)
PFS (%)
Years after treatment initation
Good (n=17)
Intermediate (n=17)
Poor (n=19)
Good (n=13)
Intermediate (n=13)
Poor (n=19)

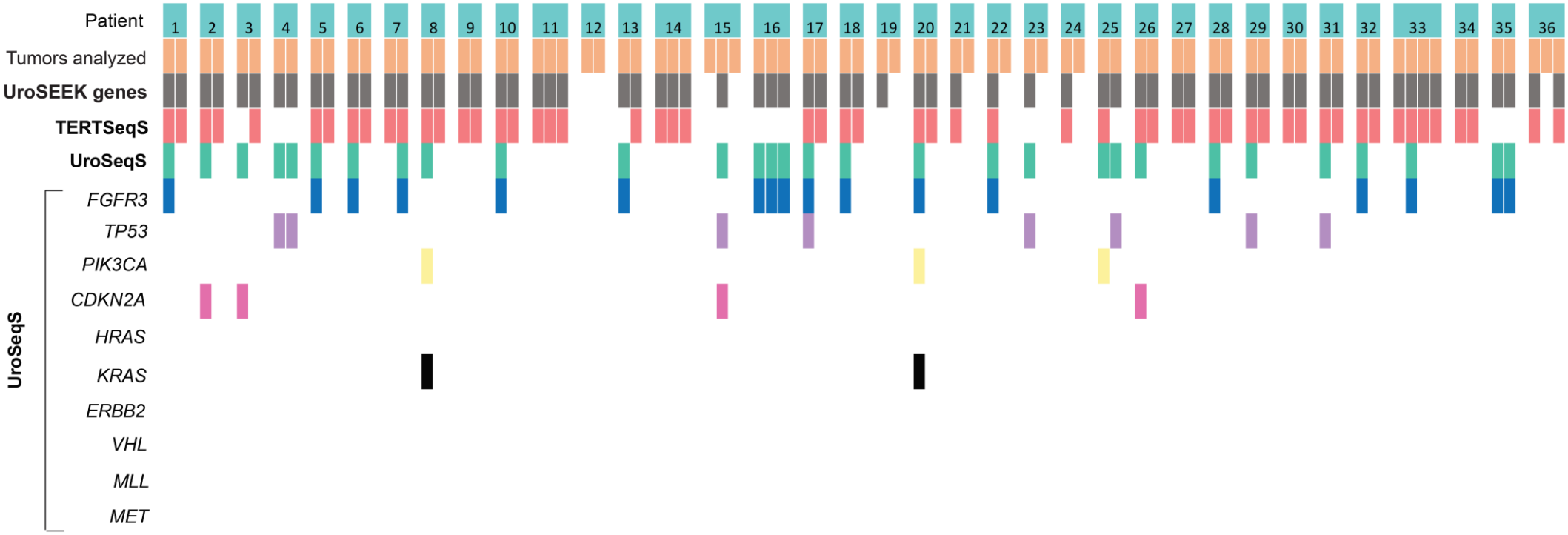


The Protecting Access to Medicare Act of 2014 (PAMA) required significant changes to how Medicare pays for clinical diagnostic laboratory tests under the Clinical Laboratory Fee Schedule (CLFS). Effective January 1, 2018, the payment amount for most tests equals the weighted median of private payor rates. Payment rates under the private payor rate-based CLFS are updated every three years.





UroSEEK in Bladder Cancer Tissue



Eich et al. Mod Pathol 2019

Next Gen Pathologist
Indispensable Member of Integrated Healthcare Delivery Team

- **Pathologist of the future** is a **vital** player in patient management team
  Molecular multidisciplinary tumor boards
  Diagnostic Management Teams (DMT)
  Cell Therapy (CAR-T Cell)

- **Elevating "Physician Profile"**
  CAP "Meet your Pathologist" efforts
  AMP gene patent victory
  COVID-19

- **Advocacy and government professional relation**
  *FDA **LDT** vs Companion Test; DTC; MOOP..*

CancerSEEK

CANCER

Detection and localization of surgically resectable cancers with a multi-analyte blood test

Joshua D. Cohen,[1,2,3,4,5] Lu Li,[6] Yuxuan Wang,[1,2,3,4] Christopher Thoburn,[3] Bahman Afsari,[7] Ludmila Danilova,[7] Christopher Douville,[1,2,3,4] Ammar A. Javed,[8] Fay Wong,[1,3,4] Austin Mattox,[1,2,3,4] Ralph. H. Hruban,[3,4,9] Christopher L. Wolfgang,[8] Michael G. Goggins,[3,4,9,10,11] Marco Dal Molin,[4] Tian-Li Wang,[3,9] Richard Roden,[3,9] Alison P. Klein,[3,4,12] Janine Ptak,[1,2,3,4] Lisa Dobbyn,[1,3,4] Joy Schaefer,[1,3,4] Natalie Silliman,[1,2,3,4] Maria Popoli,[1,3,4] Joshua T. Vogelstein,[13] James D. Browne,[14] Robert E. Schoen,[15,16] Randall E. Brand,[15] Jeanne Tie,[17,18,19,20] Peter Gibbs,[17,18,19,20] Hui-Li Wong,[17] Aaron S. Mansfield,[21] Jin Jen,[22] Samir M. Hanash,[23] Massimo Falconi,[24] Peter J. Allen,[25] Shibin Zhou,[1,3,4] Chetan Bettegowda,[1,3,4] Luis A. Diaz Jr.,[1,3,4*] Cristian Tomasetti,[3,6,7†] Kenneth W. Kinzler,[1,3,4†] Bert Vogelstein,[1,2,3,4†] Anne Marie Lennon,[3,4,8,10,11†] Nickolas Papadopoulos[1,3,4†]

Cohen, J.D., et al. Science, 2018

ctDNA
ASCO/CAP Joint Expert Panel Review

- **Insufficient** evidence of **clinical validity and utility** for majority of **advanced** cancers

- **Discordance** between ctDNA assays and tumor **tissue genotypin**g
  - **supports tumor tissue genotyping** to confirm undetected results from ctDNA

- **No evidence** of clinical utility and **little evidence** of clinical validity of ctDNA assays in **early-stage cancer**, **Rx monitoring** or **MRD detection**

- **No evidence** of clinical validity and clinical utility for **cancer screening** outside of a clinical trial

Merker, JD et al J Clin Oncol. 2018

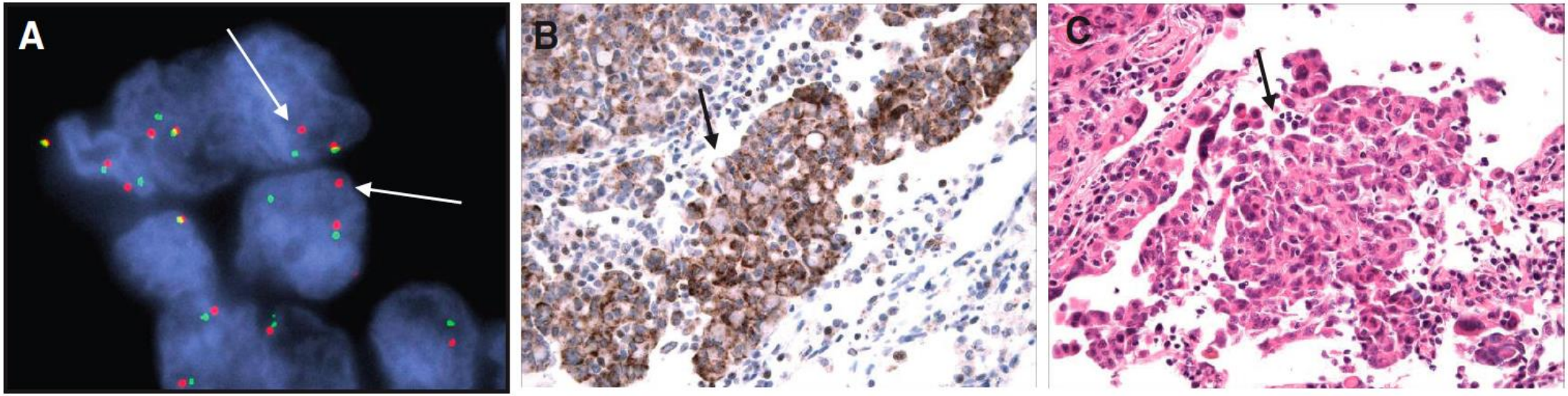
VOLUME 27 · NUMBER 26 · SEPTEMBER 10 2009

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Clinical Features and Outcome of Patients With Non–Small-Cell Lung Cancer Who Harbor *EML4-ALK*

Alice T. Shaw, Beow Y. Yeap, Mari Mino-Kenudson, Subba R. Digumarthy, Daniel B. Costa, Rebecca S. Heist, Benjamin Solomon, Hannah Stubbs, Sonal Admane, Ultan McDermott, Jeffrey Settleman, Susumu Kobayashi, Eugene J. Mark, Scott J. Rodig, Lucian R. Chirieac, Eunice L. Kwak, Thomas J. Lynch, and A. John Iafrate



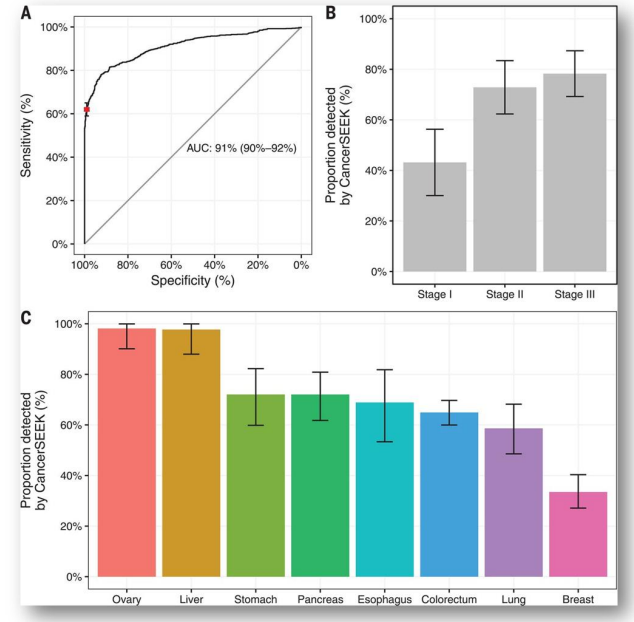
TERT promoter mutations occur frequently in gliomas and a subset of tumors derived from cells with low rates of self-renewal

Patrick J. Killela[a,1], Zachary J. Reitman[a,1], Yuchen Jiao[b,1], Chetan Bettegowda[b,c,1], Nishant Agrawal[b,d], Luis A. Diaz, Jr.[b], Allan H. Friedman[a], Henry Friedman[a], Gary L. Gallia[c,d], Beppino C. Giovanella[e], Arthur P. Grollman[f], Tong-Chuan He[g], Yiping He[a], Ralph H. Hruban[h], George I. Jallo[c], Nils Mandahl[i], Alan K. Meeker[h,m], Fredrik Mertens[i], George J. Netto[h,l], B. Ahmed Rasheed[a], Gregory J. Riggins[c], Thomas A. Rosenquist[f], Mark Schiffman[j], Ie-Ming Shih[h], Dan Theodorescu[k], Michael S. Torbenson[h], Victor E. Velculescu[b], Tian-Li Wang[h], Nicolas Wentzensen[j], Laura D. Wood[h], Ming Zhang[b], Roger E. McLendon[a], Darell D. Bigner[a], Kenneth W. Kinzler[b], Bert Vogelstein[b,2], Nickolas Papadopoulos[b], and Hai Yan[a,2]

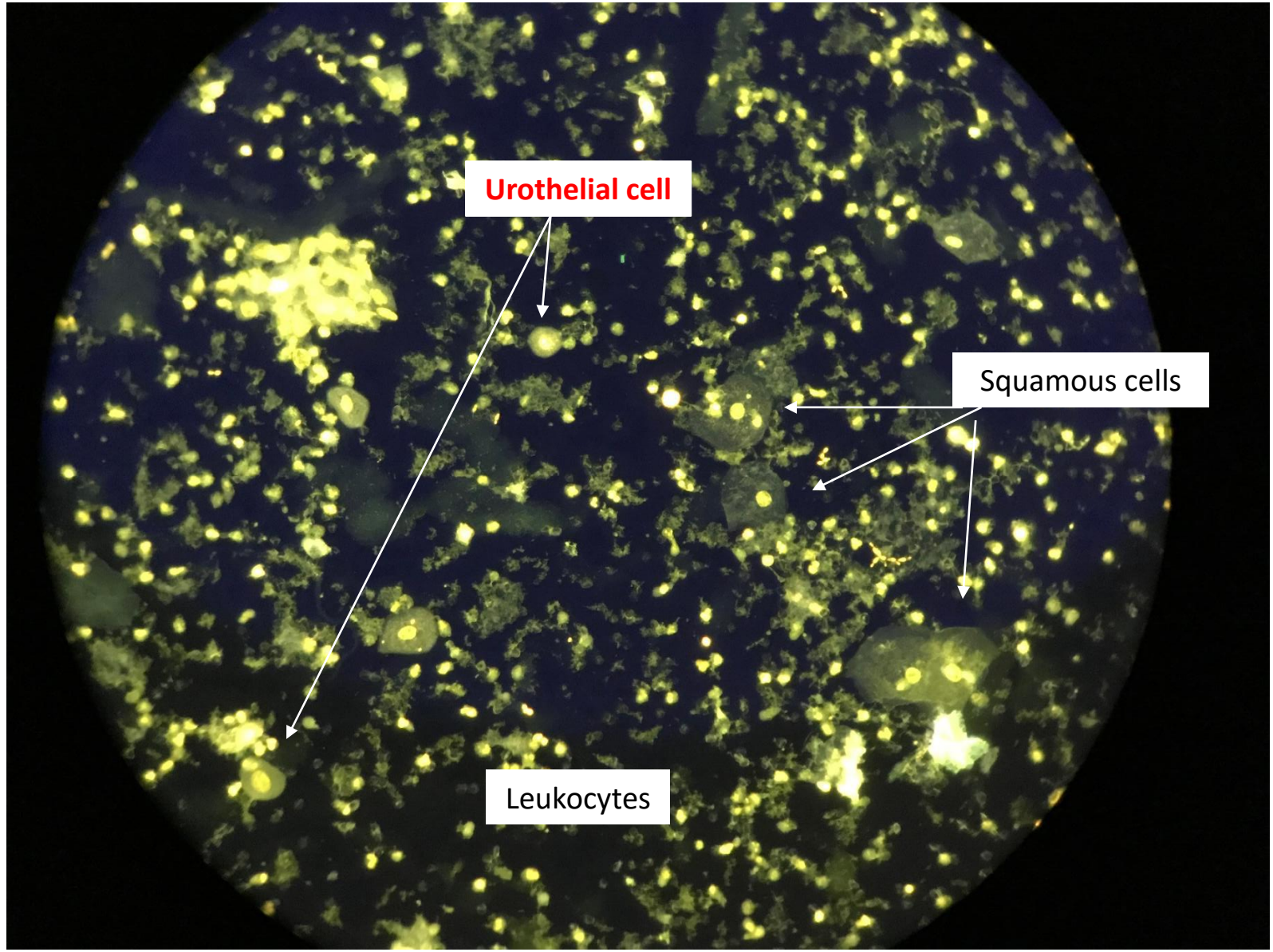
Killela PJ et al. PNAS 2013

CancerSEEK

- Detect 8 common cancer types through assessment of **circulating proteins** and **mutations in ctDNA**
- Combination of parameters increase sensitivity for early stage cancer
- **16 genes** (61 amplicon) and **8 proteins** (CA-125, CEA, CA19-9, prolactin, HGF, osteopontin , myeloperoxidase, TIMP-1)
- **1005 patients** with non-metastatic cancers (**ovary, liver, stomach, pancreas, esophagus**, **CRCa, lung, breast)**
- Median **sensitivity 70%** for eight cancer types
- Sensitivities of 69-98% for the five cancer types without current screening program
- **Specificity >99% (**7/812 healthy controls scored positive)



Cohen, J.D., et al. Science, 2018



Voided Urine Sample
99% WBCs
1% Squamous cells

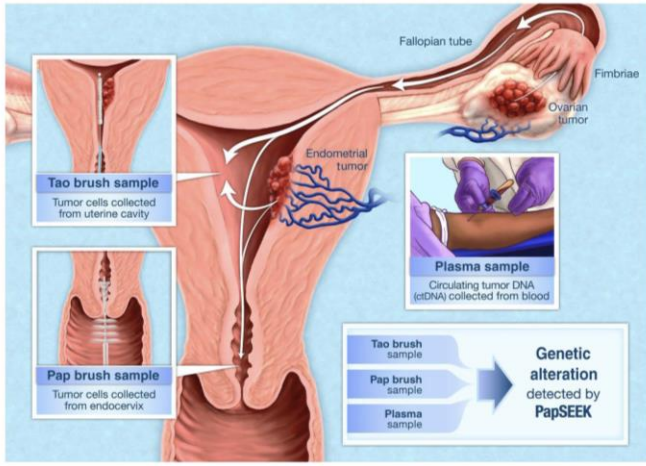
PapSEEK

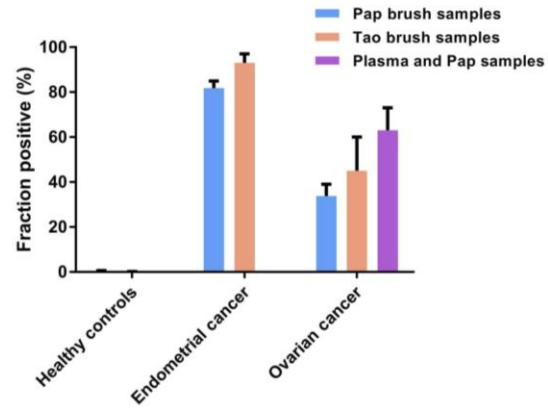
SCIENCE TRANSLATIONAL MEDICINE | RESEARCH ARTICLE

CANCER

Evaluation of liquid from the Papanicolaou test and other liquid biopsies for the detection of endometrial and ovarian cancers

Yuxuan Wang,[1] Lu Li,[2] Christopher Douville,[1] Joshua D. Cohen,[1,3] Ting-Tai Yen,[4] Isaac Kinde,[5] Karin Sundfelt,[6] Susanne K. Kjær,[7,8] Ralph H. Hruban,[9] Ie-Ming Shih,[9] Tian-Li Wang,[9] Robert J. Kurman,[9] Simeon Springer,[1] Janine Ptak,[1] Maria Popoli,[1] Joy Schaefer,[1] Natalie Silliman,[1] Lisa Dobbyn,[1] Edward J. Tanner,[4] Ana Angarita,[4] Maria Lycke,[6] Kirsten Jochumsen,[10] Bahman Afsari,[2] Ludmila Danilova,[2] Douglas A. Levine,[11] Kris Jardon,[12] Xing Zeng,[12] Jocelyne Arseneau,[12] Lili Fu,[12] Luis A. Diaz Jr.,[1] Rachel Karchin,[13] Cristian Tomasetti,[2]* Kenneth W. Kinzler,[1]* Bert Vogelstein,[1,14]* Amanda N. Fader,[4]* Lucy Gilbert,[12]* Nickolas Papadopoulos[1]*





Wang Y., et al. Sci Trans Med, 2018

UroSEEK/CancerSEEK/PapSEEK

Next Steps

CHALLENGES
Impact on Pathology and Lab Medicine

1) Unprecedented Demands on **Expertise** and **Capital** due to rapidly changing technological platforms
Evolution and adaptation of pathology work force
$$ Investment

2) **Operational challenges** of Multidisciplinary **Integration** while maintaining “turf” advantage

3) **Financial Viability** in Constrained Health Care Economics

CHALLENGES
Impact on Pathology and Lab Medicine

1) Unprecedented Demands on **Expertise** and **Capital** due to rapidly changing technological platforms
   Evolution and adaptation of pathology work force
   $$ Investment

2) **Operational challenges** of Multidisciplinary **Integration** while maintaining “turf” advantage

3) **Financial Viability** in Constrained Health Care Economics

Financial Viability of Pathology Services

Challenges of Affordable Care Act (ACA)

Episode of Care Bundling
Cost Pressure
Outcome Based Incentive

2020 Trump Admin Budget

*12% reduction in **HHS** funding*

*Deep cuts to **Medicare**, **GME**, and **Medicaid***

*Reduced funding for **NIH**, **VA** programs*

Financial Viability
“Precision” Pathology Service

- **Measurable Impact on Outcome**
  Genomic Data Integration in patient management tools
  Pharmacogenomics
  LIS/EMR

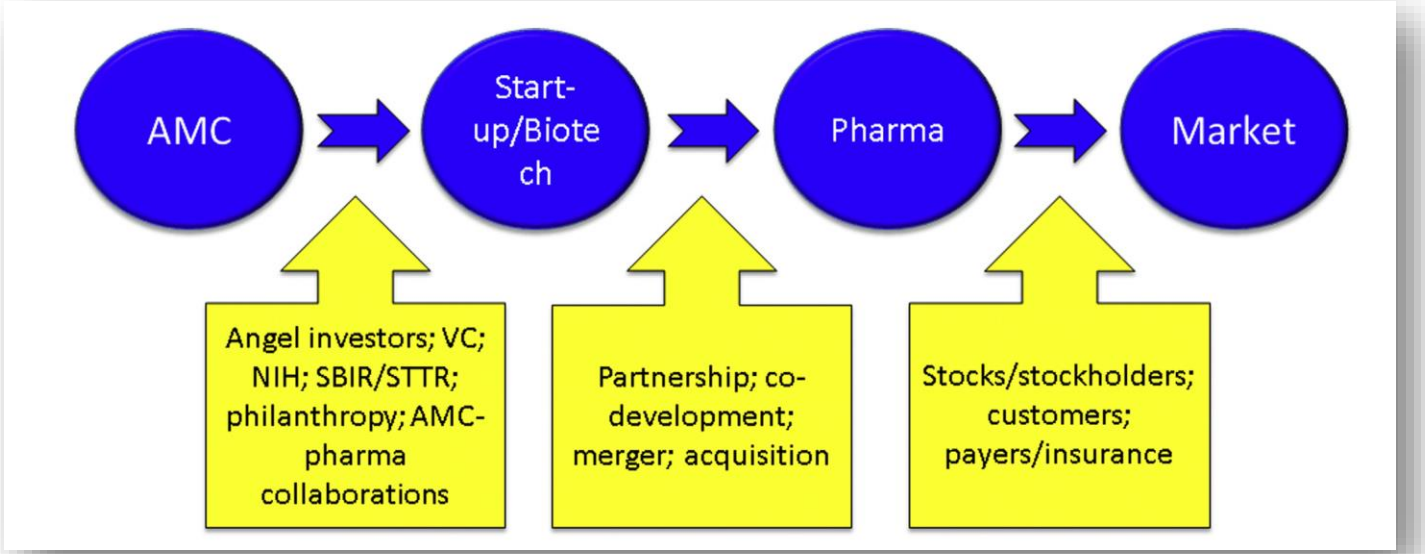
- **Big Data in Health Care**
  2/3 of medical records data is Lab Med Tests Data
  Pathologists are positioned to be the “Rock stars” of Big Data !

Financial Viability of Pathology Research Enterprise

Enhance Pathology Faculty Stream of Research Funding

- Invest in pipelines of **physician scientist career** development
- **Break Silos of EP vs LM vs AP ***
  - **Empower** Pathologist as member of **translational research teams**
- **Organic growth and/or "Acquisition"** new awards *
- **Diversify grant portfolio** into new areas of growing $$$ support **
- **Philanthropy** the **clinical face** of the pathologist

Research Financial Ecosystem
From Discovery to Market



Cummings J et al. Alzheimer's & Dementia (2018)

Financial Viability of Pathology Research Enterprise

Research Funding

- **NIH**
  2022: Biden admin proposes **$51.9 billion (21% increase)**

- **Other Governmental**
  DOD/ VA / State
- Non-Governmental **Foundations**
- **Philanthropy**
- **Industry contracts**

Congressional Research Service
Informing the legislative debate since 1914

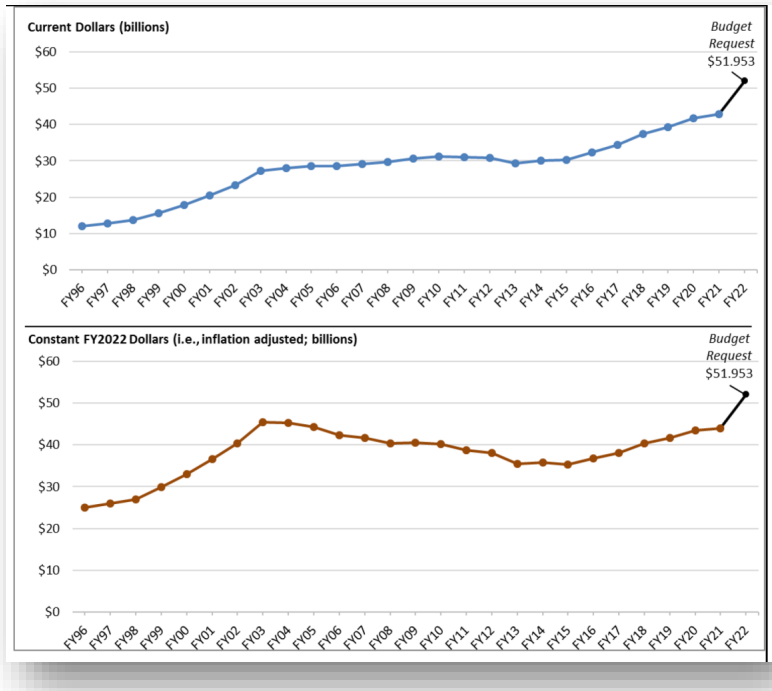


Figure 1. National Institutes of Health (NIH) Funding, FY1996-FY2022

Program Level Funding in Current and Projected Constant (FY2022) Dollars.

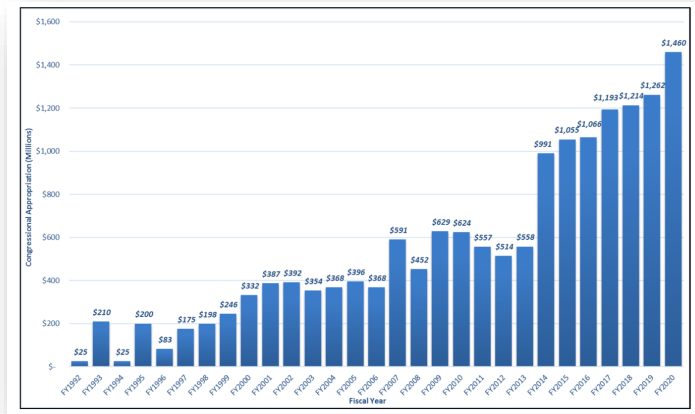
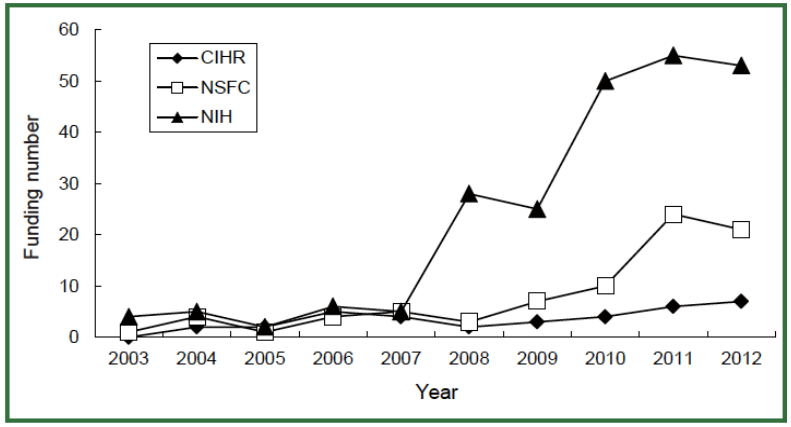


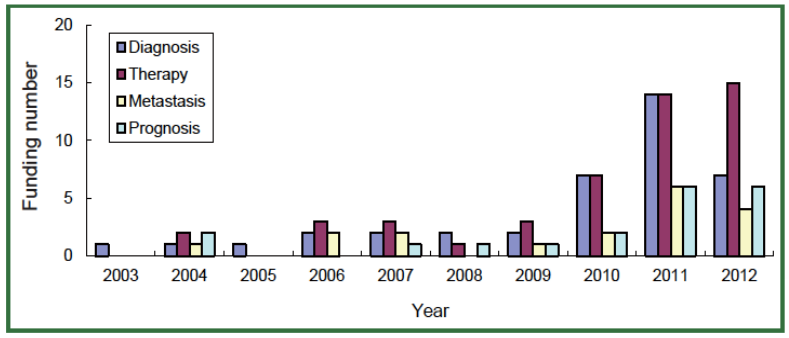
Figure 3. Congressional Appropriations for CDMRP

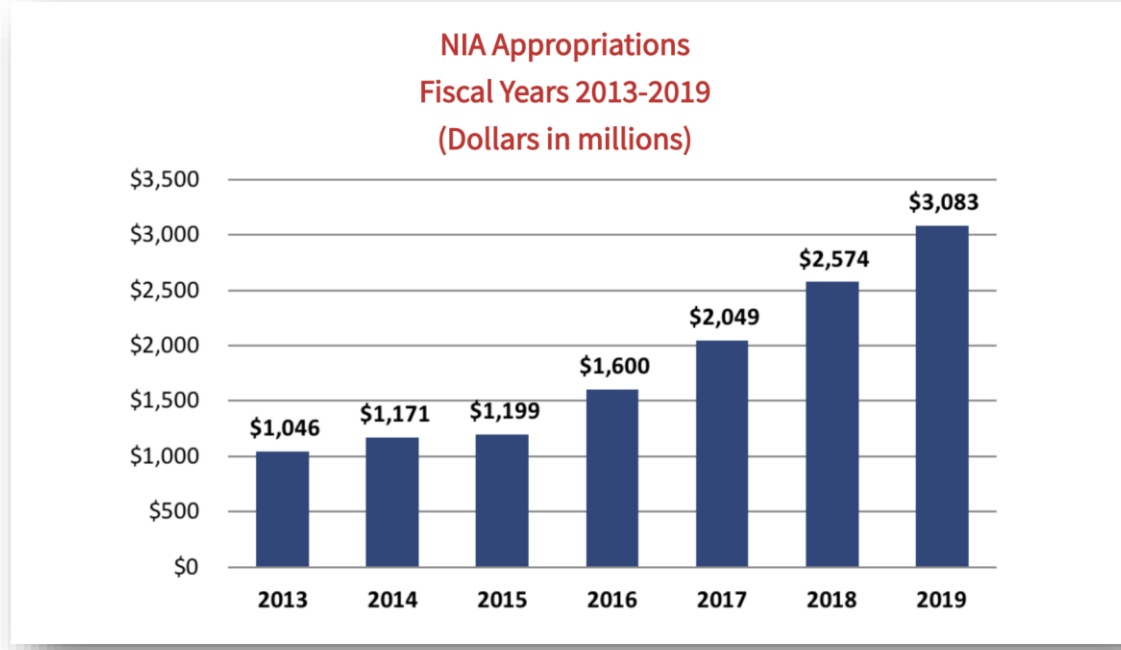
FY1992-FY2020

Strategic Targeting of Research Funding

Fynding Lung Cancer Biomarkers







https://www.nia.nih.gov/research/blog/2018/10/we-have-budget-fy-2019

Embrace Inevitable Change

- **Inherent anxiety** associated with change
- Pathology field has **constantly adapted** to health care environment changes (DRG, Managed Care..)
- Our specialty always thrives on **assimilating scientific and technologic** advances (EM, IHC, Lab automation..)

CHALLENGES
Impact on Pathology and Lab Medicine

1) Unprecedented Demands on **Expertise** and **Capital** due to rapidly changing technological platforms
   Evolution of pathology work force
   $$ Investment in Capital Equipment

2) **Operational challenges** of Multidisciplinary **Integration** while maintaining “turf” advantage

3) **Financial Viability** in Constrained Health Care Economics

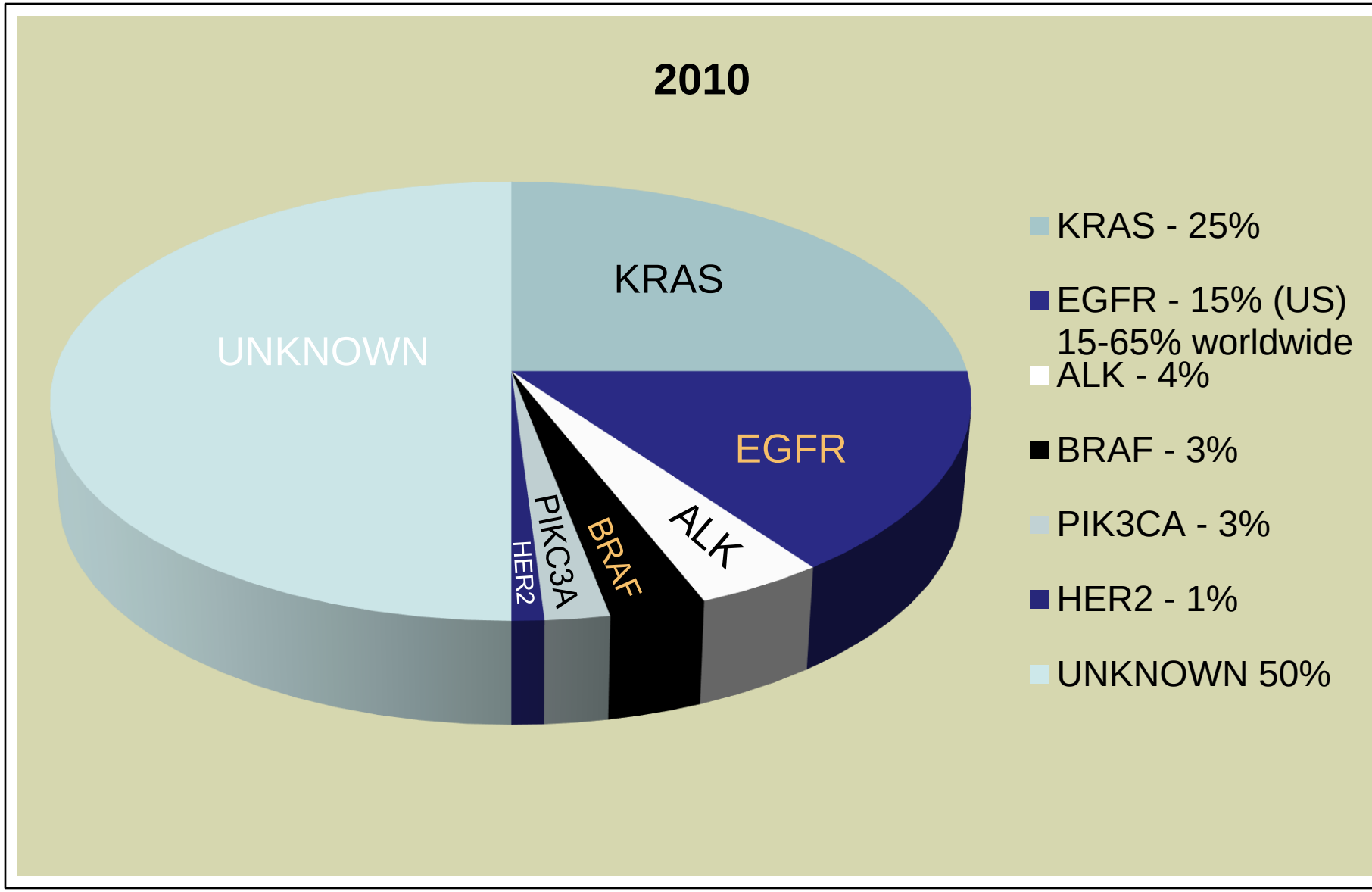
$$ Investment in Capital Equipment

NGS platforms *

- Gene Panels/WES
- Send out *vs* In House
  - Raw data: **Research/Education**
  - Expertise lead to a **seat at the multiD table**

Digital Pathology Platforms *

Genetic Alterations in Lung Adenocarcinoma

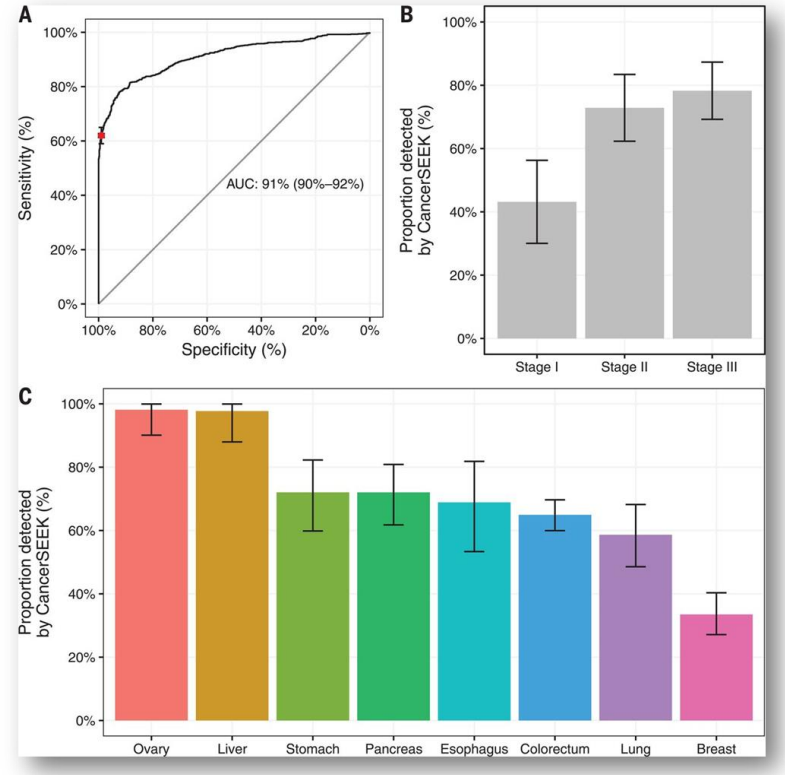


CancerSEEK

CANCER

Detection and localization of surgically resectable cancers with a multi-analyte blood test

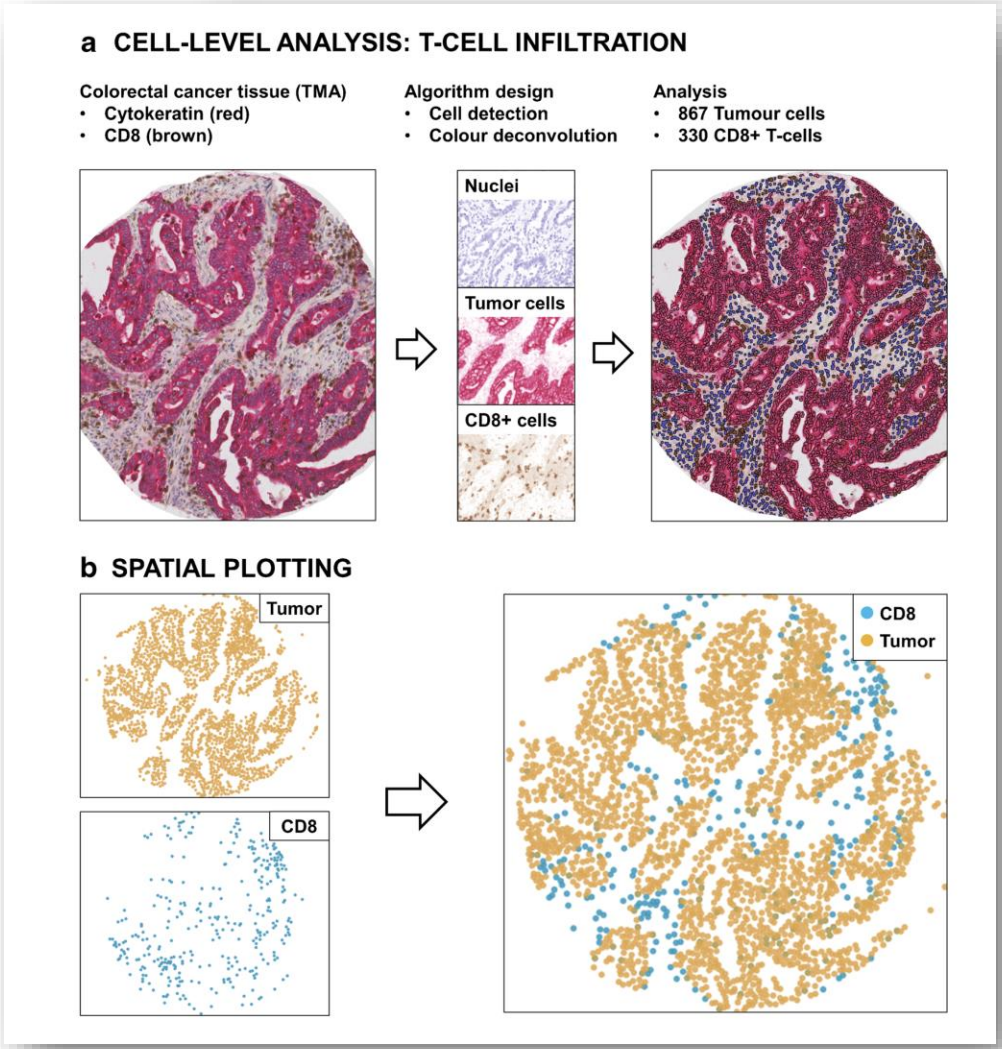
Joshua D. Cohen,[1,2,3,4,5] Lu Li,[6] Yuxuan Wang,[1,2,3,4] Christopher Thoburn,[3] Bahman Afsari,[7] Ludmila Danilova,[7] Christopher Douville,[1,2,3,4] Ammar A. Javed,[8] Fay Wong,[1,3,4] Austin Mattox,[1,2,3,4] Ralph. H. Hruban,[3,4,9] Christopher L. Wolfgang,[8] Michael G. Goggins,[3,4,9,10,11] Marco Dal Molin,[4] Tian-Li Wang,[3,9] Richard Roden,[3,9] Alison P. Klein,[3,4,12] Janine Ptak,[1,2,3,4] Lisa Dobbyn,[1,3,4] Joy Schaefer,[1,3,4] Natalie Silliman,[1,2,3,4] Maria Popoli,[1,3,4] Joshua T. Vogelstein,[13] James D. Browne,[14] Robert E. Schoen,[15,16] Randall E. Brand,[15] Jeanne Tie,[17,18,19,20] Peter Gibbs,[17,18,19,20] Hui-Li Wong,[17] Aaron S. Mansfield,[21] Jin Jen,[22] Samir M. Hanash,[23] Massimo Falconi,[24] Peter J. Allen,[25] Shibin Zhou,[1,3,4] Chetan Bettegowda,[1,3,4] Luis A. Diaz Jr.,[1,3,4]* Cristian Tomasetti,[3,6,7]† Kenneth W. Kinzler,[1,3,4]† Bert Vogelstein,[1,2,3,4]† Anne Marie Lennon,[3,4,8,10,11]† Nickolas Papadopoulos[1,3,4]†

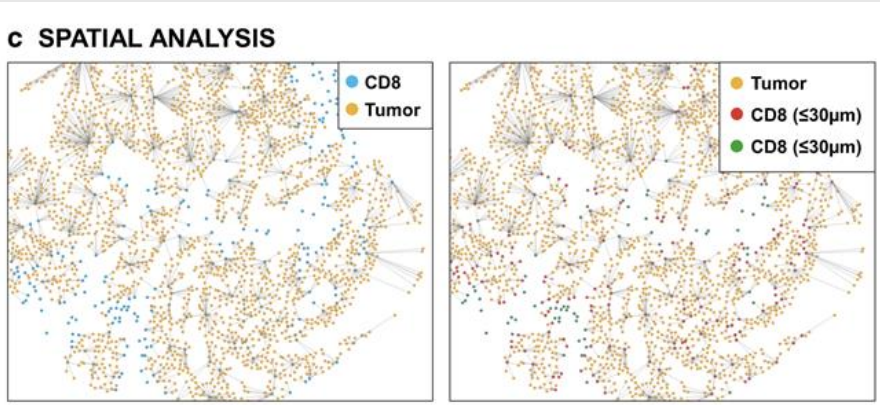


Cohen, J.D., et al. Science, 2018

Precision immunoprofiling by image analysis and artificial intelligence

Viktor H. Koelzer[1,2] · Korsuk Sirinukunwattana[3] · Jens Rittscher[3,4,5] · Kirsten D. Mertz[6]





Koelzer VH et al Virchows Arch 2018

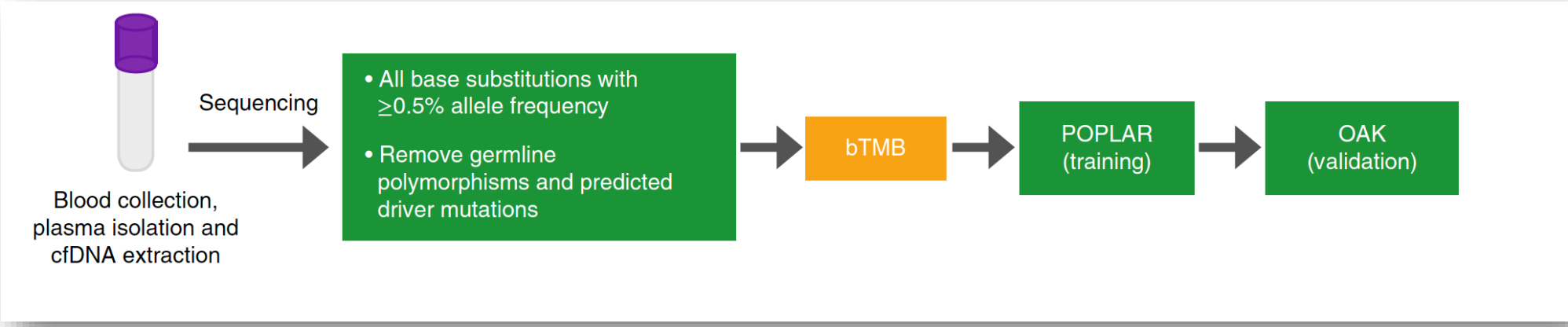
nature medicine

ARTICLES

https://doi.org/10.1038/s41591-018-0134-3

Blood-based tumor mutational burden as a predictor of clinical benefit in non-small-cell lung cancer patients treated with atezolizumab

David R. Gandara[1,7*], Sarah M. Paul[2,7], Marcin Kowanetz[2,7], Erica Schleifman[2,7], Wei Zou[2,7], Yan Li[2], Achim Rittmeyer[3], Louis Fehrenbacher[4], Geoff Otto[5], Christine Malboeuf[5], Daniel S. Lieber[5], Doron Lipson[5], Jacob Silterra[5], Lukas Amler[2], Todd Riehl[2], Craig A. Cummings[2], Priti S. Hegde[2], Alan Sandler[2], Marcus Ballinger[2], David Fabrizio[5], Tony Mok[6*] and David S. Shames[2*]



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- Foundation ACT

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MEDICINE

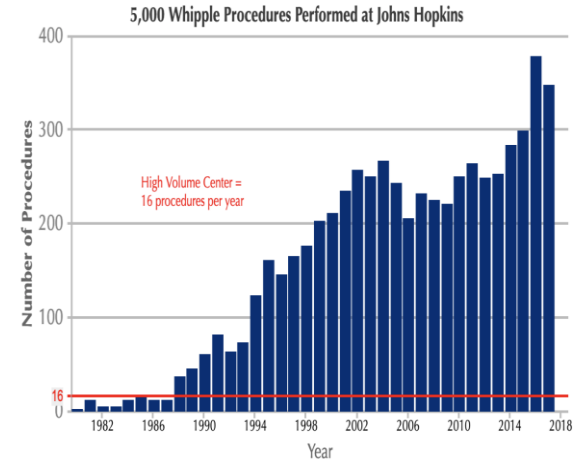
The Sol Goldman Pancreatic Cancer Research Center

For Patients & Family | Cancer Clinic | Cyst Clinic | NFPTR | Medical Professionals | Donate | Blog

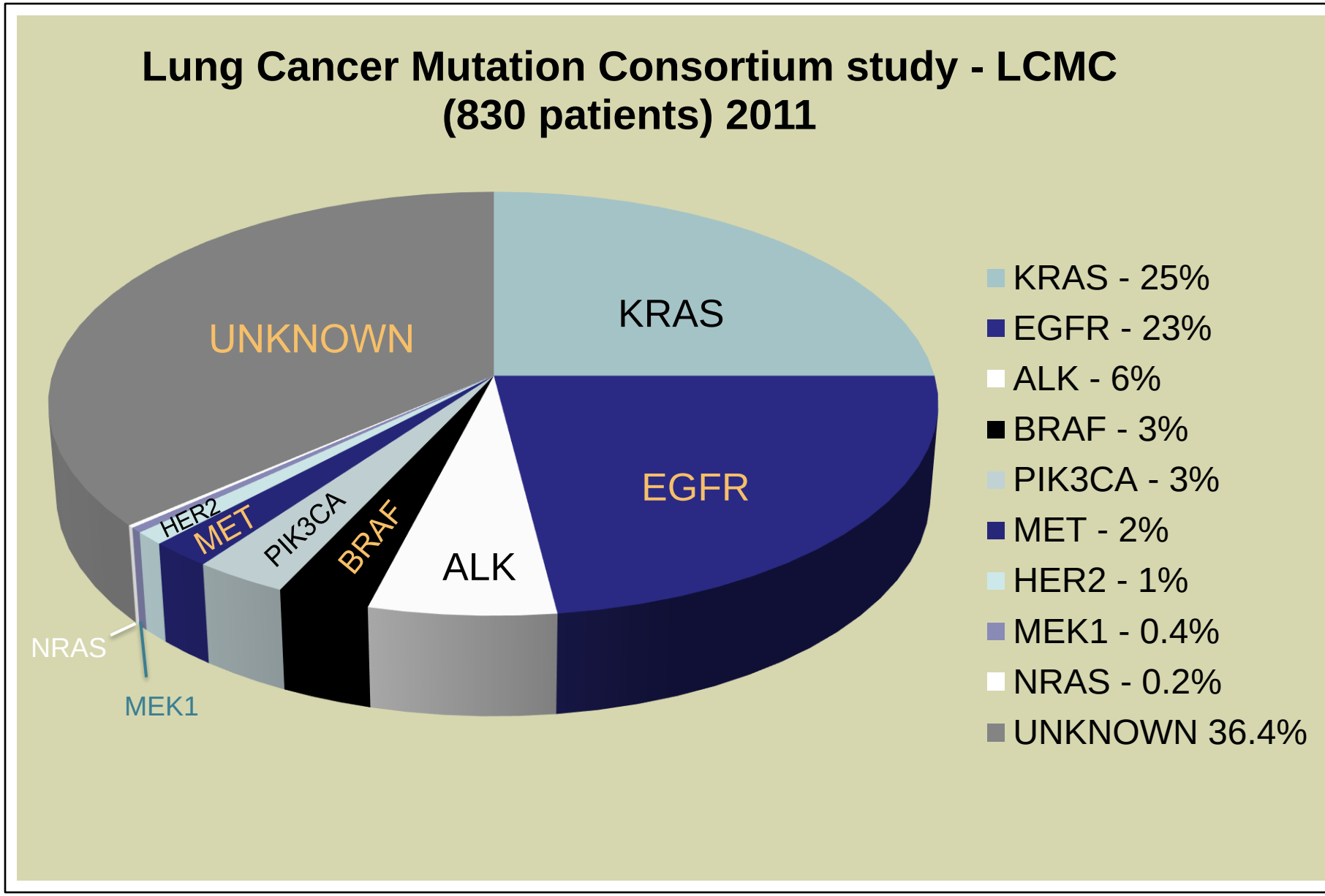
Pancreas Multidisciplinary Cancer Team

The Multidisciplinary Pancreatic Cancer Team at Johns Hopkins is committed to providing the highest level of care to individuals suffering from pancreatic cancer and related conditions. Our team is comprised of many of the world's leading experts in pancreatic cancer.

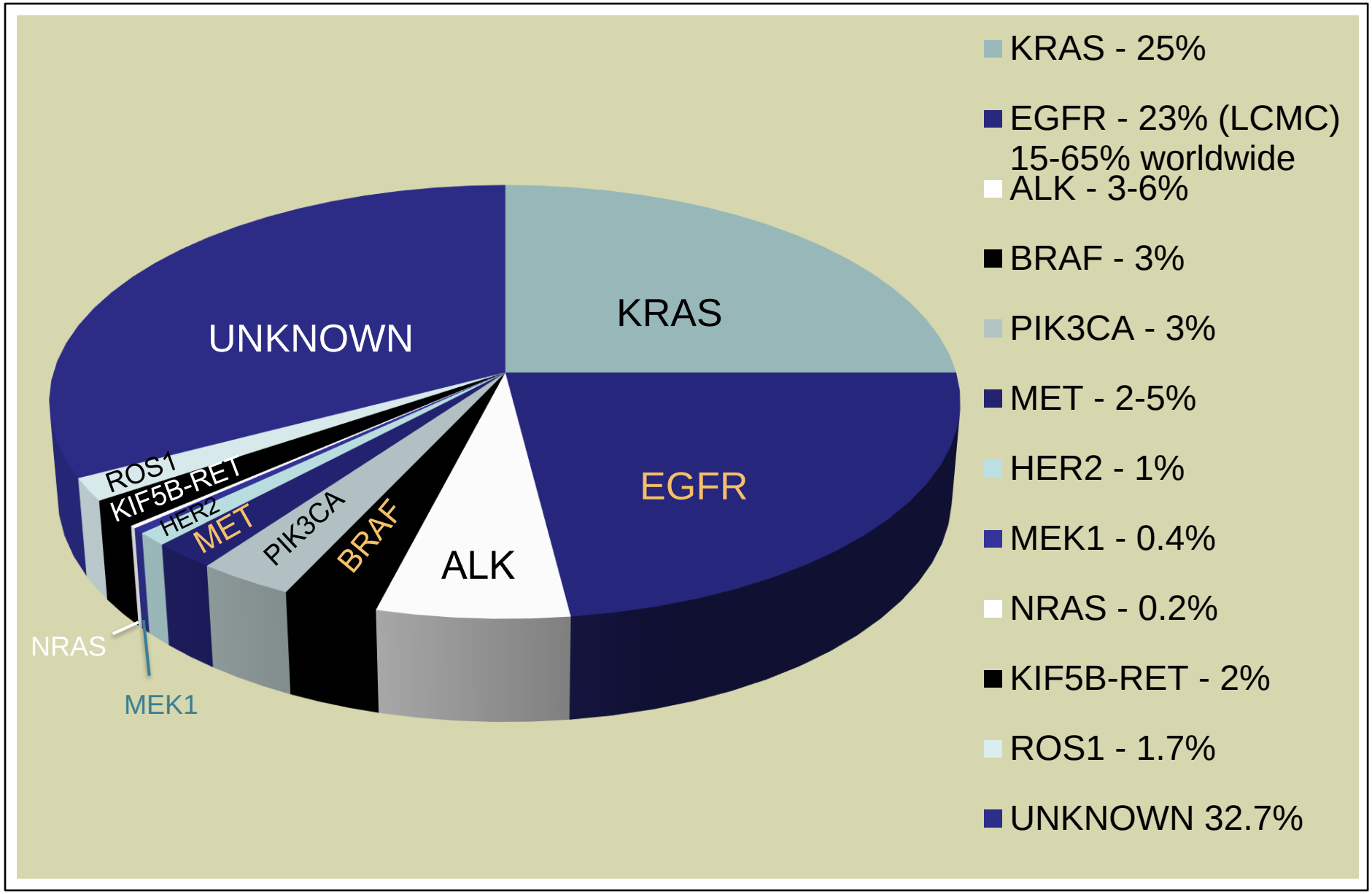
Experience is Important



Genetic Alterations in Lung Adenocarcinoma



Genetic Alterations in Lung Adenocarcinoma



Histopathology

Histopathology 2019, **74**, 372–376.

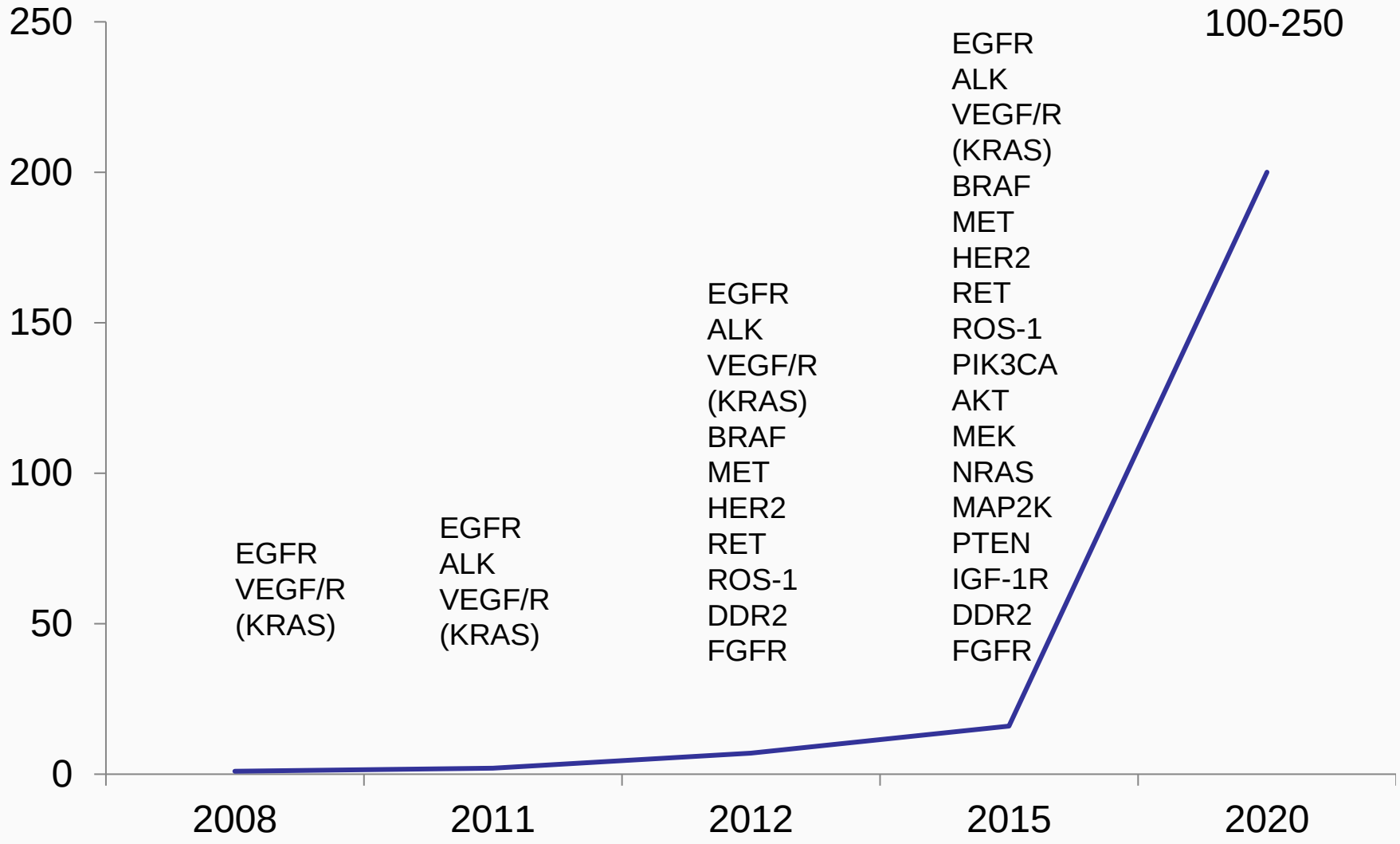
Artificial intelligence—the third revolution in pathology

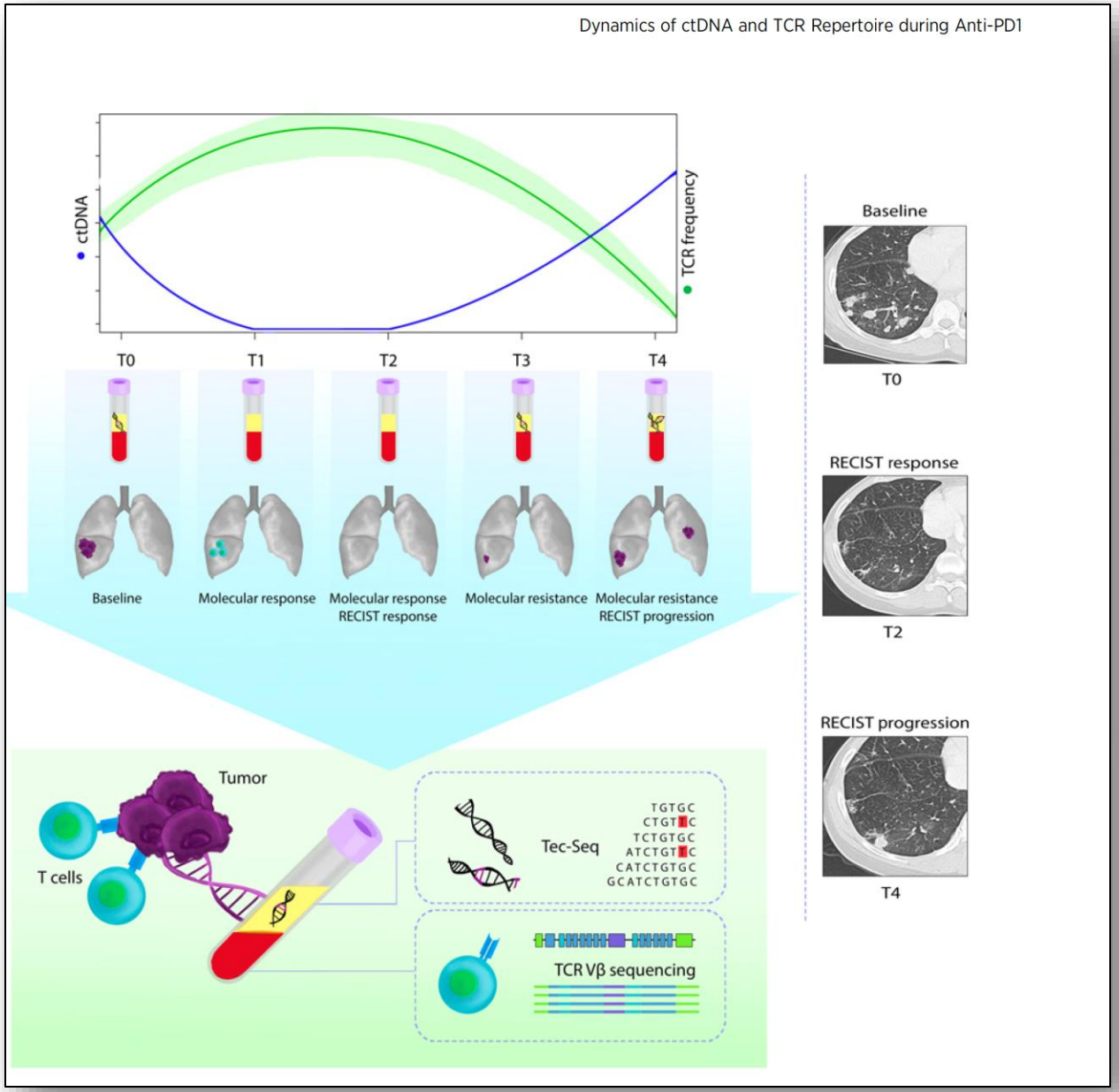
Manuel Salto-Tellez[1,2,3]
Perry Maxwell[1,2]
Peter Hamilton[4]

[1]*Precision Medicine Centre of Excellence,* [2]*Centre for Cancer Research and Cell Biology, Queen's University Belfast,* [3]*Tissue Pathology, Belfast Health and Social Care Trust, and* [4]*Philips Digital Pathology, Belfast, UK*

Will pathologists be simple facilitators and spectators of this third revolution? Will others in the medical profession drive adoption with pathologists (as appears to be the case in most areas of molecular diagnostics), or will we be the leading actors in the play?

Targetable Genetic Alterations

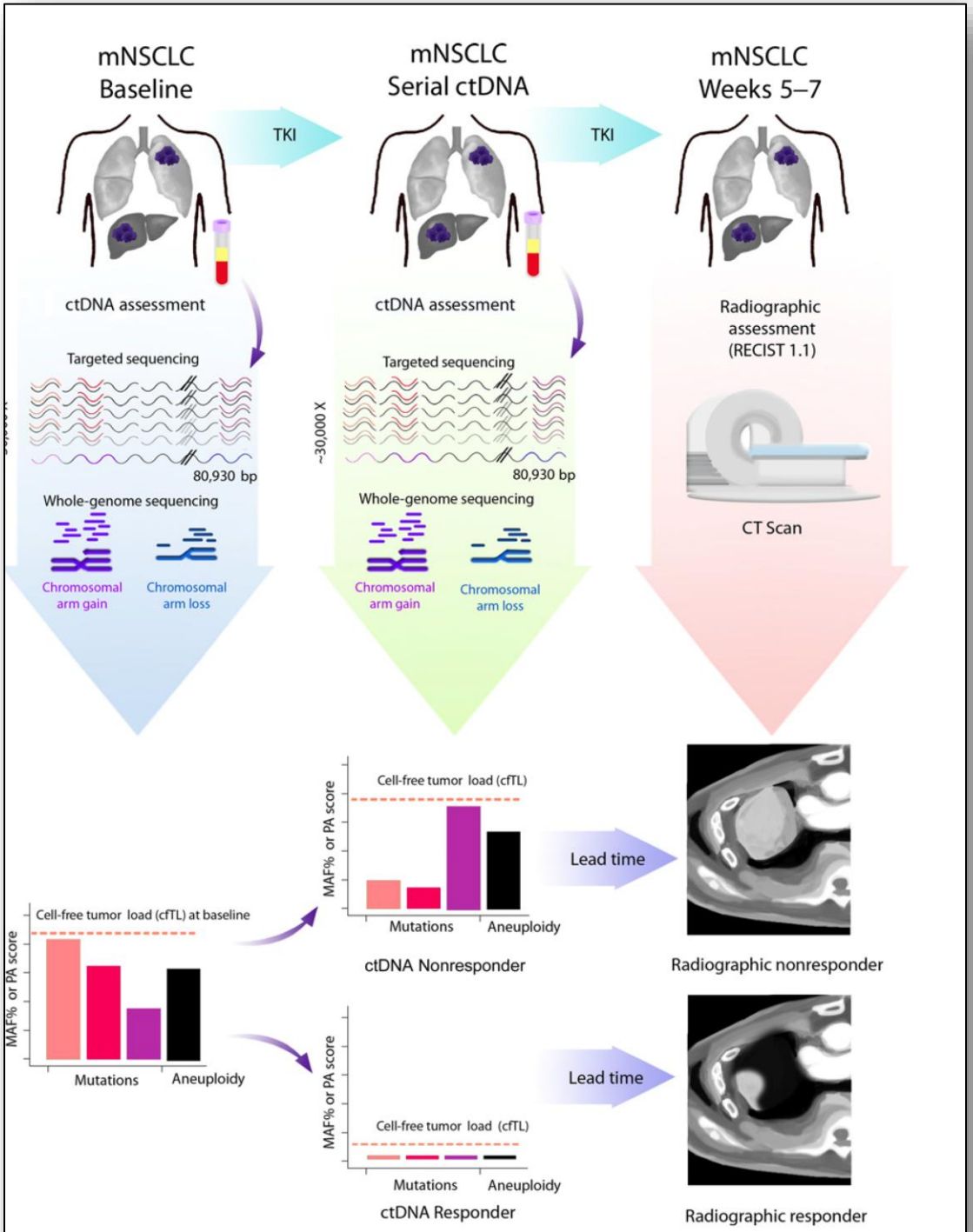




Anagnostou V et al Cancer Res 2019

Dynamics of Tumor and Immune Responses during Immune Checkpoint Blockade in Non–Small Cell Lung Cancer

Valsamo Anagnostou[1,2], Patrick M. Forde[1,2], James R. White[1], Noushin Niknafs[1], Carolyn Hruban[1], Jarushka Naidoo[1,2], Kristen Marrone[1,2], I.K. Ashok Sivakumar[1,3,4], Daniel C. Bruhm[1], Samuel Rosner[5], Jillian Phallen[1], Alessandro Leal[1], Vilmos Adleff[1], Kellie N. Smith[1,2], Tricia R. Cottrell[1,6], Lamia Rhymee[1], Doreen N. Palsgrove[1], Christine L. Hann[1], Benjamin Levy[1], Josephine Feliciano[1], Christos Georgiades[7], Franco Verde[7], Peter Illei[1,2,6], Qing Kay Li[1,6], Edward Gabrielson[1,6], Malcolm V. Brock[8], James M. Isbell[9], Jennifer L. Sauter[10], Janis Taube[1,2,6], Robert B. Scharpf[1], Rachel Karchin[1,3], Drew M. Pardoll[1,2], Jamie E. Chaft[11], Matthew D. Hellmann[11], Julie R. Brahmer[1,2], and Victor E. Velculescu[1,2,3]



Early Noninvasive Detection of Response to Targeted Therapy in Non–Small Cell Lung Cancer

Jillian Phallen[1], Alessandro Leal[1], Brian D. Woodward[2], Patrick M. Forde[1], Jarushka Naidoo[1], Kristen A. Marrone[1], Julie R. Brahmer[1], Jacob Fiksel[1], Jamie E. Medina[1], Stephen Cristiano[1], Doreen N. Palsgrove[1], Christopher D. Gocke[1], Daniel C. Bruhm[1], Parissa Keshavarzian[2], Vilmos Adleff[1], Elizabeth Weihe[2], Valsamo Anagnostou[1], Robert B. Scharpf[1], Victor E. Velculescu[1], and Hatim Husain[2]

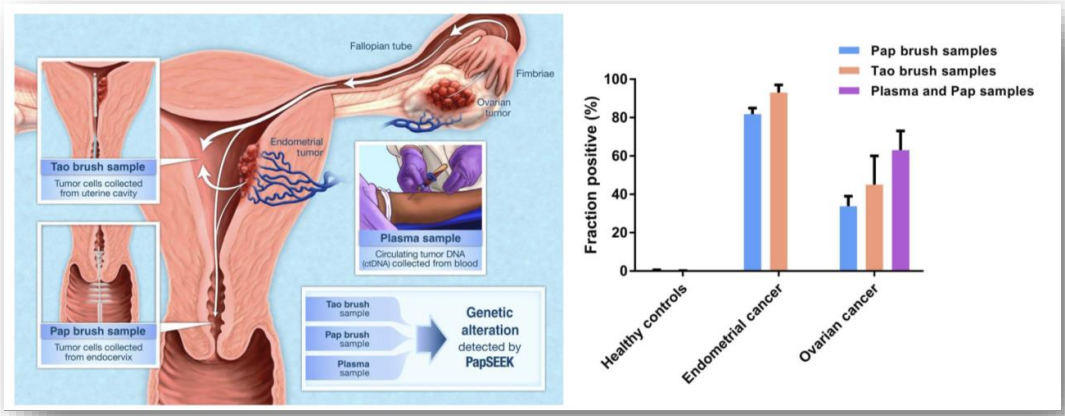
Phallen J et al Cancer Res 2019

PapSEEK

- 18 genes and Ploidy (Fast-Seq)

- Pap vs Tao Brush
  - Endometrial Ca: 81% vs 93% sensitivity
  - Ovarian Ca: 33% vs 45% sensitivity Specificity 99% vs 100%

- Plasma ctDNA
  - Ovarian Ca: 43% sensitivity
  - 63% sensitivity when combined with Pap Brush



Wang Y., et al. Sci Trans Med, 2018

Genomic complexity of urothelial bladder cancer revealed in urinary cfDNA

Fiona S Togneri[1], Douglas G Ward[2], Joseph M Foster[3], Adam J Devall[2], Paula Wojtowicz[1], Sofia Alyas[1], Fabiana Ramos Vasques[1], Assa Oumie[3], Nicholas D James[4], KK Cheng[5], Maurice P Zeegers[6], Nayneeta Deshmukh[2], Brendan O'Sullivan[7], Philippe Taniere[7], Karen G Spink[3], Dominic J McMullan[1], Mike Griffiths[1] and Richard T Bryan*[,2]

European Journal of Human Genetics 2016

Genomic Alterations in Liquid Biopsies from Patients with Bladder Cancer

Karin Birkenkamp-Demtröder[a,†,], Iver Nordentoft[a,†], Emil Christensen[a], Søren Høyer[b], Thomas Reinert[a], Søren Vang[a], Michael Borre[c], Mads Agerbæk[d], Jørgen Bjerggaard Jensen[c], Torben F. Ørntoft[a], Lars Dyrskjøt[a,**]*

EUROPEAN UROLOGY, 2016

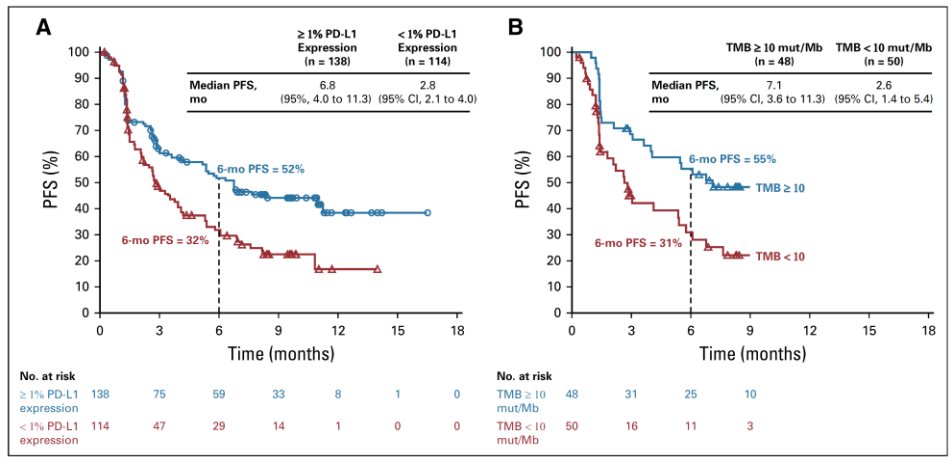
Liquid Biopsy Analysis of *FGFR3* and *PIK3CA* Hotspot Mutations for Disease Surveillance in Bladder Cancer

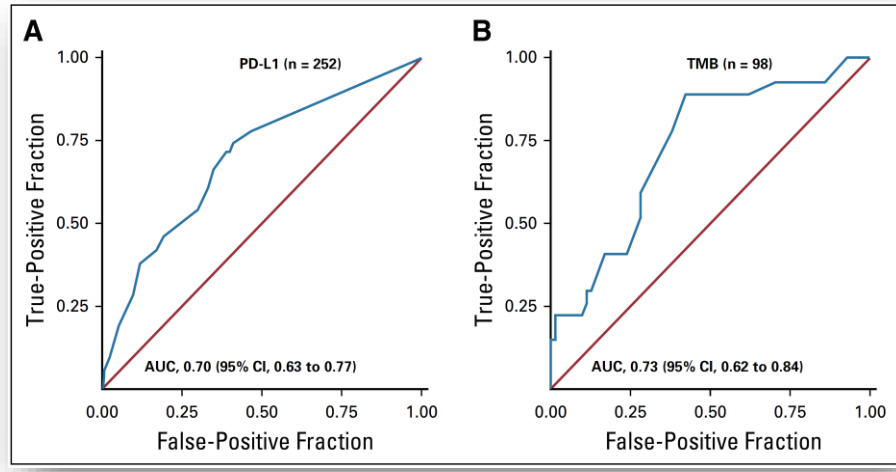
Emil Christensen[a], Karin Birkenkamp-Demtröder[a], Iver Nordentoft[a], Søren Høyer[b], Kirstin van der Keur[c], Kim van Kessel[c], Ellen Zwarthoff[c], Mads Agerbæk[d], Torben Falck Ørntoft[a], Jørgen Bjerggaard Jensen[e], Lars Dyrskjøt[a,]*

EUROPEAN UROLOGY , 2017

First-Line Nivolumab Plus Ipilimumab in Advanced Non–Small-Cell Lung Cancer (CheckMate 568): Outcomes by Programmed Death Ligand 1 and Tumor Mutational Burden as Biomarkers

Neal Ready, MD, PhD[1]; Matthew D. Hellmann, MD[2]; Mark M. Awad, MD, PhD[3]; Gregory A. Otterson, MD[4]; Martin Gutierrez, MD[5]; Justin F. Gainor, MD[6]; Hossein Borghaei, DO[7]; Jacques Jolivet, MD[8]; Leora Horn, MD[9]; Mihaela Mates, MD[10]; Julie Brahmer, MD[11]; Ian Rabinowitz, MD[12]; Pavan S. Reddy, MD[13]; Jason Chesney, MD, PhD[14]; James Orcutt, MD[15]; David R. Spigel, MD[16]; Martin Reck, PhD[17]; Kenneth John O'Byrne, MD[18]; Luis Paz-Ares, MD, PhD[19]; Wenhua Hu, PhD[20]; Kim Zerba, PhD[20]; Xuemei Li, MD[20]; Brian Lestini, MD, PhD[20]; William J. Geese, PhD[20]; Joseph D. Szustakowski, PhD[20]; George Green, PhD[20]; Han Chang, PhD[20]; and Suresh S. Ramalingam, MD[21]



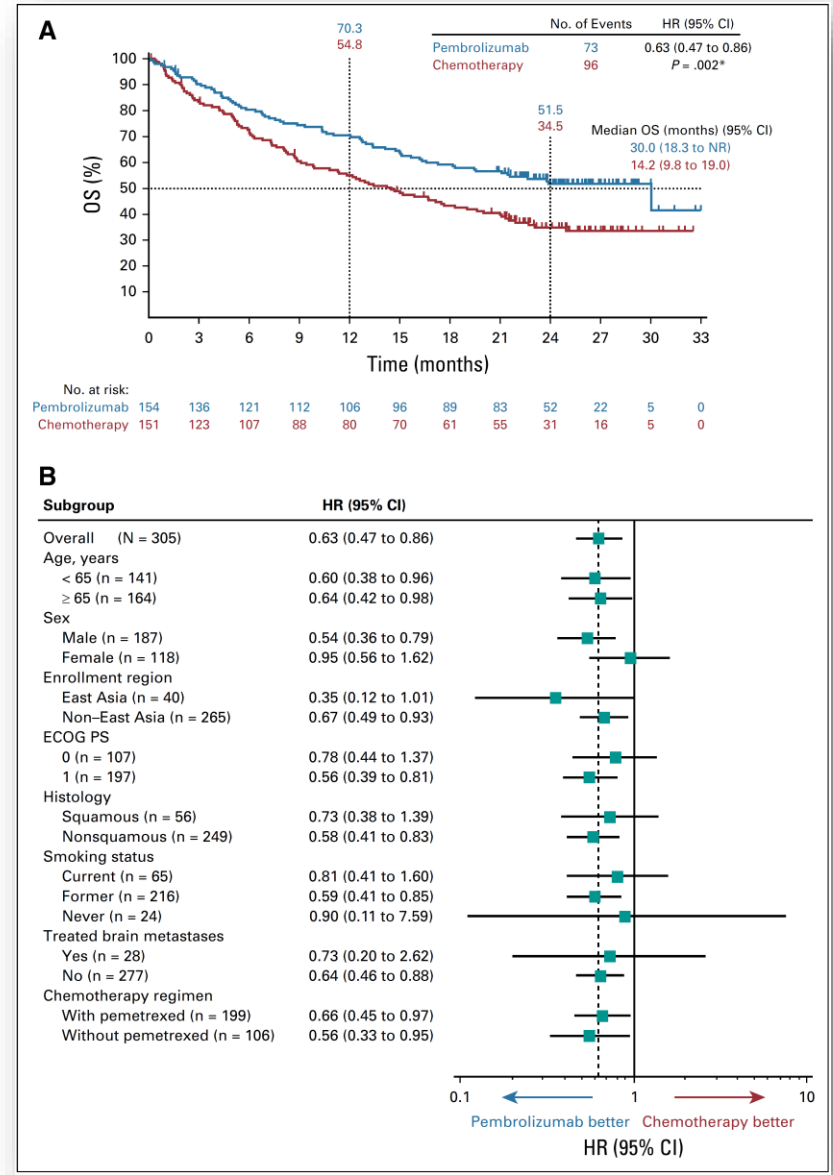


Ready N et al JCO 2019

Updated Analysis of KEYNOTE-024: Pembrolizumab Versus Platinum-Based Chemotherapy for Advanced Non–Small-Cell Lung Cancer With PD-L1 Tumor Proportion Score of 50% or Greater

Martin Reck, MD, PhD[1]; Delvys Rodríguez-Abreu, MD[2]; Andrew G. Robinson, MD[3]; Rina Hui, MBBS, PhD[4]; Tibor Csőszi, MD[5]; Andrea Fülöp, MD[6]; Maya Gottfried, MD[7]; Nir Peled, MD, PhD[8]; Ali Tafreshi, MD[9]; Sinead Cuffe, MD[10]; Mary O'Brien, MD[11]; Suman Rao, MD[12]; Katsuyuki Hotta, MD, PhD[13]; Kristel Vandormael, MSc[14]; Antonio Riccio, PhD[15]; Jing Yang, PhD[15]; M. Catherine Pietanza, MD[15]; and Julie R. Brahmer, MD[16]

Reck M et al JCO 2019



Financial Viability
“Precision” Pathology Service

- **Measurable Impact on Outcome**
  Genomic Data Integration in patient management tools
  Pharmacogenomics
  LIS/EMR

- **Big Data in Health Care**
  2/3 of medical records data is Lab Med Tests Data
  Pathologists are positioned to be the “Rock stars” of Big Data !

CHALLENGES

Impact on Pathology and Lab Medicine

1) Unprecedented Demands on **Expertise** and **Capital** due to rapidly changing technological platforms
   Evolution and adaptation of pathology work force
   $$ Investment

2) **Operational challenges** of Multidisciplinary **Integration** while maintaining “turf” advantage

3) **Financial Viability** in Constrained Health Care Economics

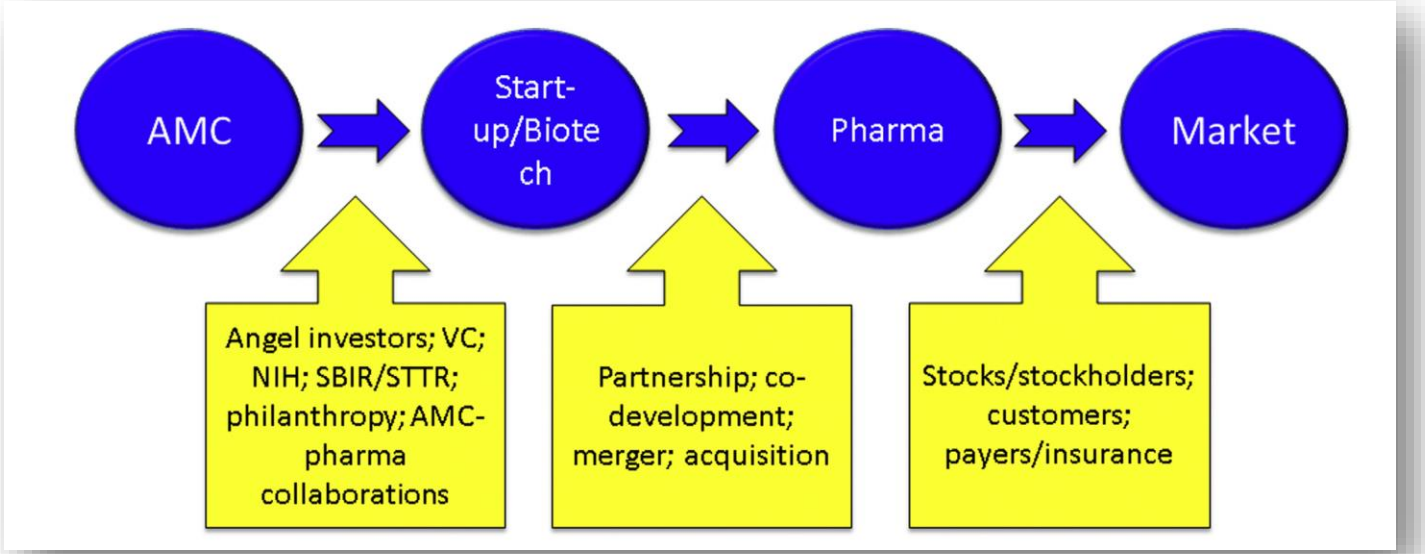
Next Gen Pathologist
Indispensable Member of
Integrated Healthcare Delivery Team

- **Pathologist of The Future** is a **vital** player in patient management team
  Molecular multidisciplinary tumor boards
  Cell Therapy (CAR-T Cell)

- **Elevating "Physician Profile"** through patient exposure & communication
  CAP "Meet your Pathologist" efforts
  AMP gene patent victory

- **Advocacy** for protecting our deservedly earned "Expertise Turf"
  FDA LDT vs Companion Test; DTC; MOOP…

Research Financial Ecosystem
From Discovery to Market



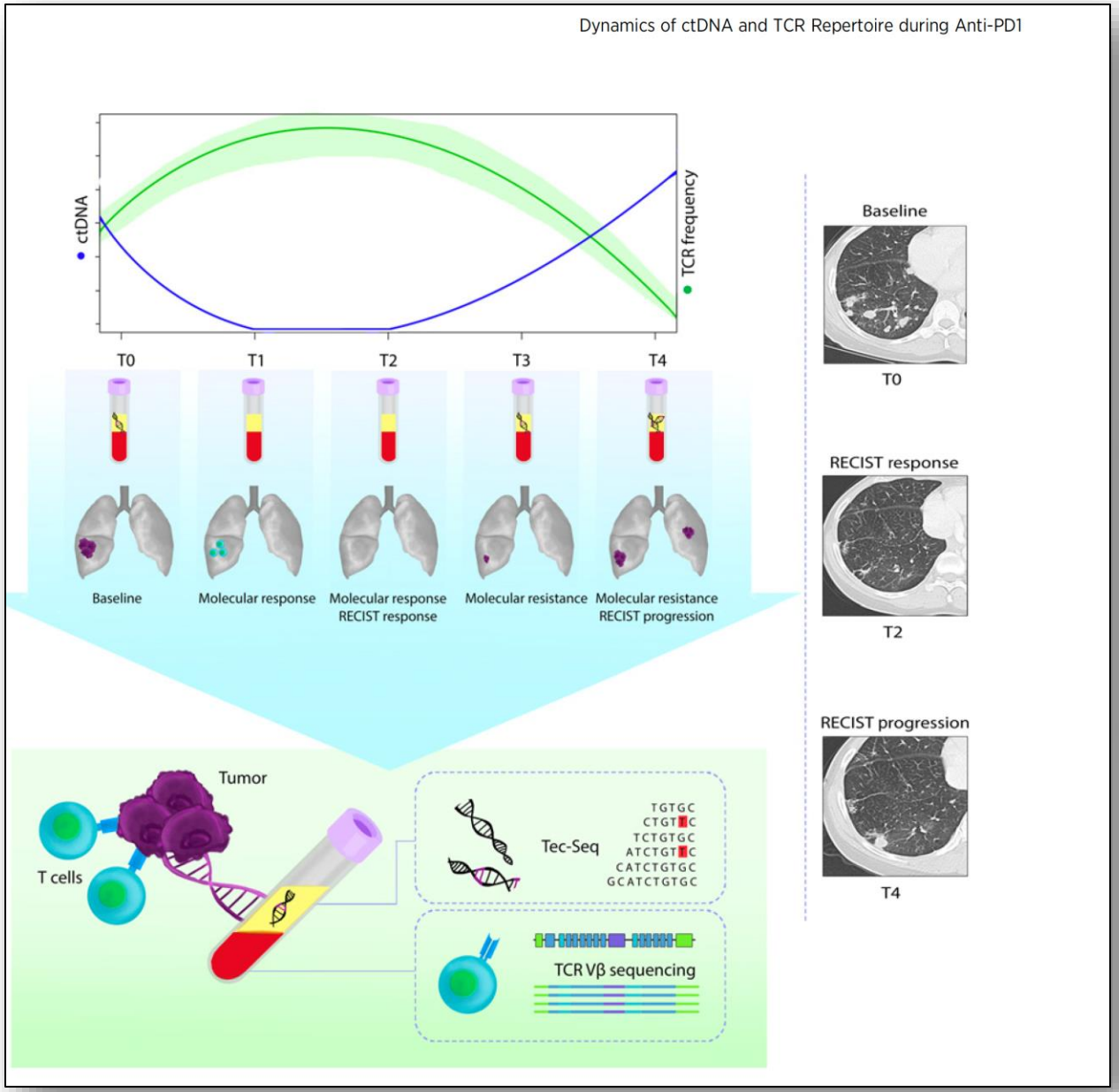
Cummings J et al. Alzheimer's & Dementia (2018)

Financial Viability of Pathology Research Enterprise

Trials Registered in ClinicalTrials.gov From 2006 -2014

	Total No. of Trials[b]	Funding Agency, No. (%)[c]			
		National Institutes of Health	Industry	Other US Federal Agency	All Others
Year of trial start					
2006	9321	1376 (14.8)	4585 (49.2)	263 (2.8)	3240 (34.8)
2007	11 122	1247 (11.2)	5462 (49.1)	275 (2.5)	4284 (38.5)
2008	13 942	1333 (9.6)	7046 (50.5)	327 (2.3)	5385 (38.6)
2009	13 712	1162 (8.5)	6390 (46.6)	327 (2.4)	5963 (43.5)
2010	13 816	1113 (8.1)	5923 (42.9)	309 (2.2)	6595 (47.7)
2011	14 202	1057 (7.4)	5839 (41.1)	320 (2.3)	7127 (50.2)
2012	15 468	1015 (6.6)	5738 (37.1)	344 (2.2)	8507 (55.0)
2013	16 217	1074 (6.6)	5355 (33.0)	363 (2.2)	9566 (59.0)
2014	18 400	1048 (5.7)	6550 (35.6)	339 (1.8)	10 597 (57.6)
% Difference (95% CI)[d,e]		−9.1 (−9.9 to −8.3)	−13.6 (−14.8 to −12.3)	−1.0 (−1.4 to −0.6)	22.8 (21.6 to 24.0)
Absolute difference, No. (%)[e]	9079 (97.4)	−328 (−23.8)	1965 (42.9)	76 (28.9)	7357 (227.1)

JAMA December 15, 2015



Anagnostou V et al Cancer Res 2019

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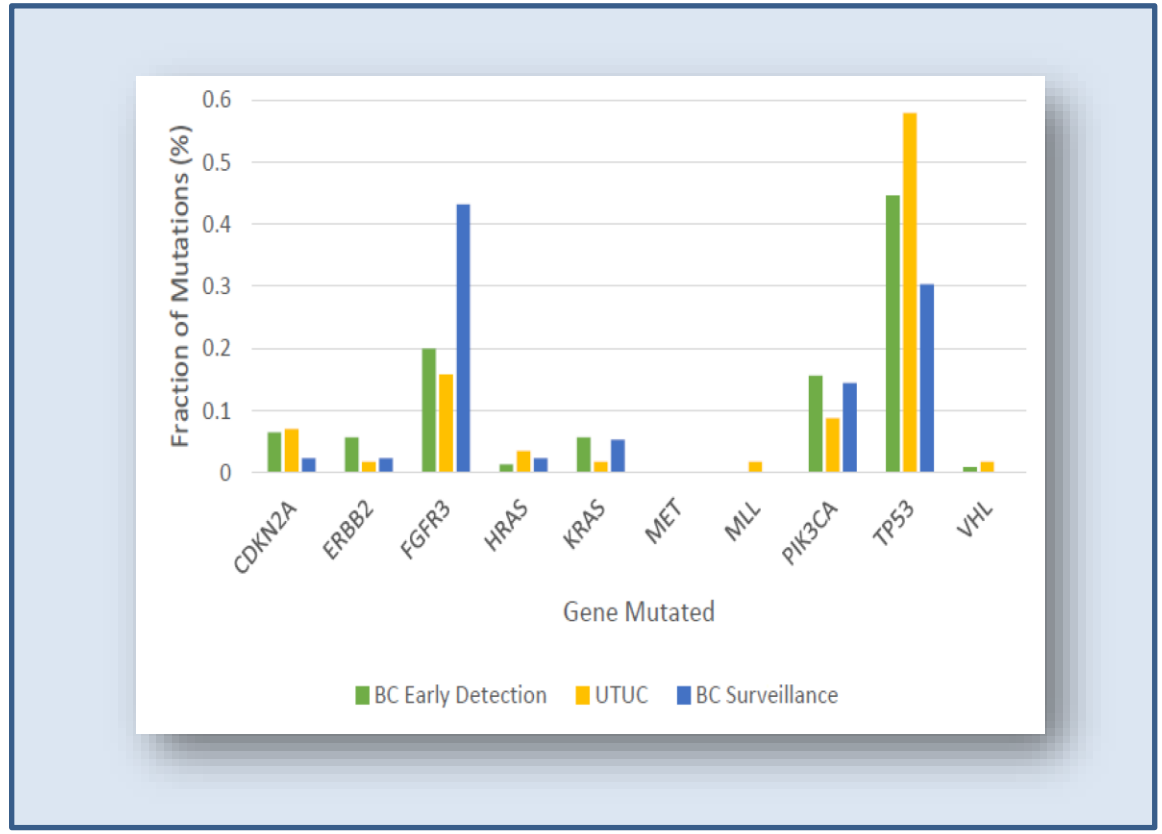
Valsamo Anagnostou[1,2], Patrick M. Forde[1,2], James R. White[1], Noushin Niknafs[1], Carolyn Hruban[1], Jarushka Naidoo[1,2], Kristen Marrone[1,2], I.K. Ashok Sivakumar[1,3,4], Daniel C. Bruhm[1], Samuel Rosner[5], Jillian Phallen[1], Alessandro Leal[1], Vilmos Adleff[1], Kellie N. Smith[1,2], Tricia R. Cottrell[1,6], Lamia Rhymee[1], Doreen N. Palsgrove[1], Christine L. Hann[1], Benjamin Levy[1], Josephine Feliciano[1], Christos Georgiades[7], Franco Verde[7], Peter Illei[1,2,6], Qing Kay Li[1,6], Edward Gabrielson[1,6], Malcolm V. Brock[8], James M. Isbell[9], Jennifer L. Sauter[10], Janis Taube[1,2,6], Robert B. Scharpf[1], Rachel Karchin[1,3], Drew M. Pardoll[1,2], Jamie E. Chaft[11], Matthew D. Hellmann[11], Julie R. Brahmer[1,2], and Victor E. Velculescu[1,2,3]


0.6
0.5
0.4
0.3
0.2
0.1
0
Fraction of Mutations (%)
CDKN2A
ERBB2
FGFR3
HRAS
KRAS
MET
MLL
PIK3CA
TP53
VHL
Gene Mutated
BC Early Detection
UTUC
BC Surveillance

Disruptive Forces in Healthcare & Pathology

- **Technological/Computational**
  - **Genomic** Technology and **Bioinformatics** Advances
  - **Computational** Advances: **AI**, Machine Learning, Digital Pathology
  - Health Care **Information Technology**/Big Data

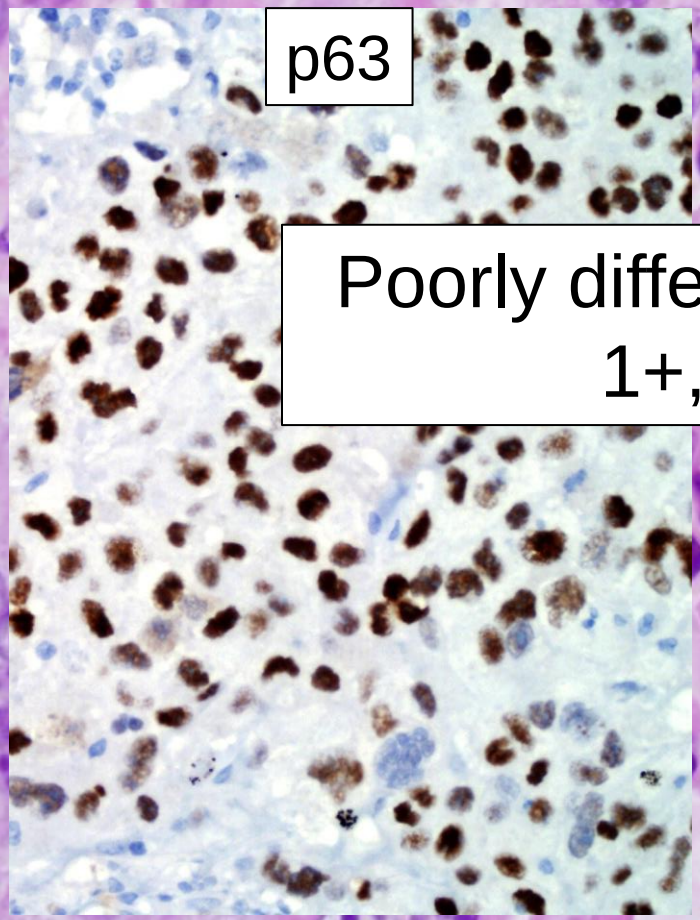
- **Financial**
  - **Value Based Reimbursement** replacing Fee For Service
  - **Constrained Health Care Economic** echo system
    Clinical and Research $$$

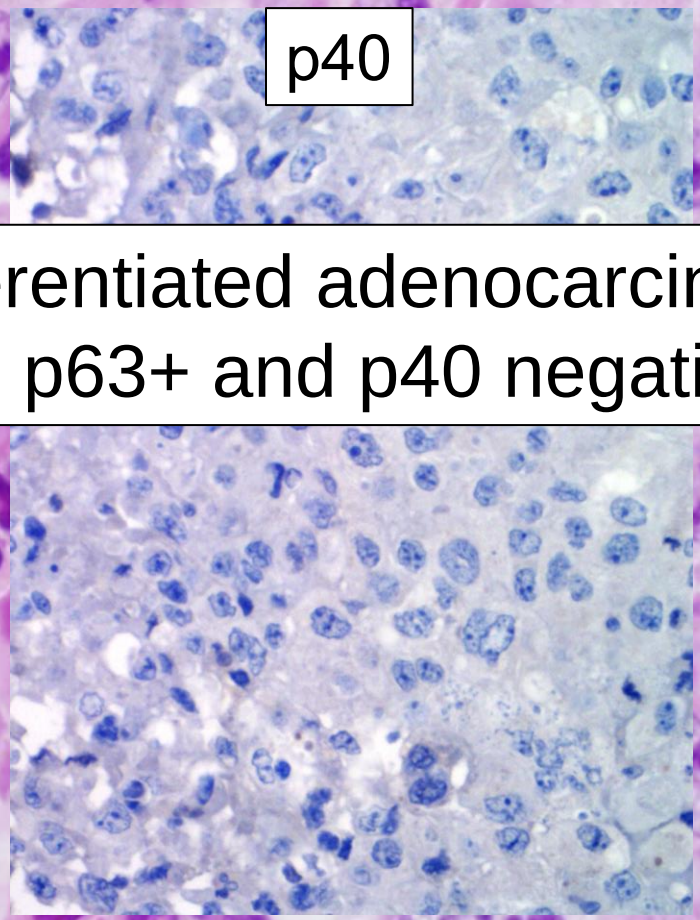
Opportunities
“Precision” Pathology Service

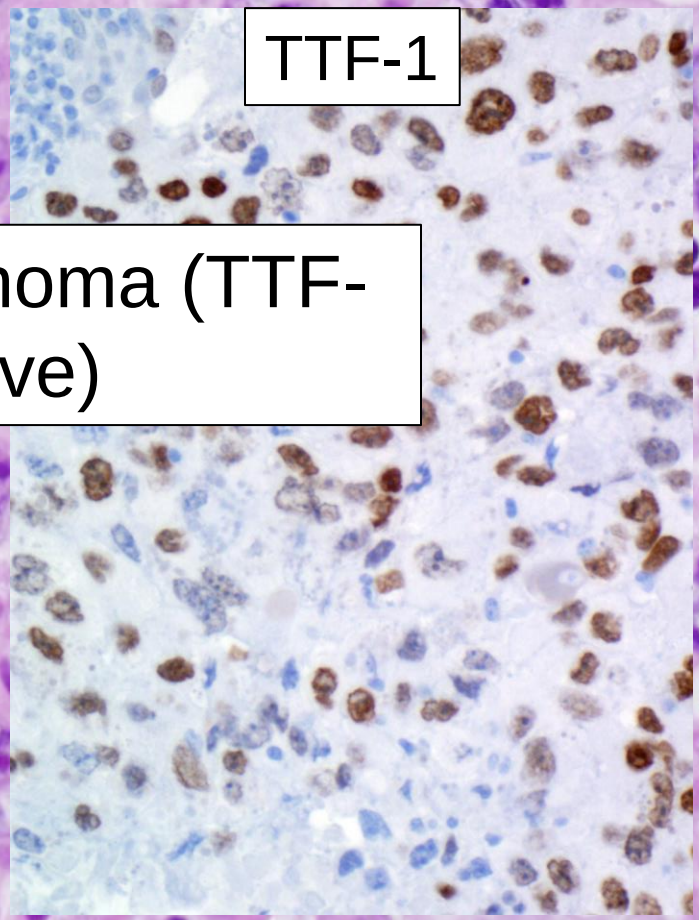
- Less than two decades following The Human Genome Project, the revolutionary progress in Human Genomics is reshaping our approach to Diagnosis, Prognostics and Therapy

- It is estimated that 5-10% of all laboratory tests are DNA/RNA based analyses

Lung mass







Poorly differentiated adenocarcinoma (TTF-1+, p63+ and p40 negative)

The Future is even more PERSONAL !

CHALLENGES
Impact on Pathology and Lab Medicine

- Unprecedented Demands on **Expertise** and **Capital** due to rapidly changing technological platforms
  Evolution and adaptation of pathology work force
  $$ Investment

- Operational challenges of **Multidisciplinary Integration** while maintaining **“turf”** advantage

- **Financial Viability** in Constrained Health Care Economics

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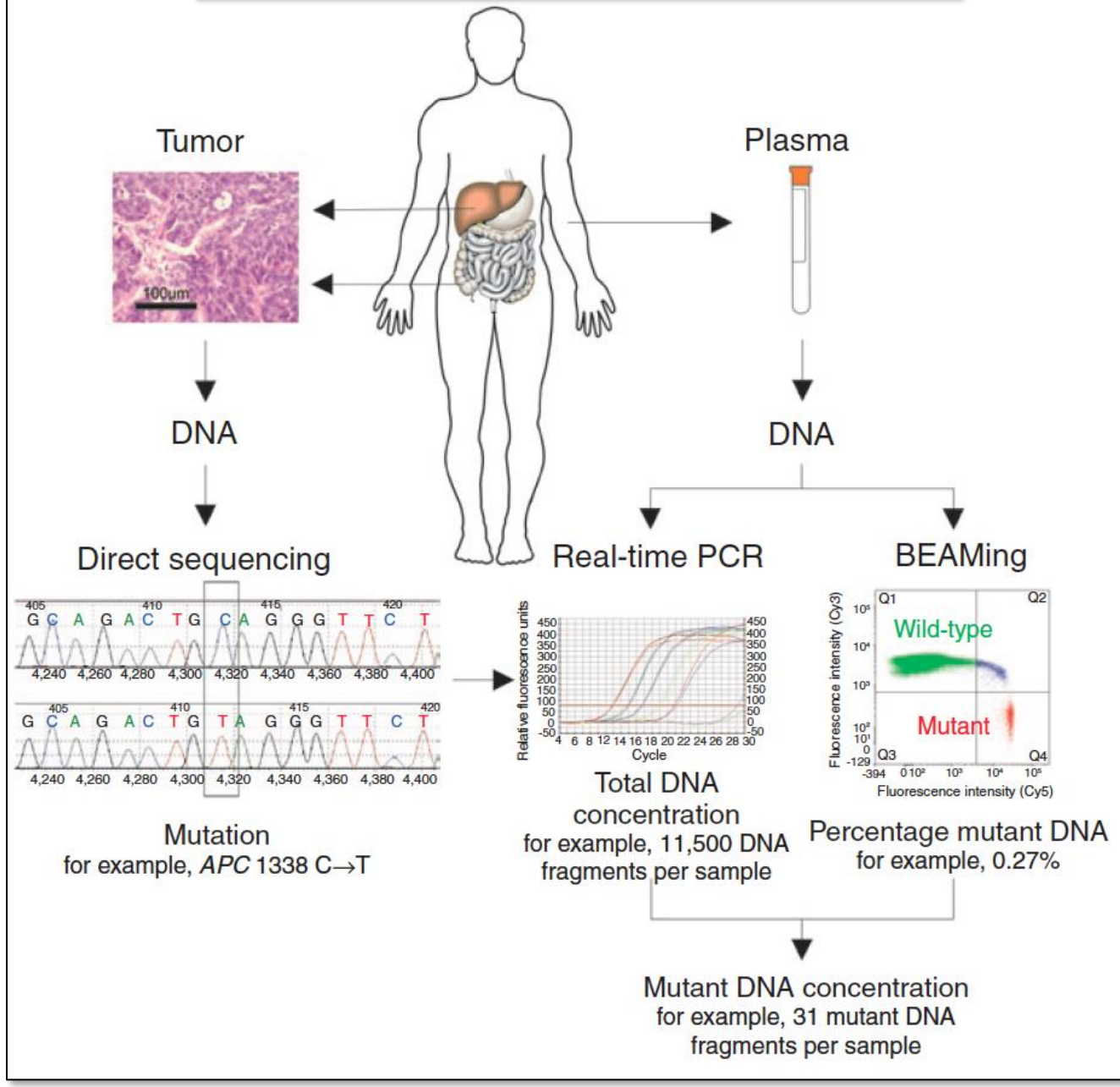
nature medicine

Circulating mutant DNA to assess tumor dynamics

Frank Diehl[1,5], Kerstin Schmidt[1,5], Michael A Choti[2], Katharine Romans[1], Steven Goodman[3], Meng Li[1], Katherine Thornton[1], Nishant Agrawal[1], Lori Sokoll[4], Steve A Szabo[1], Kenneth W Kinzler[1], Bert Vogelstein[1] & Luis A Diaz Jr[1]

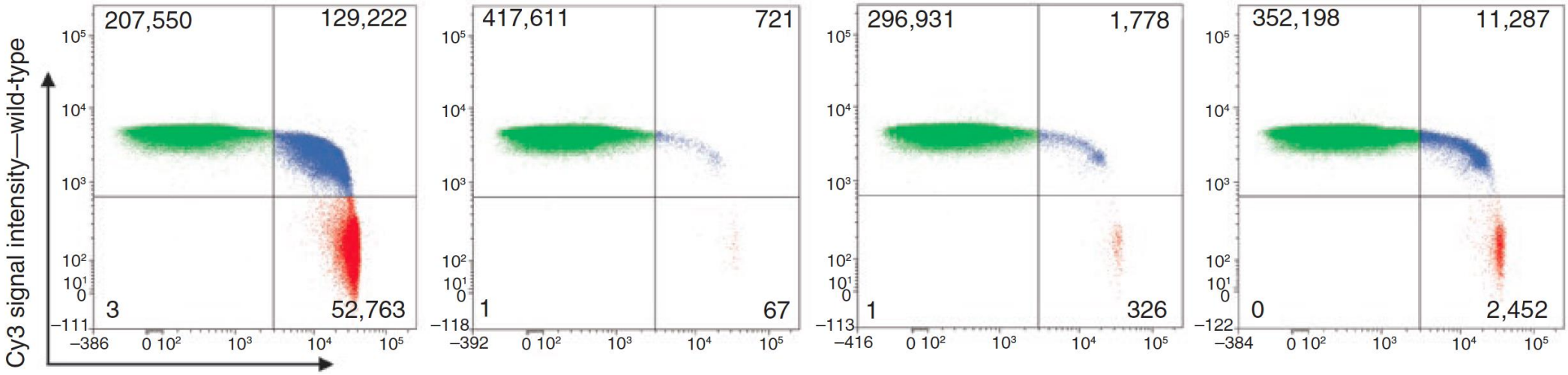
Plasma ctDNA Rx Monitoring



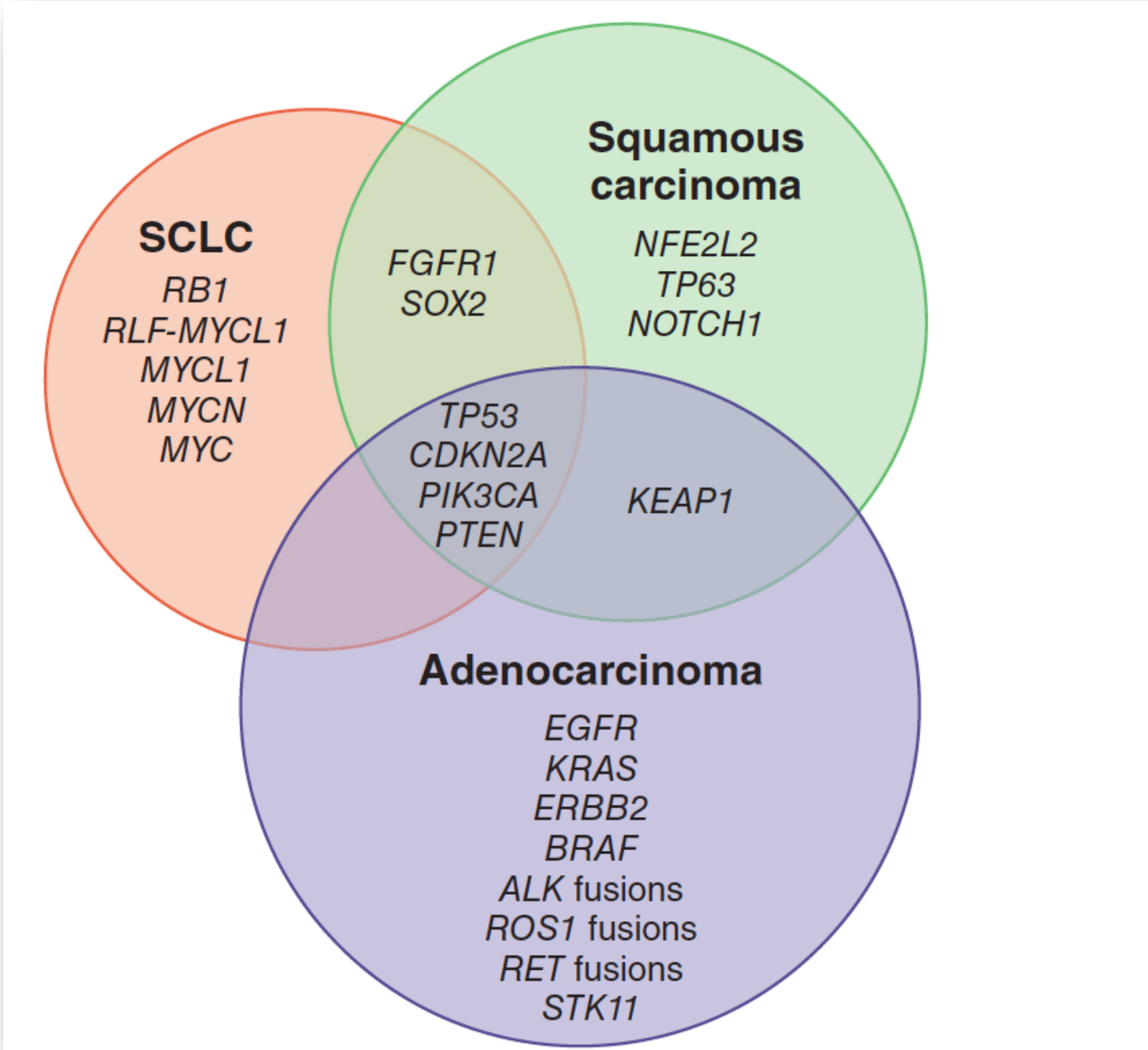
Plasma ctDNA Rx Monitoring

CT scan negative

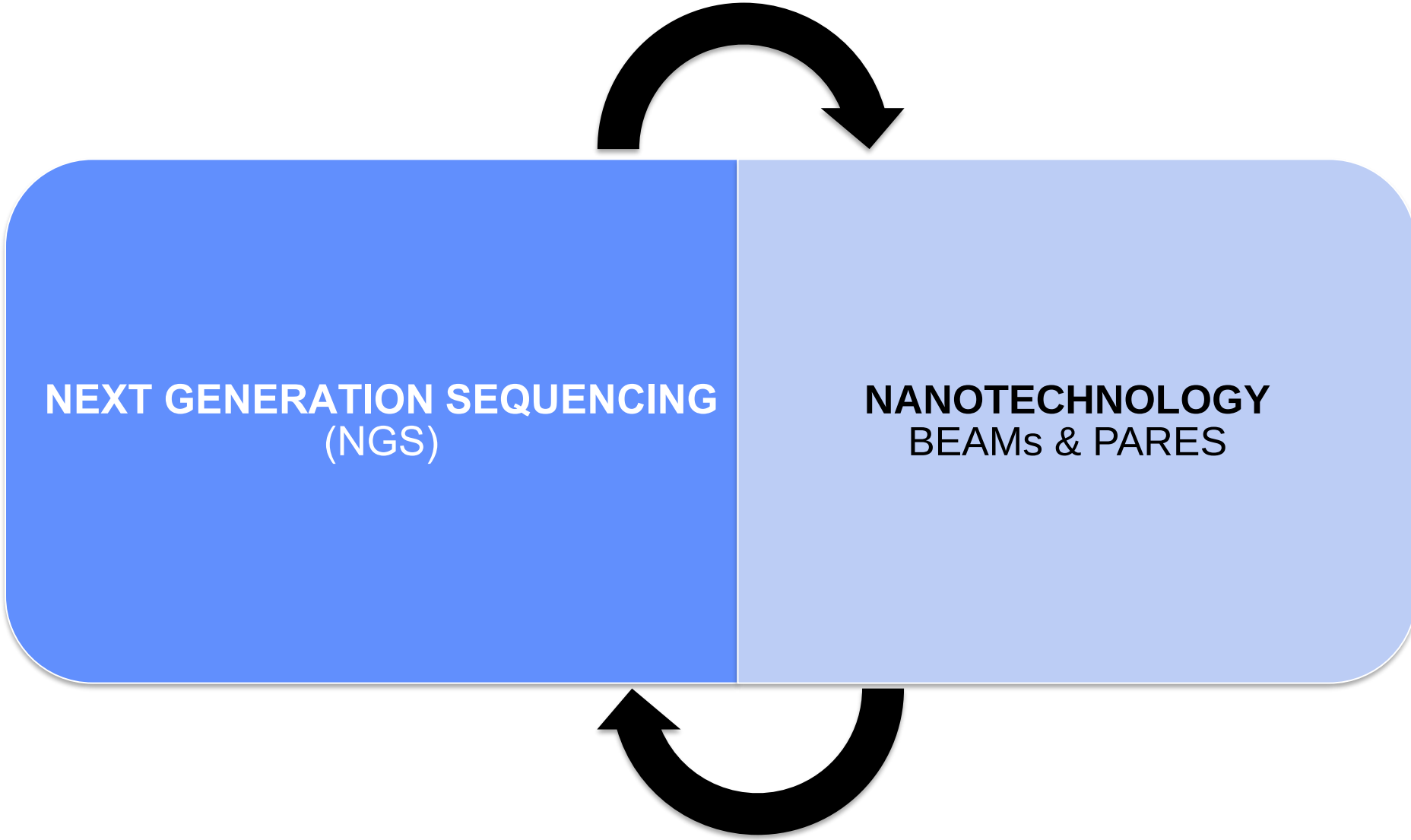
CT scan positive

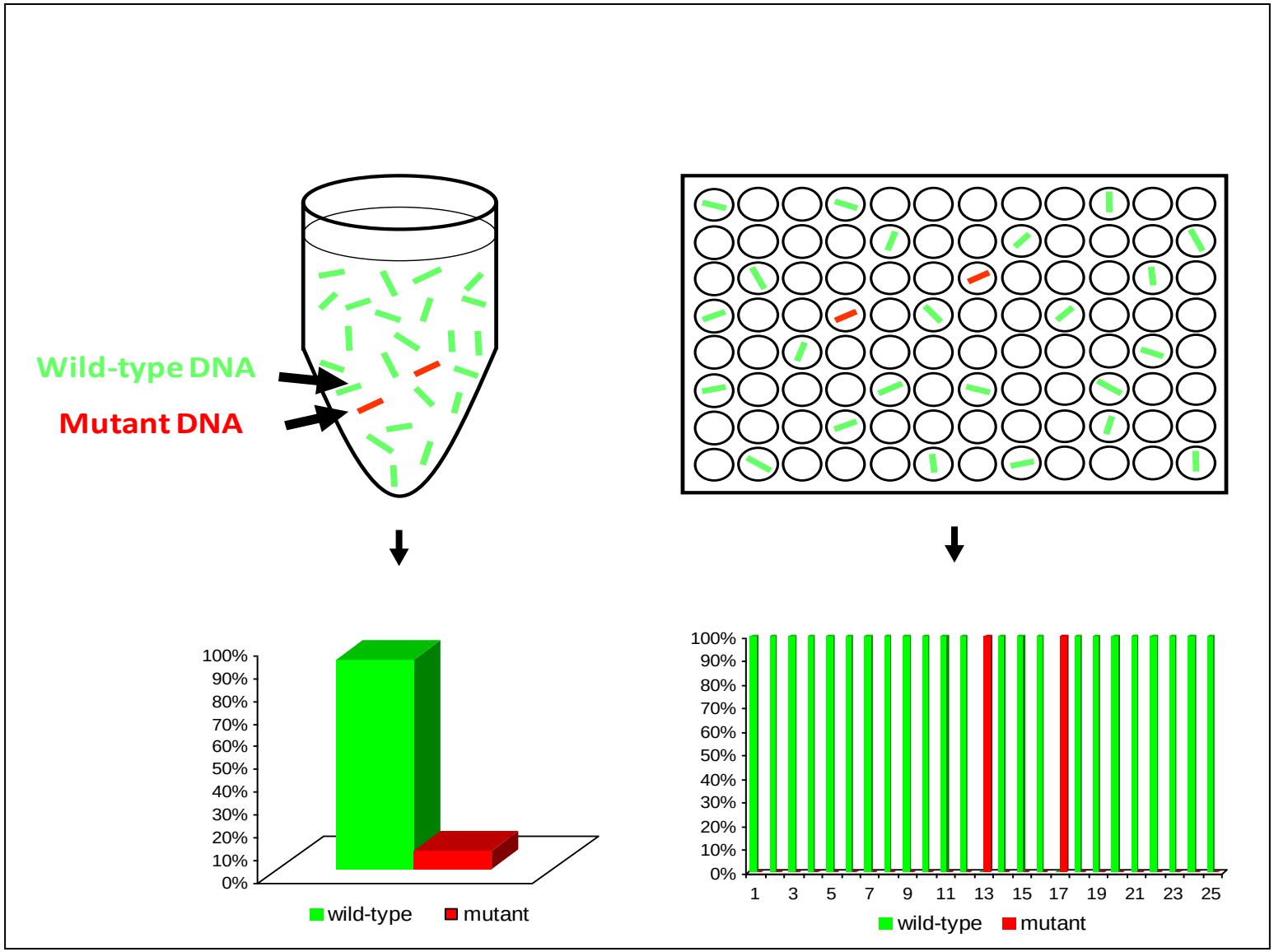


Pre-Op Day 0	Day 3 post-Op	Day 44 post-Op	Day 244 post-Op
MUTANT DNA 13.4 %	0.015 %	0.11 %	0.66 %



Pietanaza and Ladanyi Nature Genetics 2012


NEXT GENERATION SEQUENCING
(NGS)
NANOTECHNOLOGY
BEAMs & PARES


Wild-type DNA
Mutant DNA
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
wild-type
mutant
1
3
5
7
9
11
13
15
17
19
21
23
25

BEAMing

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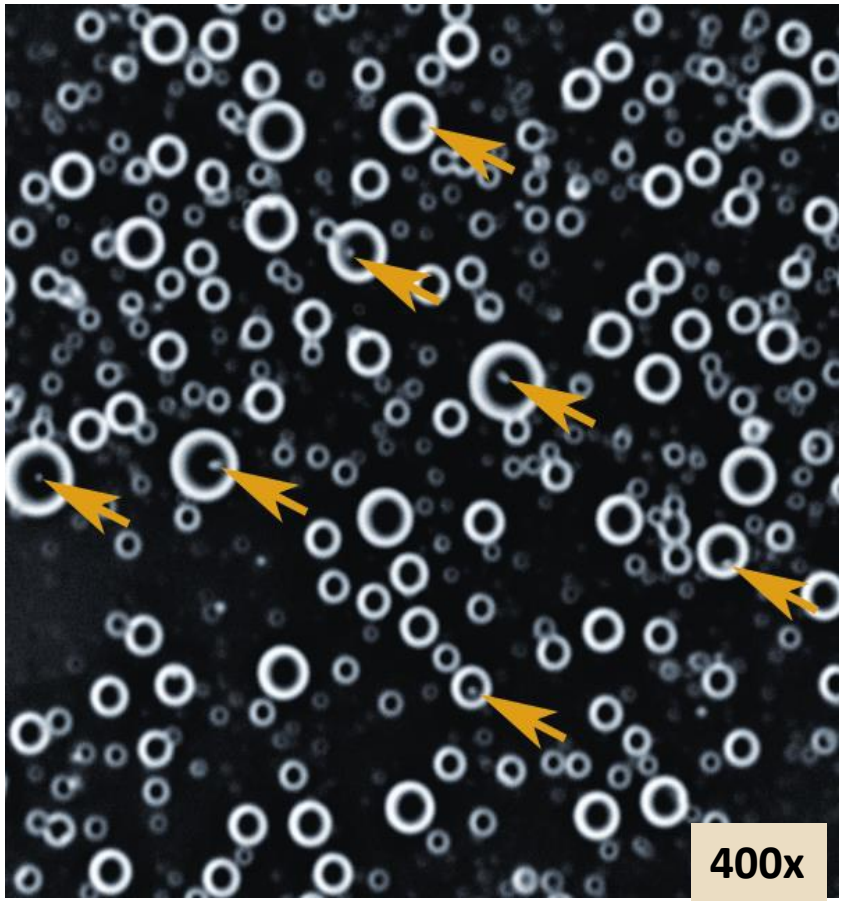
Beads

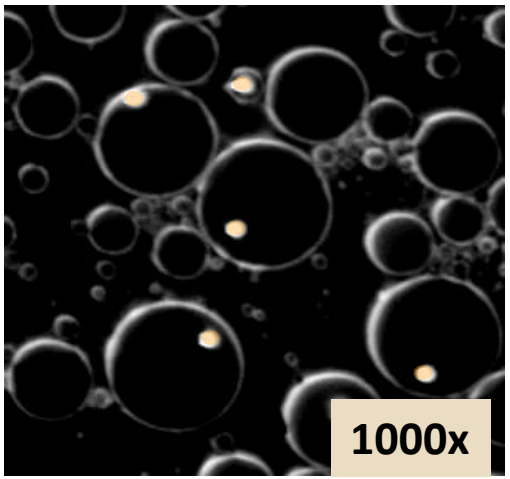
Emulsion

Amplification

Magnetics

Water-in-Oil Emulsion with 1 µm Microbeads





Aqueous compartments:

3-10 µm diameter

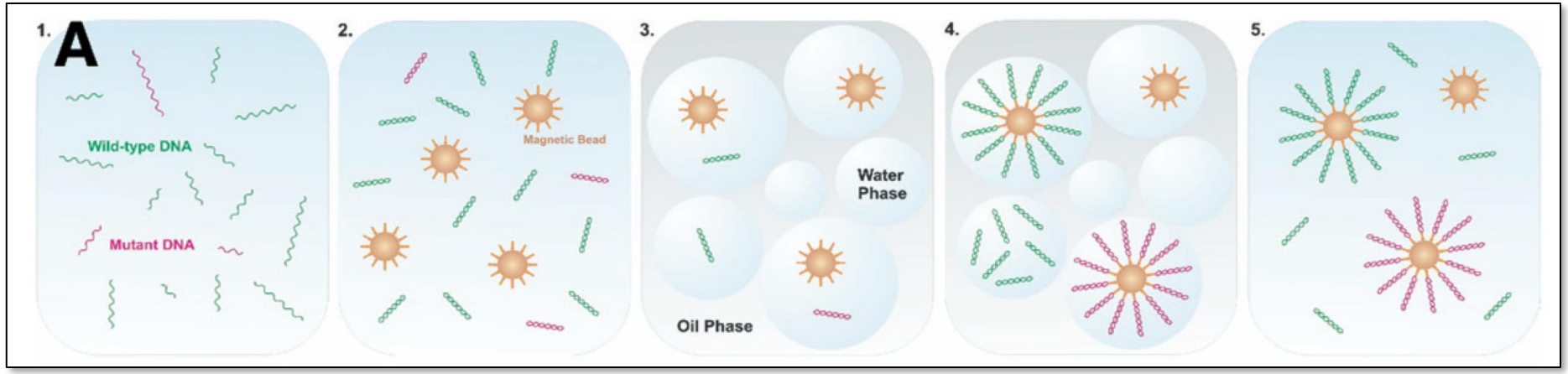
14-380 fl volume

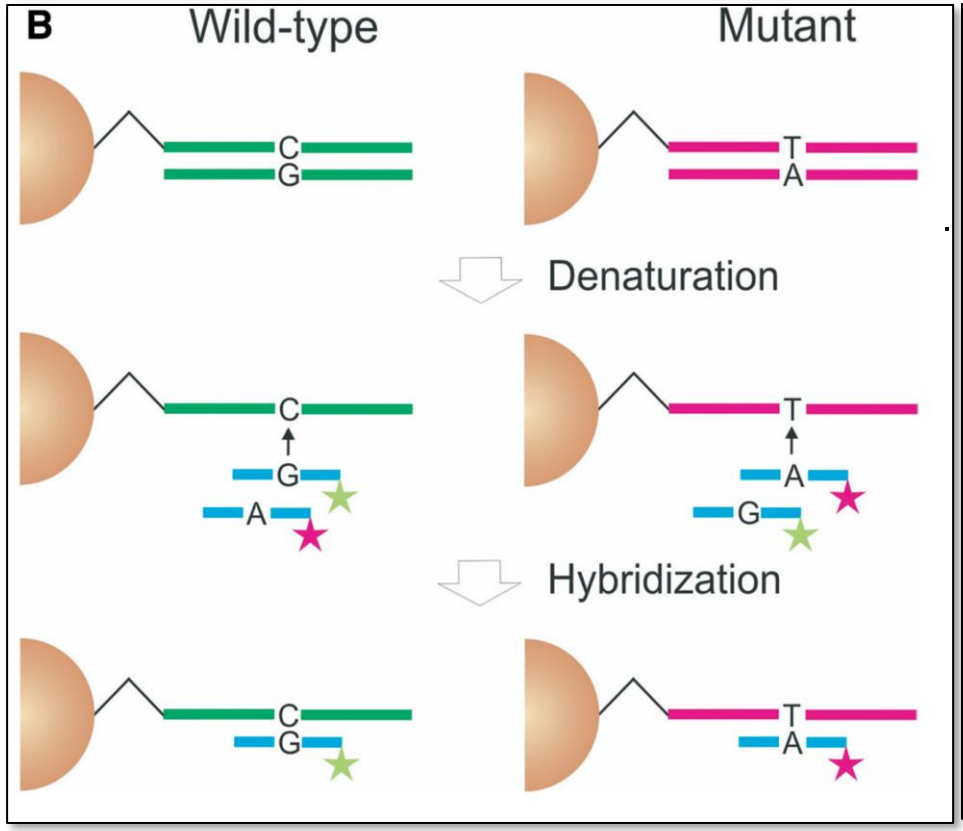
Aqueous Phase:

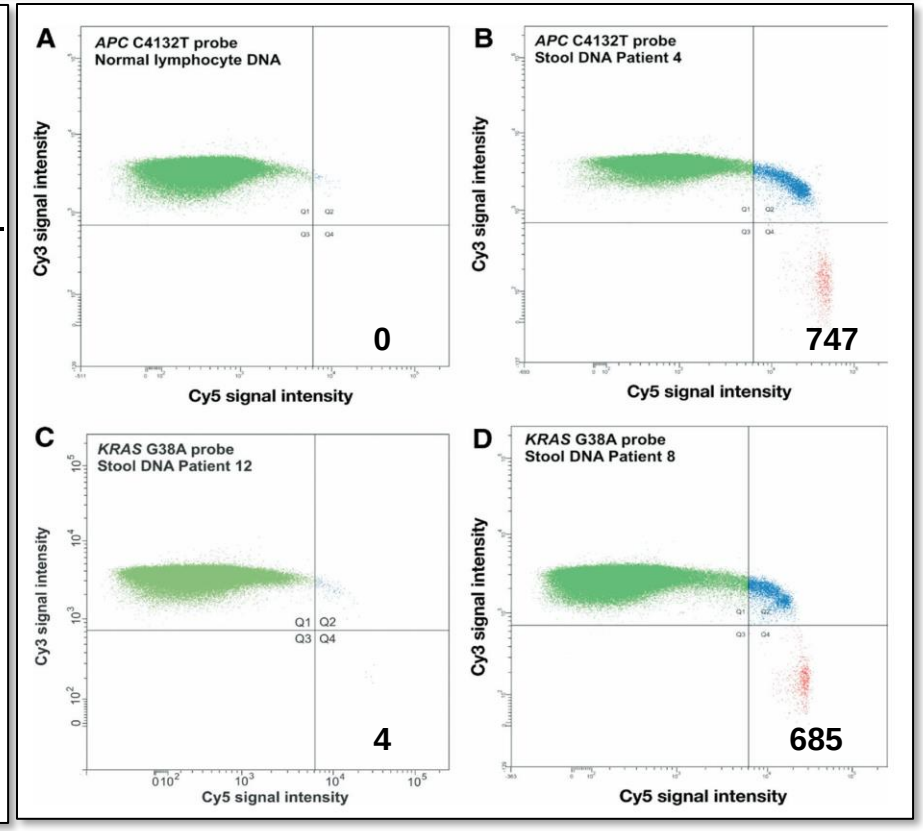
~10 Billion bubbles/ ml

Luis Diaz MD PhD

Diehl *et al.* Nat. Methods 2006


A
1.
Wild-type DNA
Mutant DNA
2.
Magnetic Bead
3.
Water Phase
Oil Phase
4.
5.


B
Wild-type
Mutant
C
G
T
A
Denaturation
Hybridization


A
APC C4132T probe
Normal lymphocyte DNA
0
B
APC C4132T probe
Stool DNA Patient 4
747
C
KRAS G38A probe
Stool DNA Patient 12
4
D
KRAS G38A probe
Stool DNA Patient 8
685
Cy3 signal intensity
Cy5 signal intensity
Q1
Q2
Q3
Q4

nature medicine
2008

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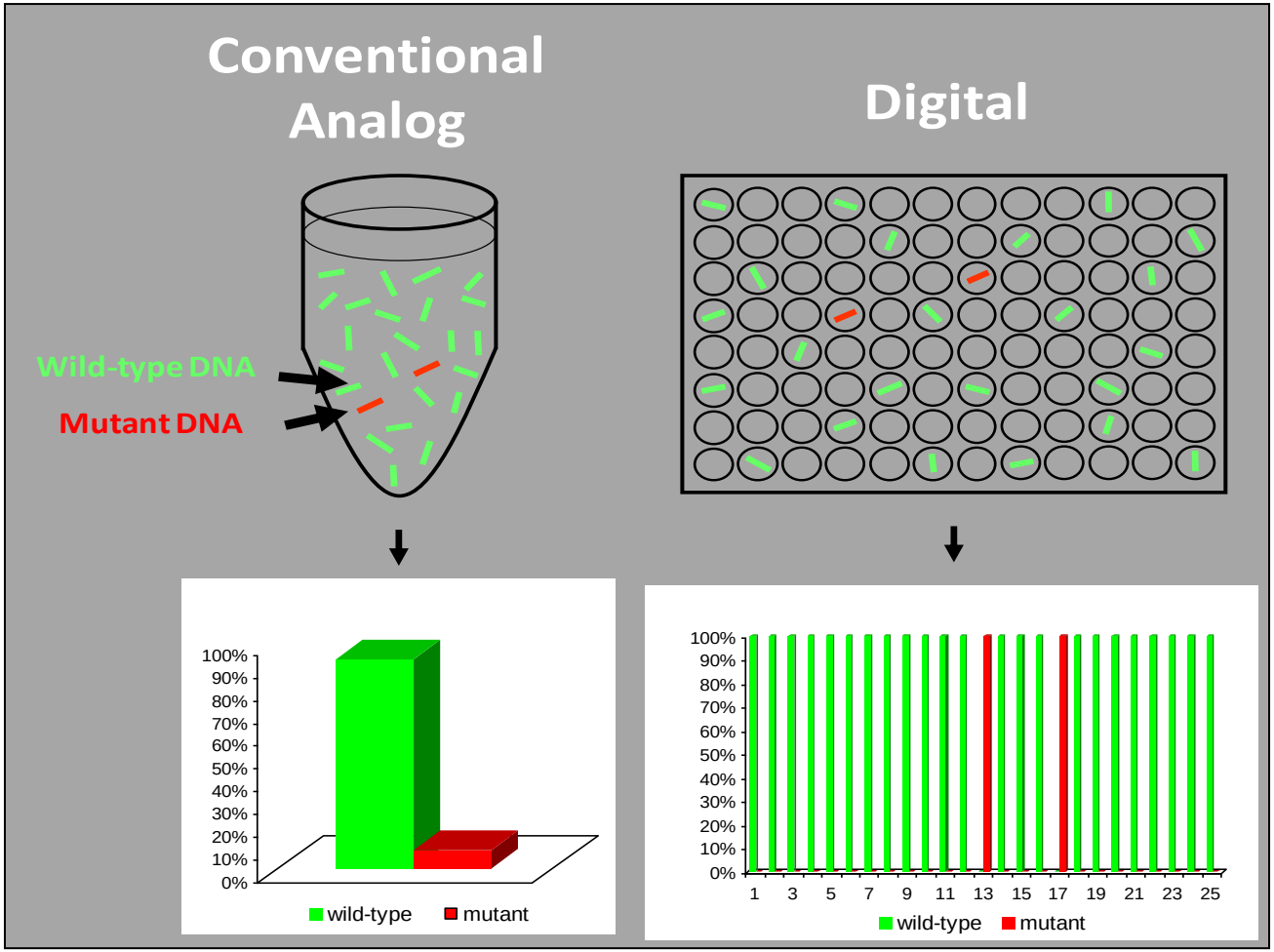
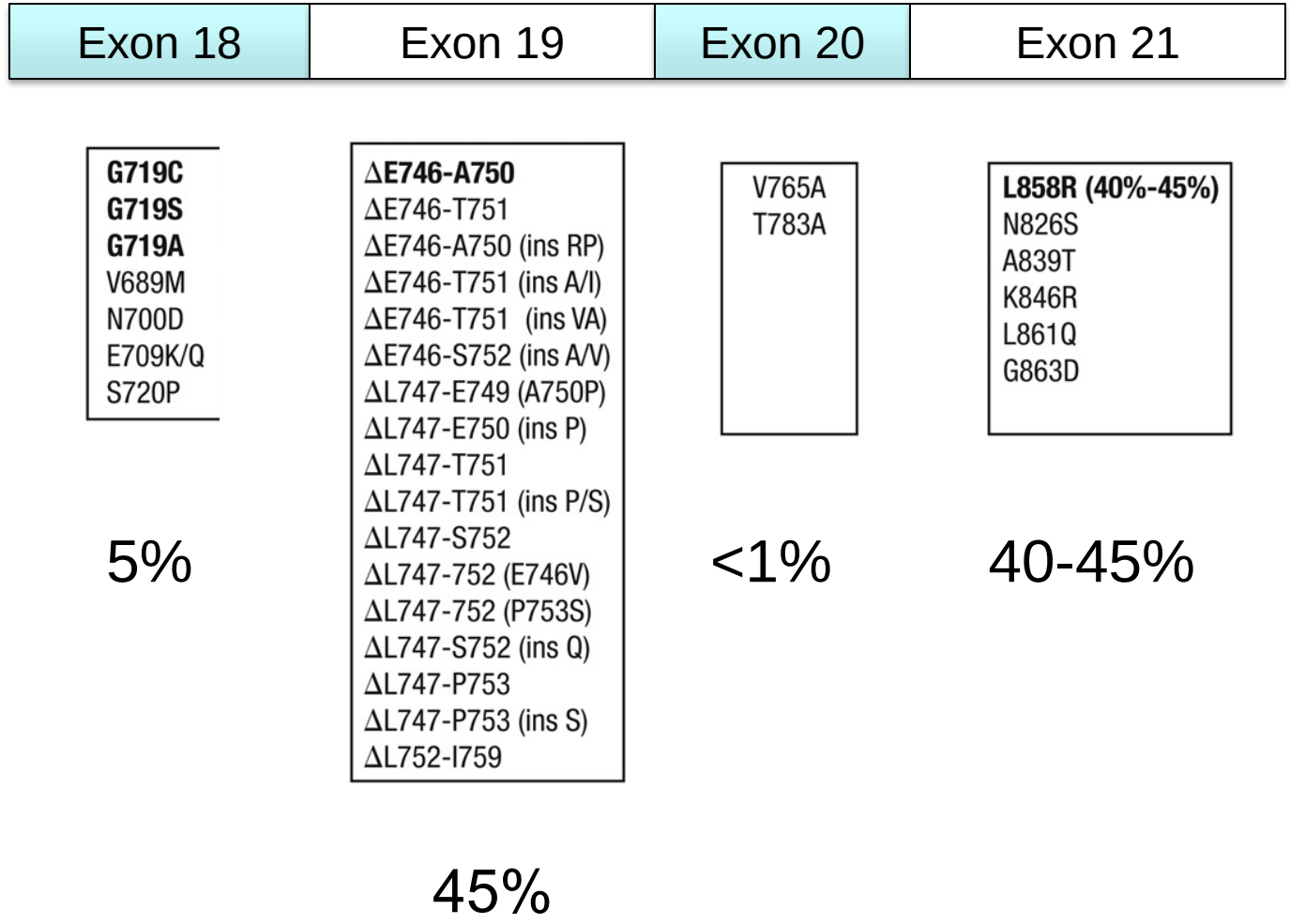
- Tumor Sequencing for APC,TP53, KRAS and PIK3CA ⇨ ≥1 mutation in each CRCa sample
- DNA from stool/plasma samples assessed for identified mutations by "BEAMing Technology"

Digital PCR



Luis Diaz MD PhD

EGFR Mutations Associated with Sensitivity

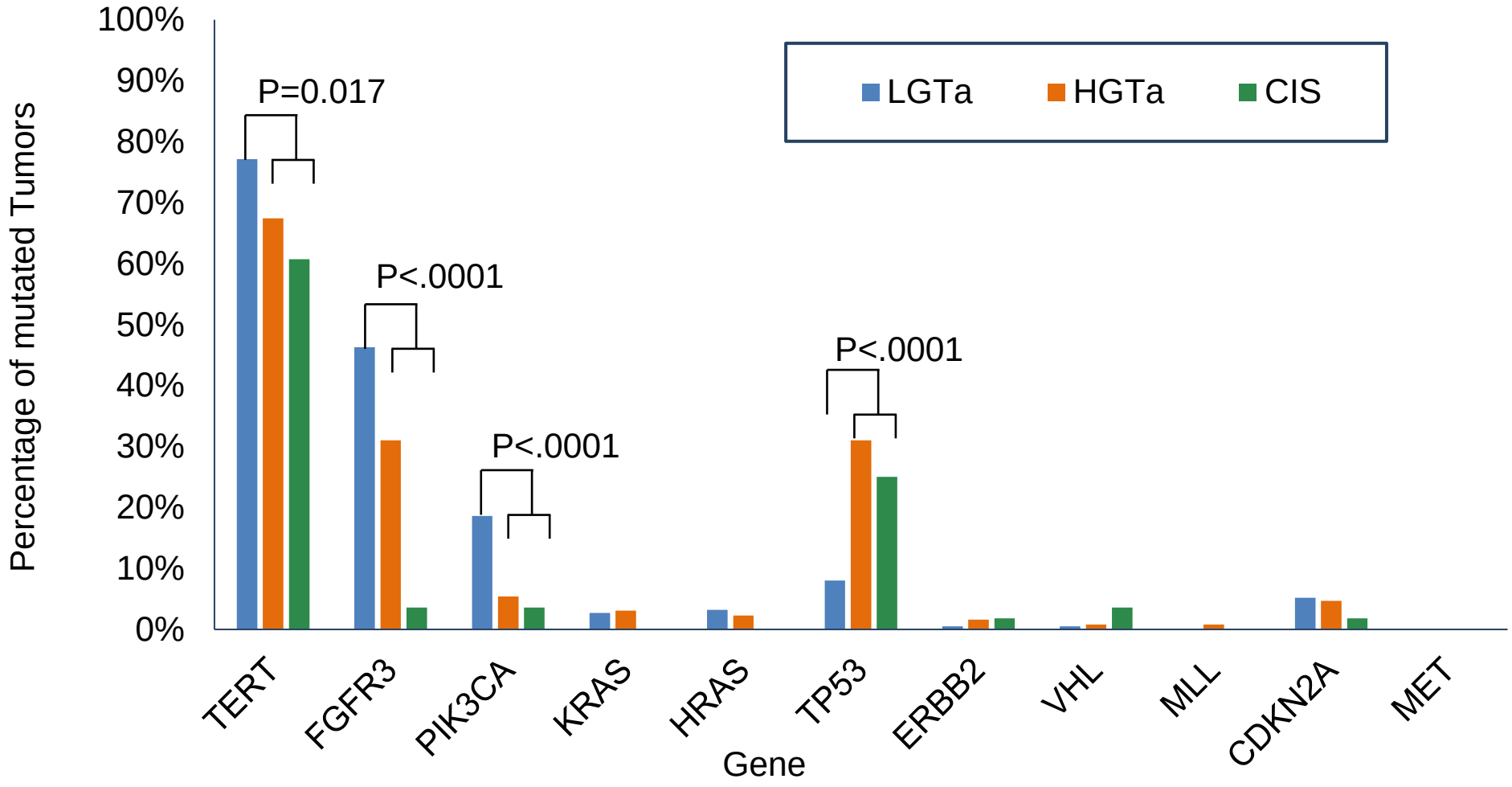


EGFR and K-ras Mutation in NSCLC Carcinoma

	EGFR mutation	EGRF wild type	K-ras mutation	K-ras wild type
AdenoCA*	20%	80%	22%	78%
Non-AdenoCA	13%	87%	5%	95%
Female	18%	82%	14%	86%
Male	16%	84%	15%	85%
Smokers#	14%	86%	16%	84%
Never smoker	28%	72%	11%	89%
Asian	38%	62%	0%	100%
Non-Asian	15%	85%	16%	84%

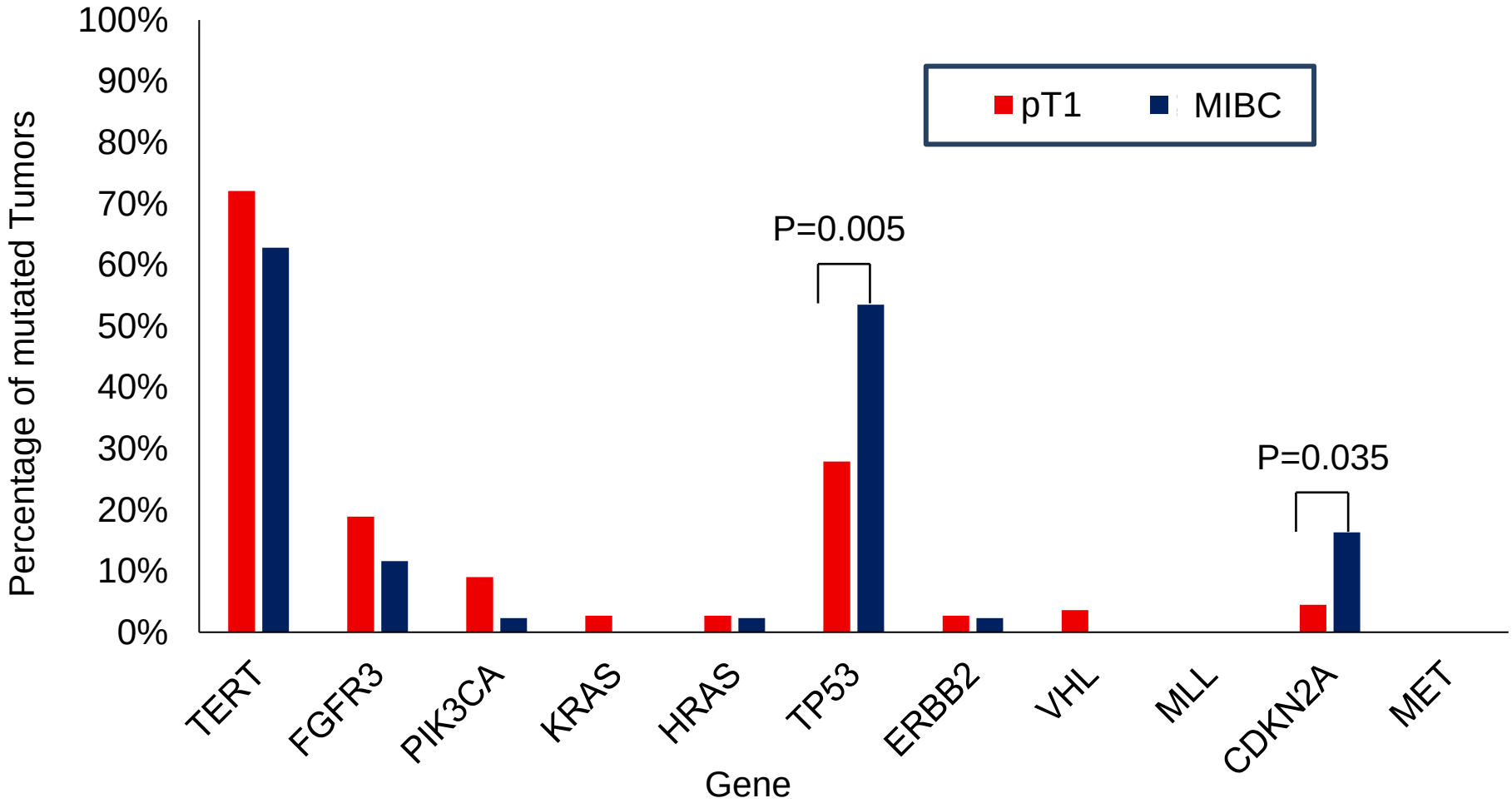
NCICC Trials Group study BR.21 J Clin Oncol 26:4268-4275, 2008.

UroSEEK in Non-Invasive Bladder Cancer Tissue

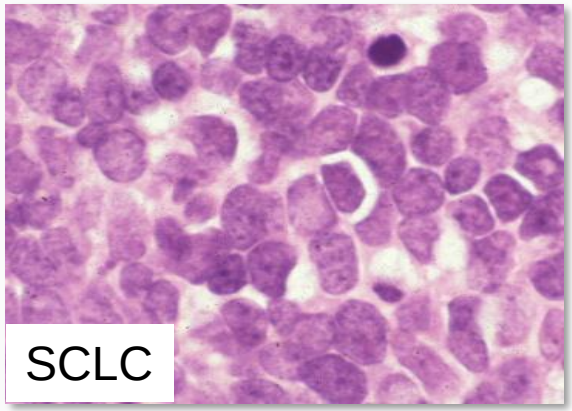


Eich et al. Mod Pathol 2019

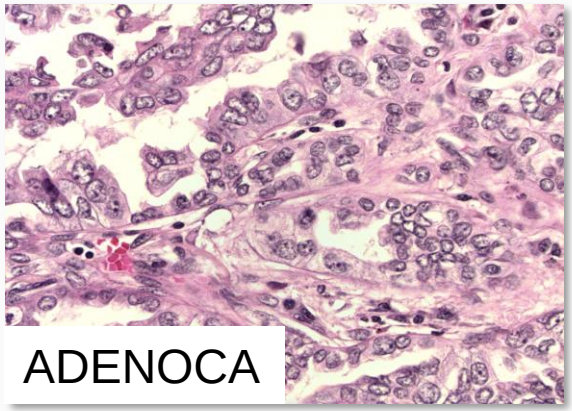
UroSEEK in Invasive Bladder Cancer Tissue



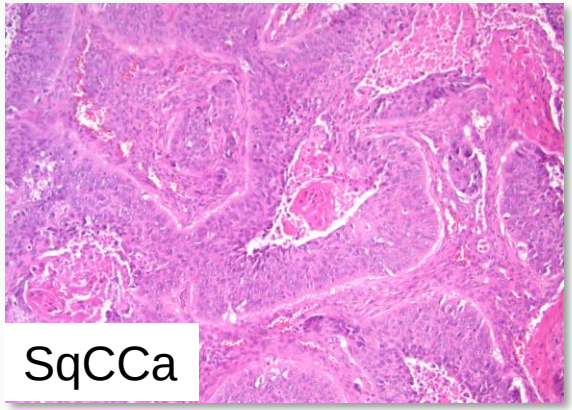
Eich et al. Mod Pathol 2019



SCLC → H&E → Syn, Chrom, CD56



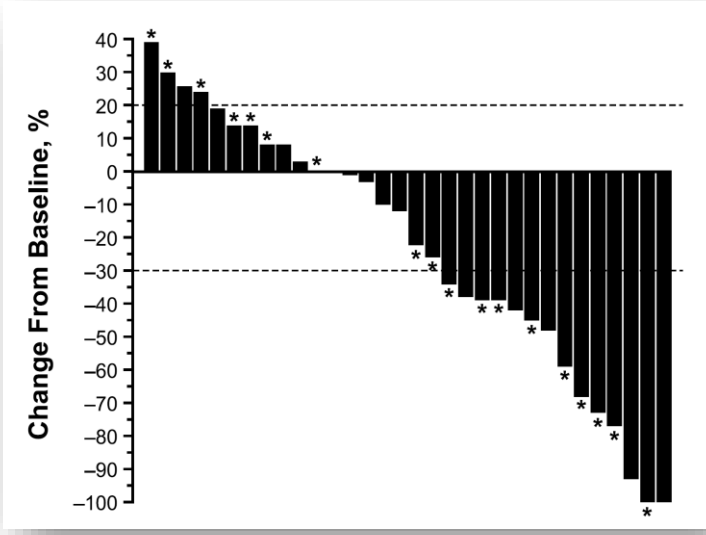
ADENOCA → Mucicarmine PASD → TTF-1 Surfactant Napsin



SqCCa → Mucicarmine PASD → CK 5/6 p63/p40

Pembrolizumab in combination with ipilimumab as second-line or later therapy for advanced non–small-cell lung cancer: KEYNOTE-021 cohorts D and H

Matthew A. Gubens[a,*], Lecia V. Sequist[b], James P. Stevenson[c], Steven F. Powell[d], Liza C. Villaruz[e], Shirish M. Gadgeel[f], Corey J. Langer[g], Amita Patnaik[h], Hossein Borghaei[i], Shadia I. Jalal[j], Joseph Fiore[k,1], Sanatan Saraf[k], Harry Raftopoulos[k,2], Leena Gandhi[l,m,3]



Gubens MA et al Lung Cancer 2019