

# End of Life In-patient Hospice and Rapid Autopsy to Study Tumor Heterogeneity in Lung Cancer

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I have no conflict of interest to disclose

Slides developed by the National Cancer Institute, and the NIH Clinical Center Nursing Department and used with permission.

# Outline of Talk

Tumor heterogeneity - Science and Controversies

A unique case report of unprecedented heterogeneity  
(the benefit of sequential biopsy protocols)

A review of a couple of published rapid autopsy series

Ethics guidelines for conducting such studies

Thoracic Malignancies Rapid Autopsy at the NIH Clinical  
Center.

*" Things should be made as simple as possible, but not simpler"  
- Albert Einstein*

EDITORIALS



## Tumor Heterogeneity and Personalized Medicine

Dan L. Longo, M.D.

EDITORIALS

validation that the mutant genes are expressed and have altered function. On top of this, the authors show widespread alterations in the total number of chromosomes in the tumor cells (aneuploidy) and detect many allelic imbalances at the chromosome level, in which one allele of a gene pair is lost. These imbalances can be due to chromosome loss or gene imprinting and may alter gene expression.

Another key finding is that different regions of the tumor have different mutations in the very same genes (so-called convergent evolution), including in *SETD2*, *PTEN*, and *KDM5C*, which under-

The news for personalized-medicine advocates is not all bad. The findings confirm that the genetic lesions that are found in the original tumor cells, the trunk of the evolutionary tree, are consistently expressed (e.g., the von Hippel–Lindau gene in renal-cell cancer). In addition, given that the tumor will do whatever is necessary to activate certain genes and inactivate others, the genes that are affected by convergent evolution may be suitable targets for functional inhibition or restoration. However, the simple view of directing therapy on the basis of genetic tumor markers is probably too simple.

# *The* NEW ENGLAND JOURNAL *of* MEDICINE

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## **Intratumor Heterogeneity and Branched Evolution Revealed by Multiregion Sequencing**

Marco Gerlinger, M.D., Andrew J. Rowan, B.Sc., Stuart Horswell, M.Math., James Larkin, M.D., Ph.D.,  
David Endesfelder, Dip.Math., Eva Gronroos, Ph.D., Pierre Martinez, Ph.D., Nicholas Matthews, B.Sc.,  
Aengus Stewart, M.Sc., Patrick Tarpey, Ph.D., Ignacio Varela, Ph.D., Benjamin Phillipmore, B.Sc., Sharmin Begum, M.Sc.,  
Neil Q. McDonald, Ph.D., Adam Butler, B.Sc., David Jones, M.Sc., Keiran Raine, M.Sc., Calli Latimer, B.Sc.,  
Claudio R. Santos, Ph.D., Mahrokh Nohadani, H.N.C., Aron C. Eklund, Ph.D., Bradley Spencer-Dene, Ph.D.,  
Graham Clark, B.Sc., Lisa Pickering, M.D., Ph.D., Gordon Stamp, M.D., Martin Gore, M.D., Ph.D., Zoltan Szallasi, M.D.,  
Julian Downward, Ph.D., P. Andrew Futreal, Ph.D., and Charles Swanton, M.D., Ph.D.

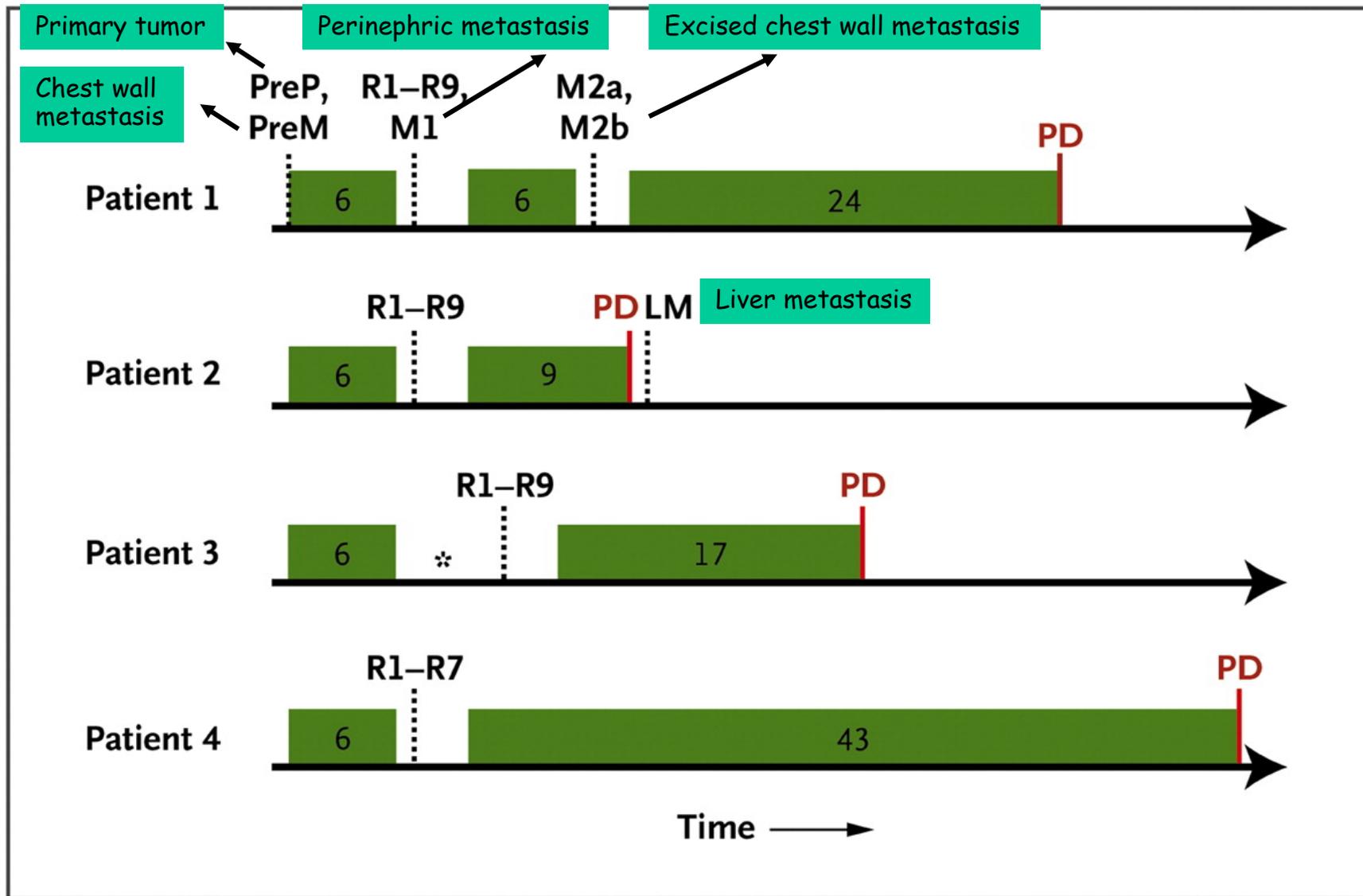
Tumor biopsy samples analyzed from **4 consecutive patients** with metastatic RCC

Whole exome sequencing performed on different regions of the specimens from patients 1 and 2- paired-end reads of 72 bp and 75bp on Illumina Genome analyzer IIx and Hiseq platforms.

SNP array analysis on Illumina Omni2.5 (copy number)

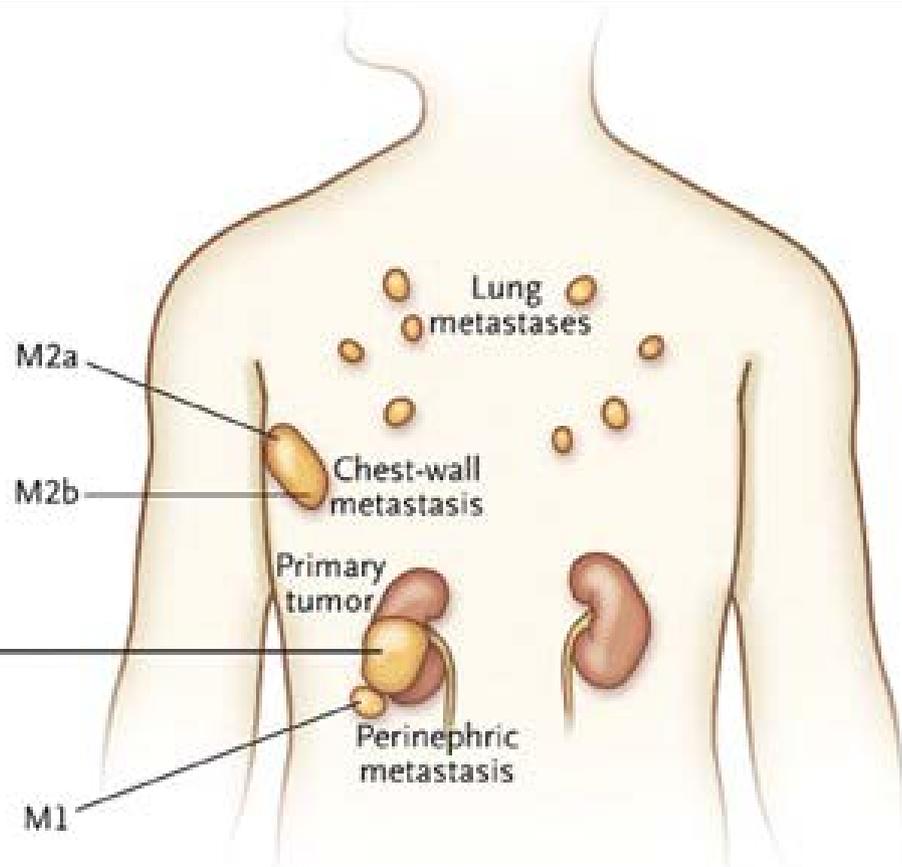
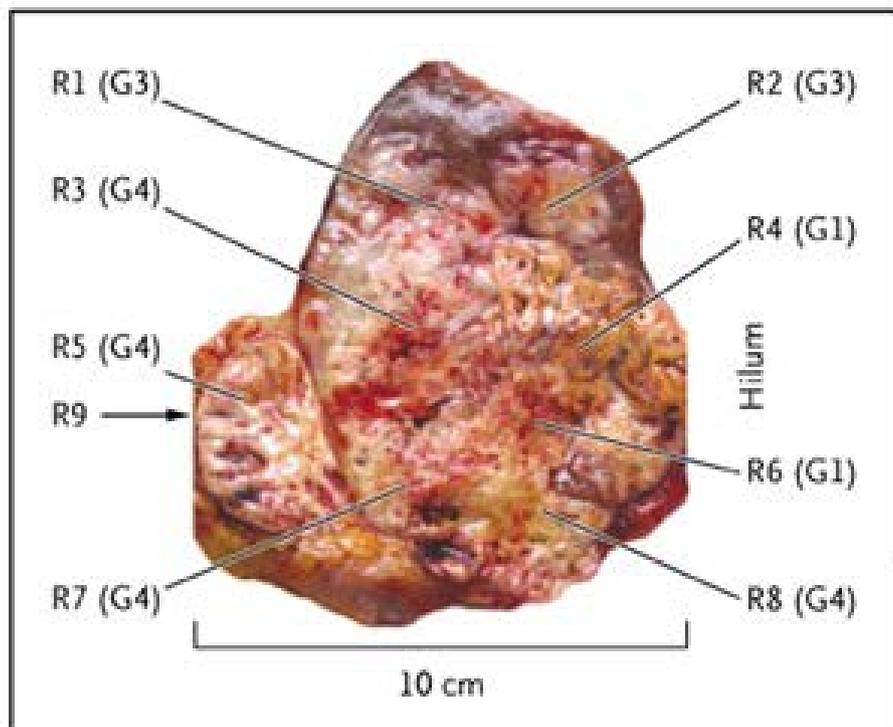
mRNA expression profiling on Affymetrix Gene 1.0 arrays

# Biopsy and Treatment Timelines for the Four Patients.



# Samples for intratumor and intertumor heterogeneity- Patient 1

## A Biopsy Sites



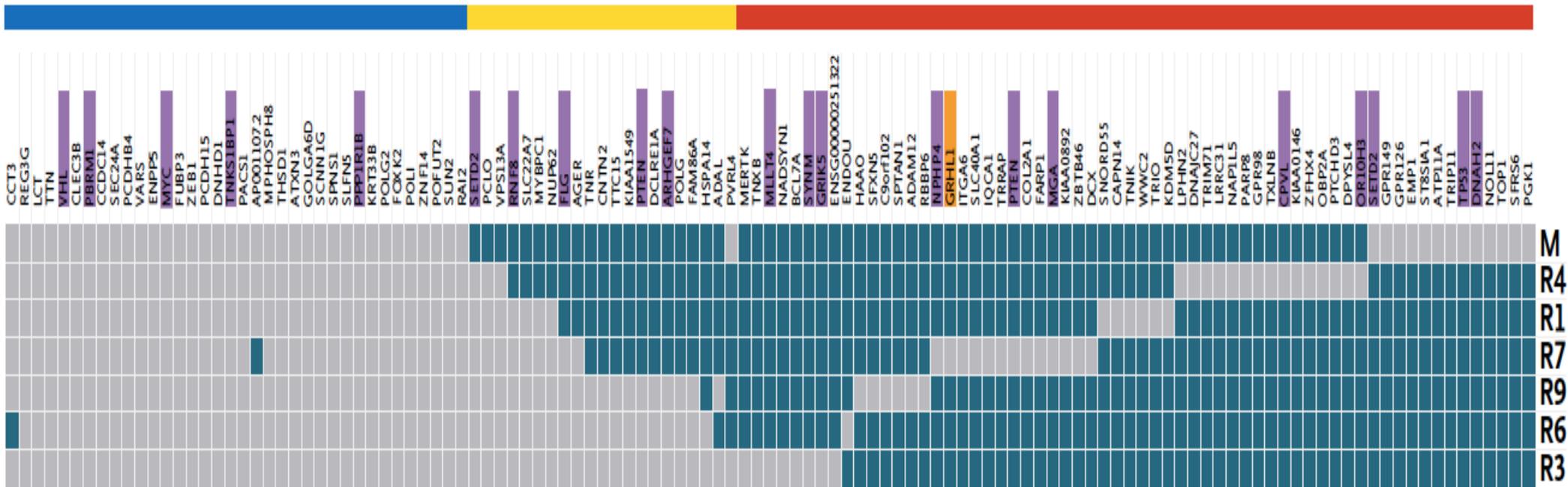
# Genetic intratumor heterogeneity and phylogeny in Patient 2

## A Regional Distribution of Mutations

Ubiquitous

Shared

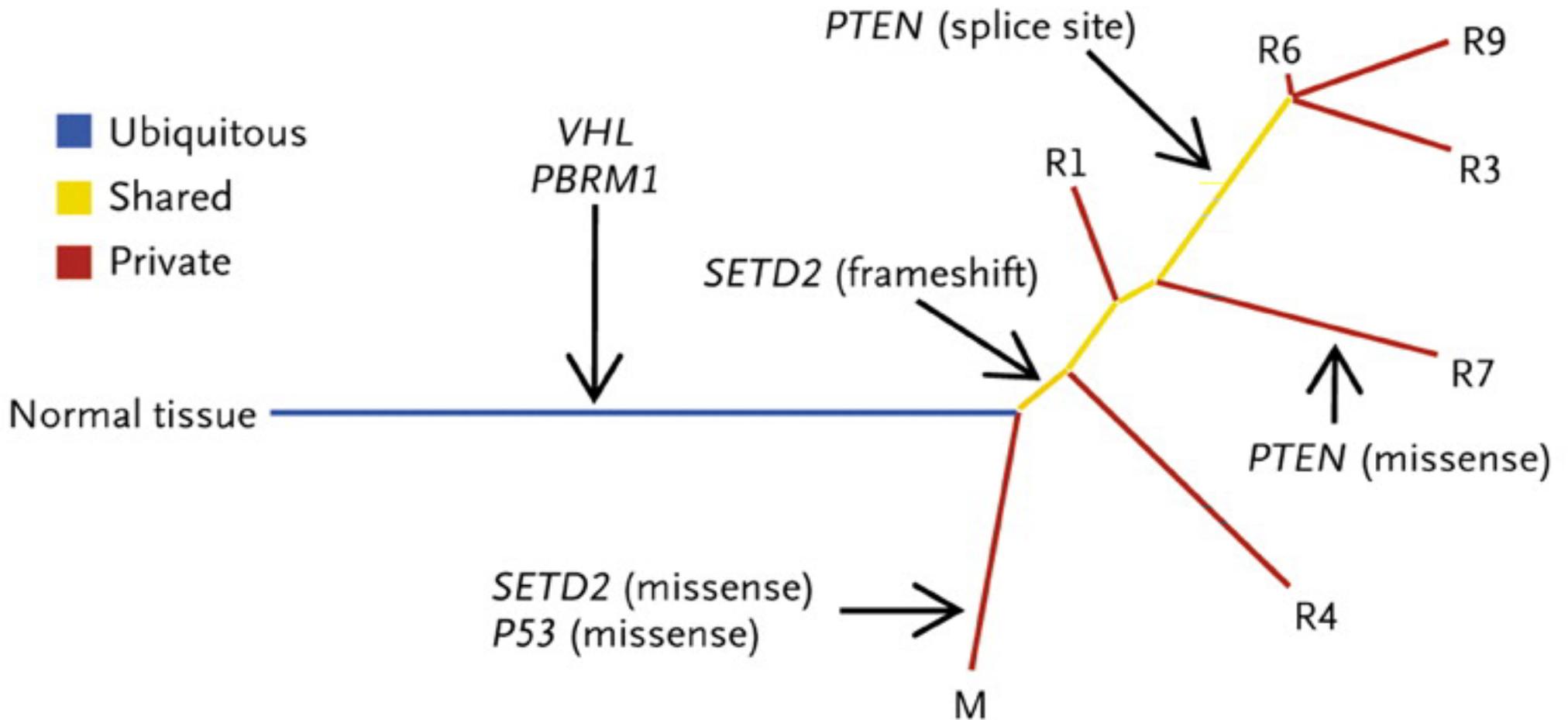
Private



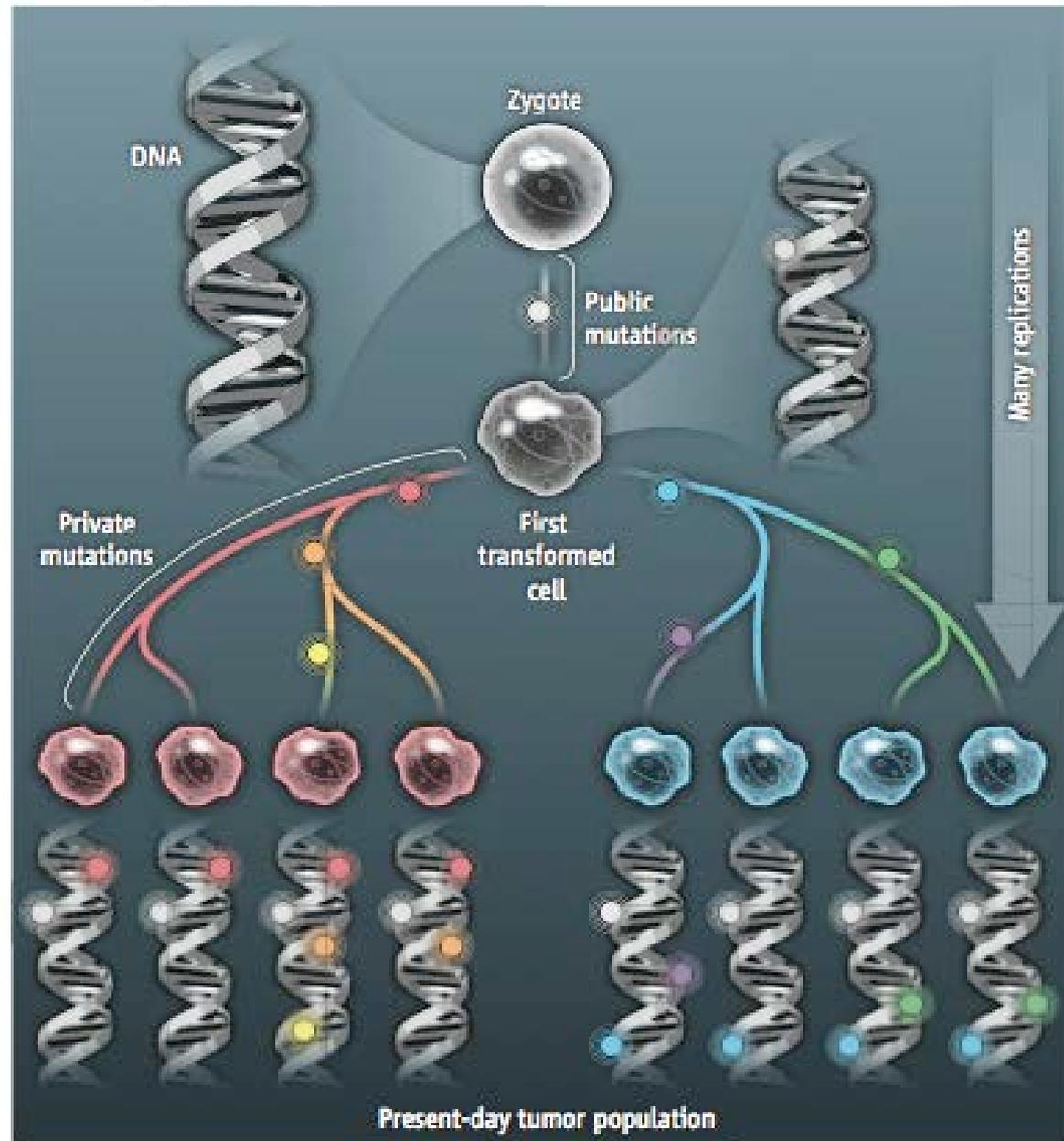
Grey: mutation detected

Blue: NO mutation

# Genetic Intratumor Heterogeneity and Phylogeny in Patient 2. (119 somatic mutations detected)



# Mutation history and tumor's past, present, and future



# Tumor evolution

```
graph TD; A[Tumor evolution] --> B[LINEAR]; A --> C[BRANCHED];
```

## LINEAR

Founding clone

Selection of more fitter clones

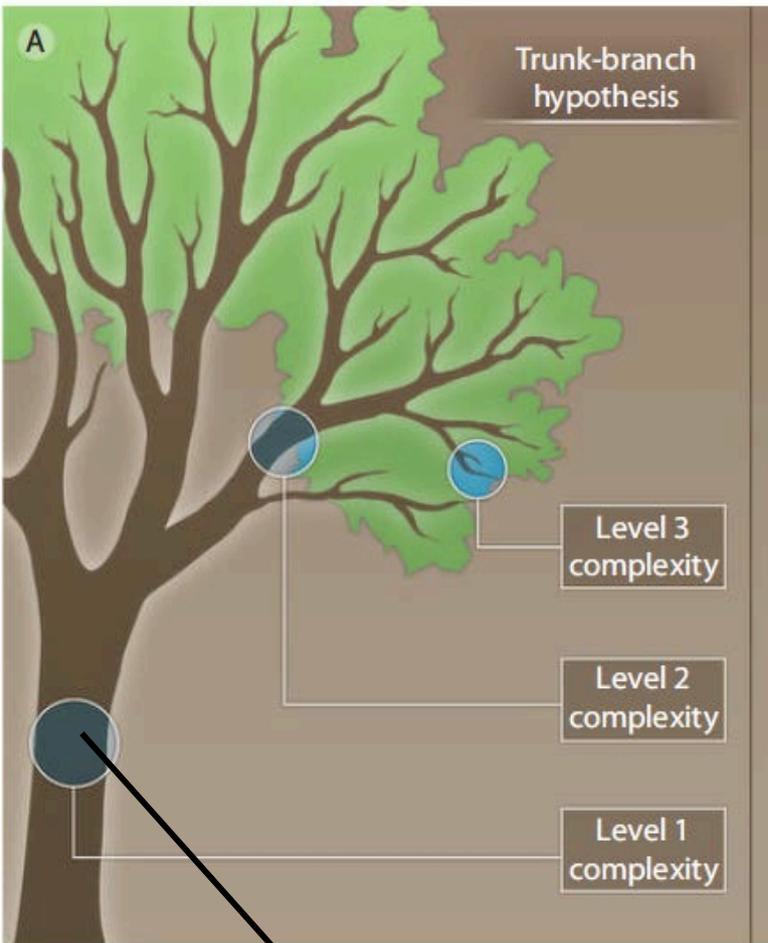
## BRANCHED

Multiple subclones

Present simultaneously

COMPLEX HETEROGENEOUS  
TUMOR

# A trunk branch model of intratumor heterogeneity



**LEVEL 1:** Trunk-driver mutations  
Branches- neutral mutations

**LEVEL 2:** Trunk-driver mutations  
Branches- neutral or additional driver mutations – convergent phenotypes.

(distinct mutations in SETD2 and PTEN in different regions of Renal cancer- converge on same pathway)

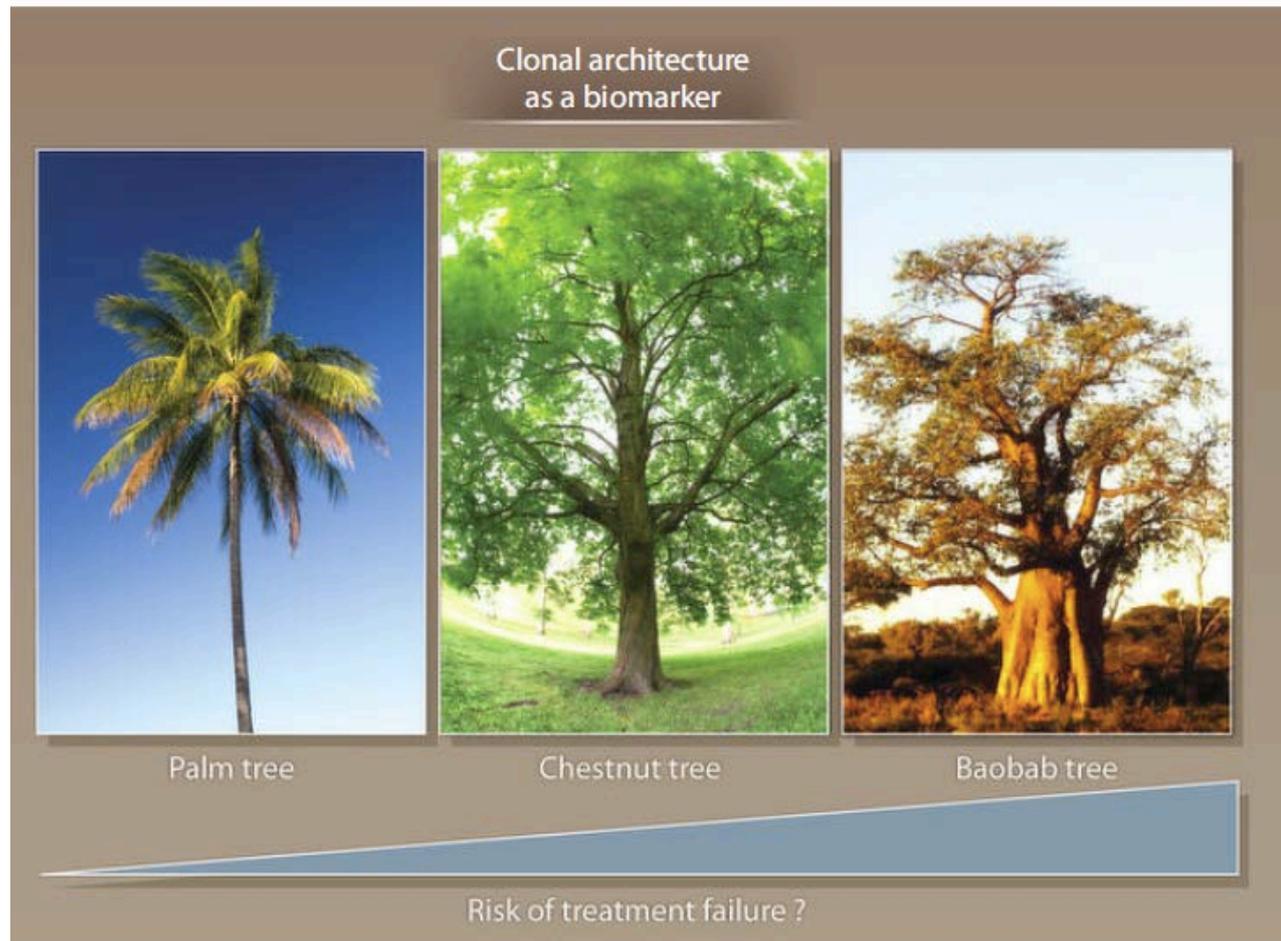
**LEVEL 3:** Level 1 and Level 2 events AND neutral mutations on trunk or branches that become drivers under selection pressure  
(T790M, ALK acquired resistance etc.)

Founding ubiquitous  
Driver mutations



Biomarkers and  
Therapeutic targets ??

# A trunk branch model of intratumor heterogeneity (Clonal architecture as a biomarker)



“Palm-tree like” tumors- Ubiquitous genetic events  $\gg$  heterogeneous genetic events  
**Good prognosis!**

“Baobab tree-like” tumors – Heterogeneous genetic events  $\gg$  ubiquitous events  
**Bad prognosis!**

that a meiosis I-specific factor from budding yeast, monoplin, generates kinetochores with more microtubule-binding elements and greater strength. These findings provide direct evidence that sister kinetochore fusion underlies the cosegregation of sister chromatids during meiosis I.

#### REFERENCES AND NOTES

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#### LUNG CANCER EVOLUTION

# Spatial and temporal diversity in genomic instability processes defines lung cancer evolution

Elza C. de Bruin,<sup>1\*</sup> Nicholas McGranahan,<sup>2,3\*</sup> Richard Mitter,<sup>2\*</sup> Max Salm,<sup>2\*</sup> David C. Wedge,<sup>4\*</sup> Lucy Yates,<sup>4,5,†</sup> Mariam Jamal-Hanjani,<sup>1,†</sup> Seema Shafi,<sup>1</sup> Nirupa Murugaesu,<sup>1</sup> Andrew J. Rowan,<sup>2</sup> Eva Grönroos,<sup>2</sup> Madiha A. Muhammad,<sup>1</sup> Stuart Horswell,<sup>2</sup> Marco Gerlinger,<sup>2</sup> Ignacio Varela,<sup>6</sup> David Jones,<sup>4</sup> John Marshall,<sup>4</sup> Thierry Voet,<sup>4,7</sup> Peter Van Loo,<sup>4,7</sup> Doris M. Rassl,<sup>8</sup> Robert C. Rintoul,<sup>8</sup> Sam M. Janes,<sup>9</sup> Siow-Ming Lee,<sup>1,10</sup> Martin Forster,<sup>1,10</sup> Tanya Ahmad,<sup>10</sup> David Lawrence,<sup>10</sup> Mary Falzon,<sup>10</sup> Arrigo Capitanio,<sup>10</sup> Timothy T. Harkins,<sup>11</sup> Clarence C. Lee,<sup>11</sup> Warren Tom,<sup>11</sup> Enock Teefe,<sup>11</sup> Shann-Ching Chen,<sup>11</sup> Sharmin Begum,<sup>2</sup> Adam Rabinowitz,<sup>2</sup> Benjamin Phillimore,<sup>2</sup> Bradley Spencer-Dene,<sup>2</sup> Gordon Stamp,<sup>2</sup> Zoltan Szallasi,<sup>12,13</sup> Nik Matthews,<sup>2</sup> Aengus Stewart,<sup>2</sup> Peter Campbell,<sup>4</sup> Charles Swanton<sup>1,2,‡</sup>

WES and/or WGS on 25 spatially distinct regions

7 localized NSCLC tumor samples (surgical specimens)

1/3<sup>rd</sup> of all non-silent mutations were present in at least one region, but not other regions.

Branched evolution- key driver mutations present both before, and even after subclonal diversification.

## LUNG CANCER EVOLUTION

# Intratumor heterogeneity in localized lung adenocarcinomas delineated by multiregion sequencing

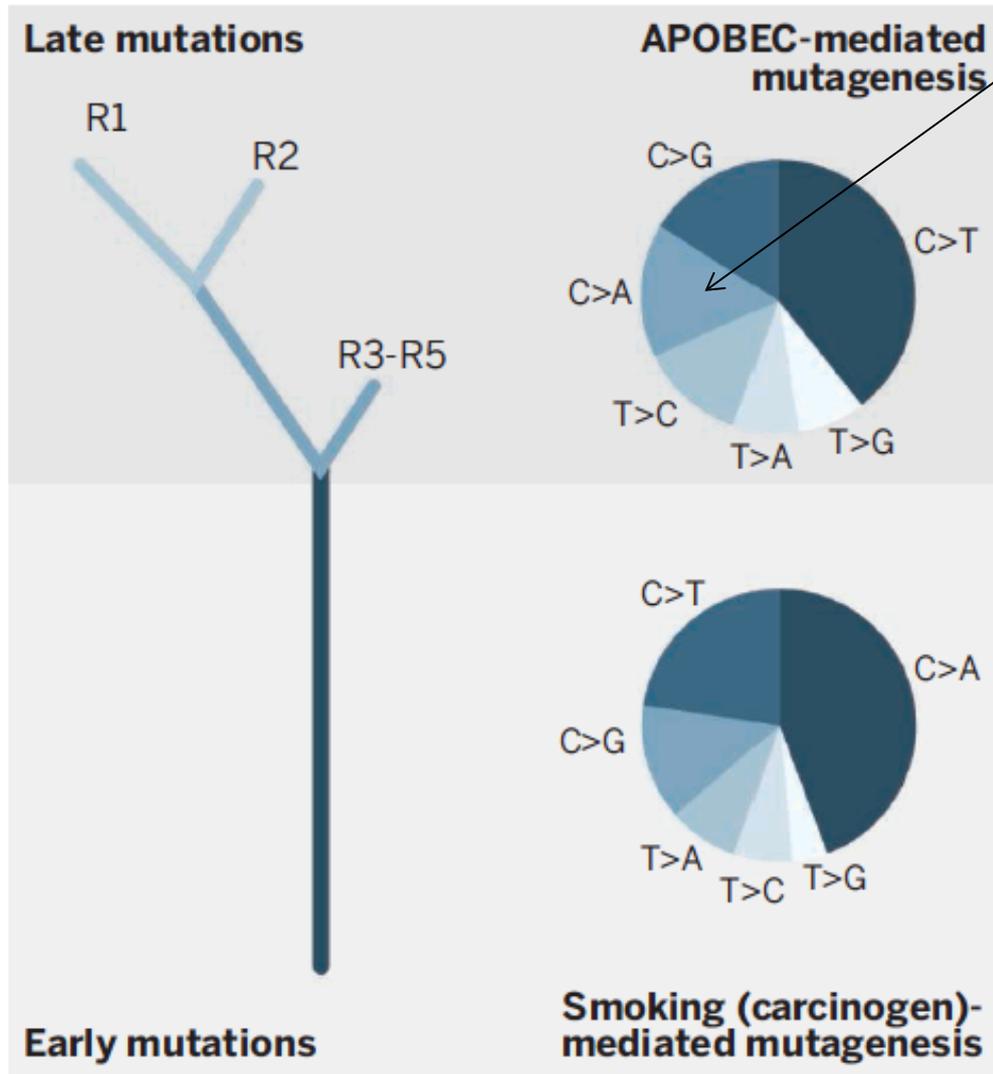
Jianjun Zhang,<sup>1,2</sup> Junya Fujimoto,<sup>3</sup> Jianhua Zhang,<sup>4</sup> David C. Wedge,<sup>5</sup> Xingzhi Song,<sup>4</sup> Jiexin Zhang,<sup>6</sup> Sahil Seth,<sup>4</sup> Chi-Wan Chow,<sup>3</sup> Yu Cao,<sup>1</sup> Curtis Gumbs,<sup>1</sup> Kathryn A. Gold,<sup>2</sup> Neda Kalhor,<sup>7</sup> Latasha Little,<sup>1</sup> Harshad Mahadeshwar,<sup>4</sup> Cesar Moran,<sup>7</sup> Alexei Protopopov,<sup>4</sup> Huandong Sun,<sup>4</sup> Jiabin Tang,<sup>4\*</sup> Xifeng Wu,<sup>8</sup> Yuanqing Ye,<sup>8</sup> William N. William,<sup>2</sup> J. Jack Lee,<sup>9</sup> John V. Heymach,<sup>2,10</sup> Waun Ki Hong,<sup>2</sup> Stephen Swisher,<sup>11</sup> Ignacio I. Wistuba,<sup>3</sup> P. Andrew Futreal<sup>1,12†</sup>

Multiregion WES on 11 lung adenocarcinomas (48 tumor regions)  
(median depth- 277x)

20 out of 21 known cancer genes in all regions of individual tumors.  
76% of all mutations were present in all regions

3 patients with a larger fraction of subclonal population developed recurrent disease after surgery- **intratumoral heterogeneity as a biomarker of poor prognosis.**

# Phylogenetic tree showing the clonal evolution of lung cancer



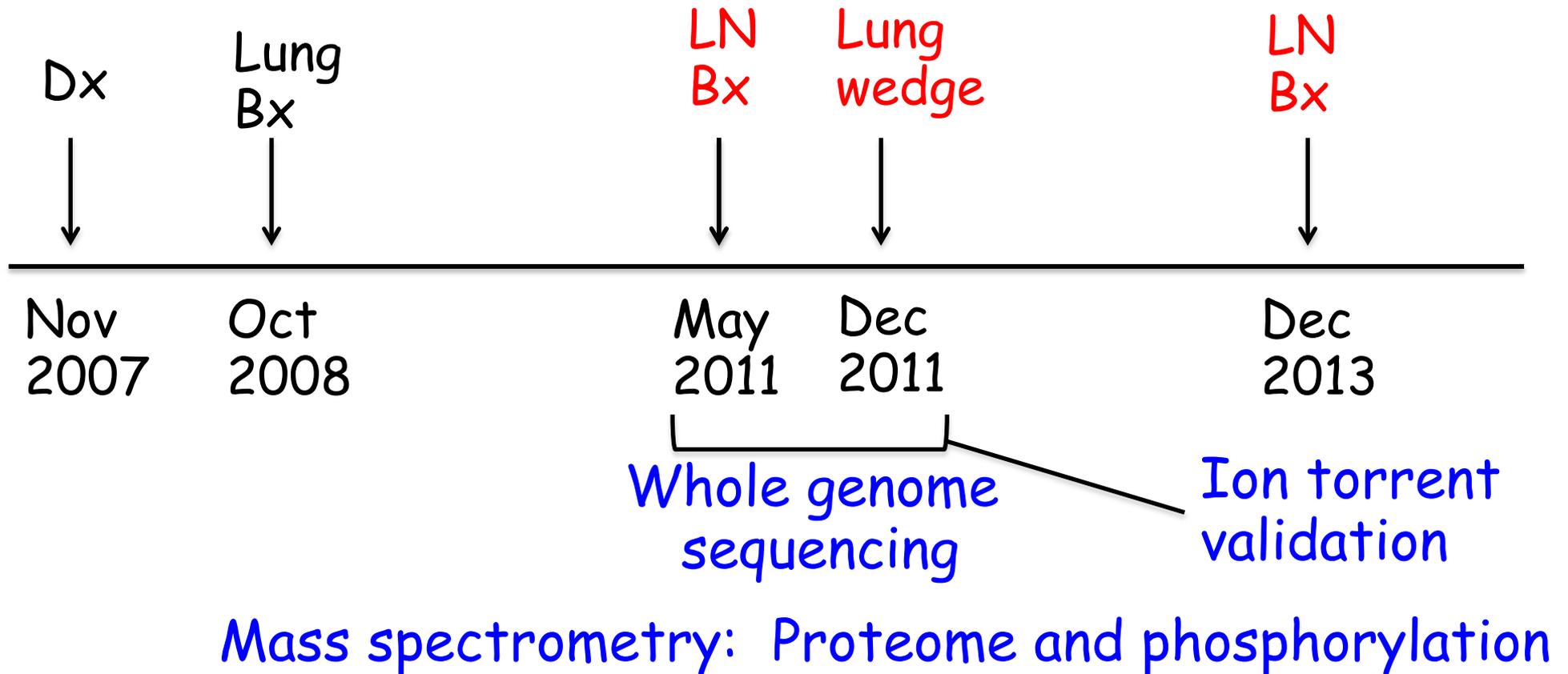
**Clonal evolution.** An example of a phylogenetic tree showing the clonal evolution of lung cancer. Pie charts show the spectrum of six types of mutations during early tumor evolution (smoking-induced mutations) and late evolution (APOBEC mediated) (10). R indicates regions of the tumor.

- Smoking-related genomic events occur quite early.
- Prolonged latency from the first driver events to clinical presentation.
- Even in presence of continued smoking, carcinogen related genomic events decreased over time.
- Increase in mutagenesis related to activation of a class of enzyme Apolipoprotein B mRNA editing-Enzyme-catalytic, polypeptide-like Cytidine deaminase (APOBEC)

# Sequential biopsies to correlate proteo-genomic alterations with tumor heterogeneity and response to targeted treatment

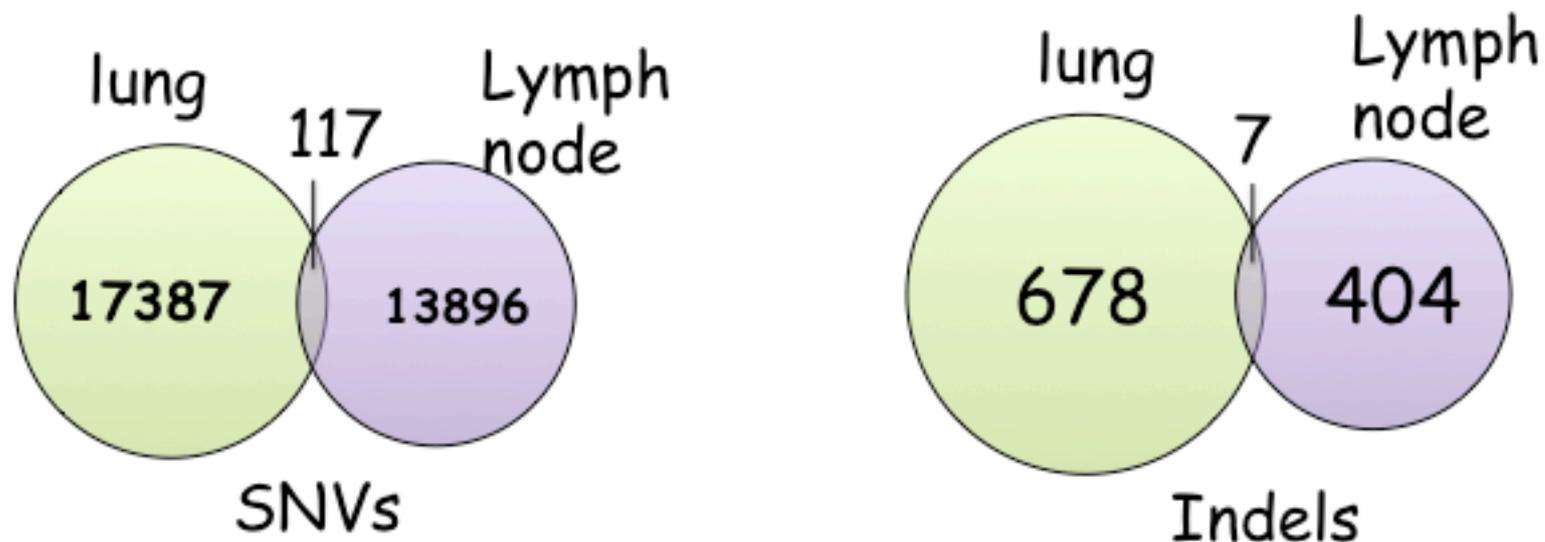
(a Case study of an African American male never smoker)

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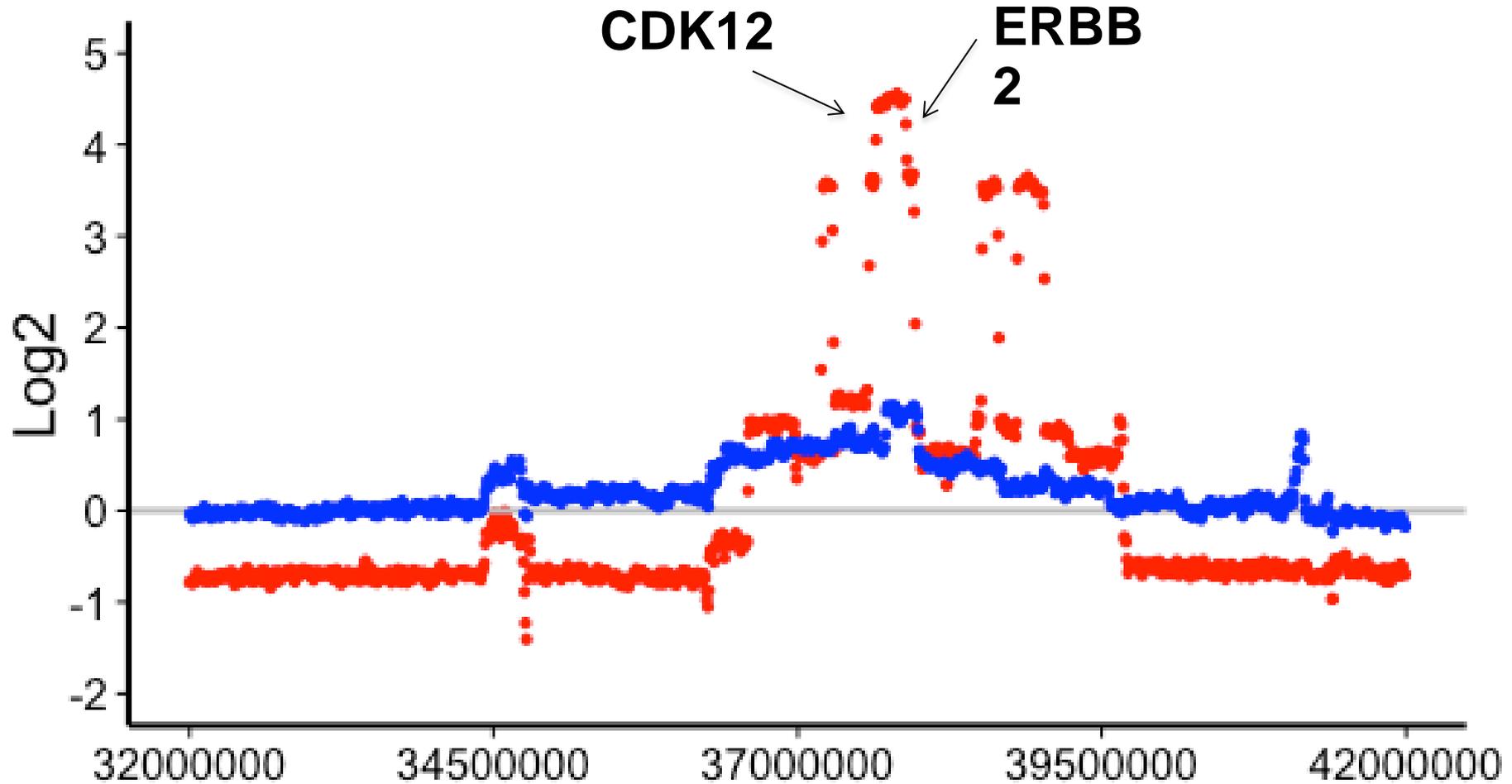
Less than 1% of SNVs and less than 2% of Indels are common between the two metastatic sites

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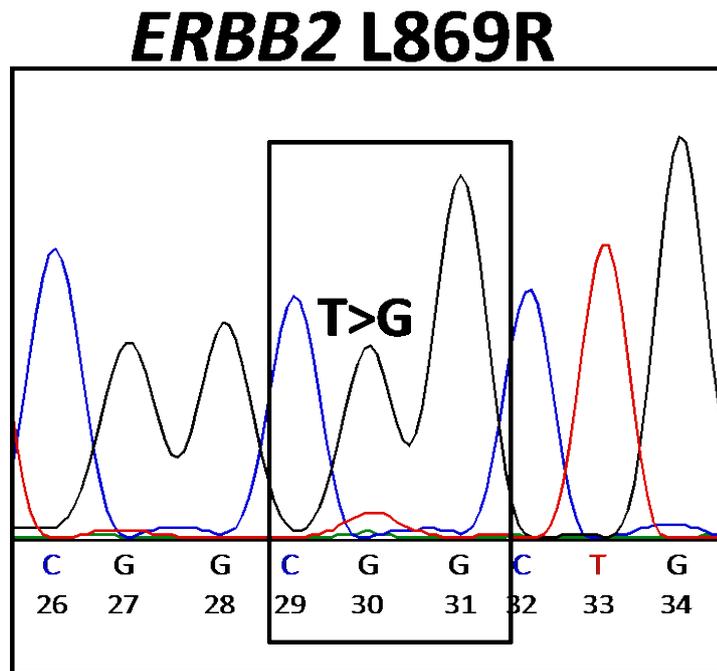


Ch. 17 region with high copy number amplifications in lung tumor (red) and metastatic lymph node (blue) as accessed on WGS by CNV-Seq

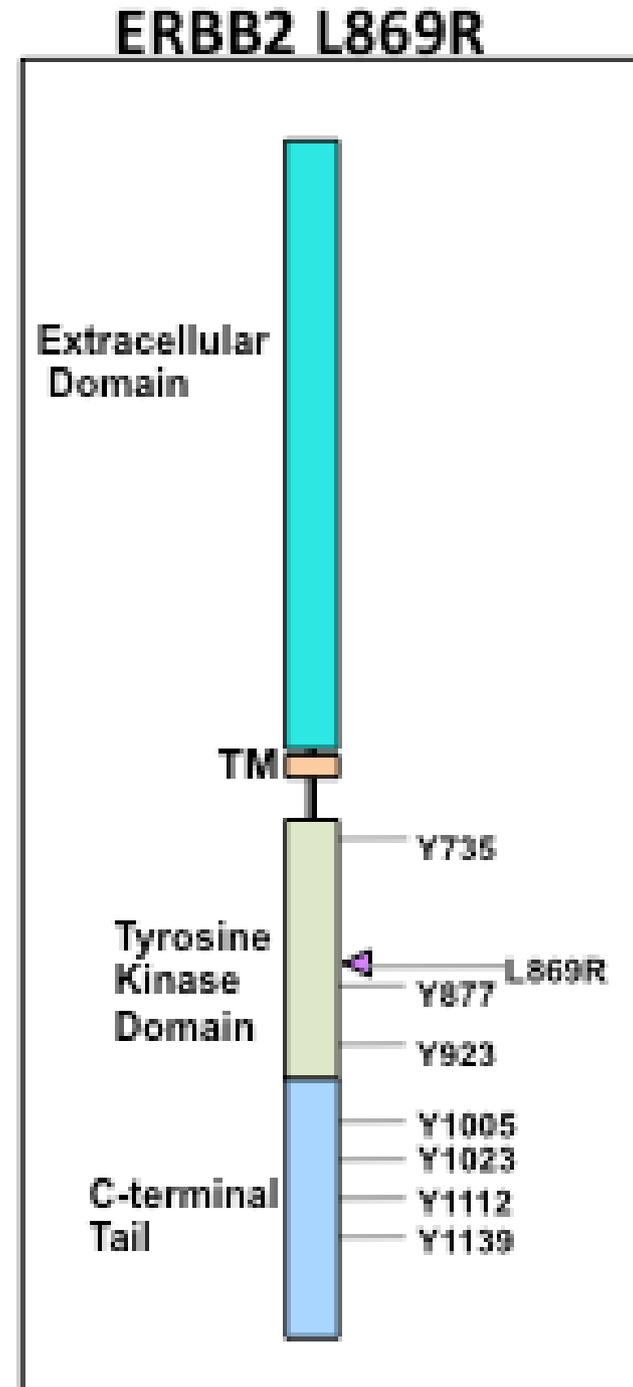
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ERBB2 L869R mutation is only present in the lymph node metastasis



Similar to EGFR L861R



# Commonality in genomic alteration affecting a key hallmark - proliferation

## LUNG

↑↑ ERBB2

KRAS

PI3K

MAPK

AKT

mTOR

↓ CDKN2A

↑ CCND1

CDK12- G879V

Inactivation



Unstable genome

## Lymph Node

↑ ERBB2-L869R

KRAS

PI3K

MAPK

AKT

mTOR

TP53-  
Del E339-F341

p21

↑ CCNE1

No mutation in CDK12

# Rapid ("warm") autopsies to obtain tumor and normal tissues

- All possible areas of disease can be sampled
  - Adjacent "normal" tissue can be collected
  - Cell lines and xenografts can be generated
- Tissue can be sampled and stored to preserve quality
  - RNA and Protein analyses can be performed

## **Rapid (“Warm”) Autopsy Study for Procurement of Metastatic Prostate Cancer<sup>1</sup>**

**Mark A. Rubin,<sup>2</sup> Mathew Putzi, Neil Mucci,  
David C. Smith, Kirk Wojno, Susan Korenchuk,  
and Kenneth J. Pienta**

Departments of Pathology [M. A. R., M. P., N. M., K. W.] and  
Internal Medicine [K. J. P., D. C. S., S. K.] and Section of Urology  
[M. A. R., D. C. S., K. J. P.], University of Michigan, Ann Arbor,  
Michigan 48109

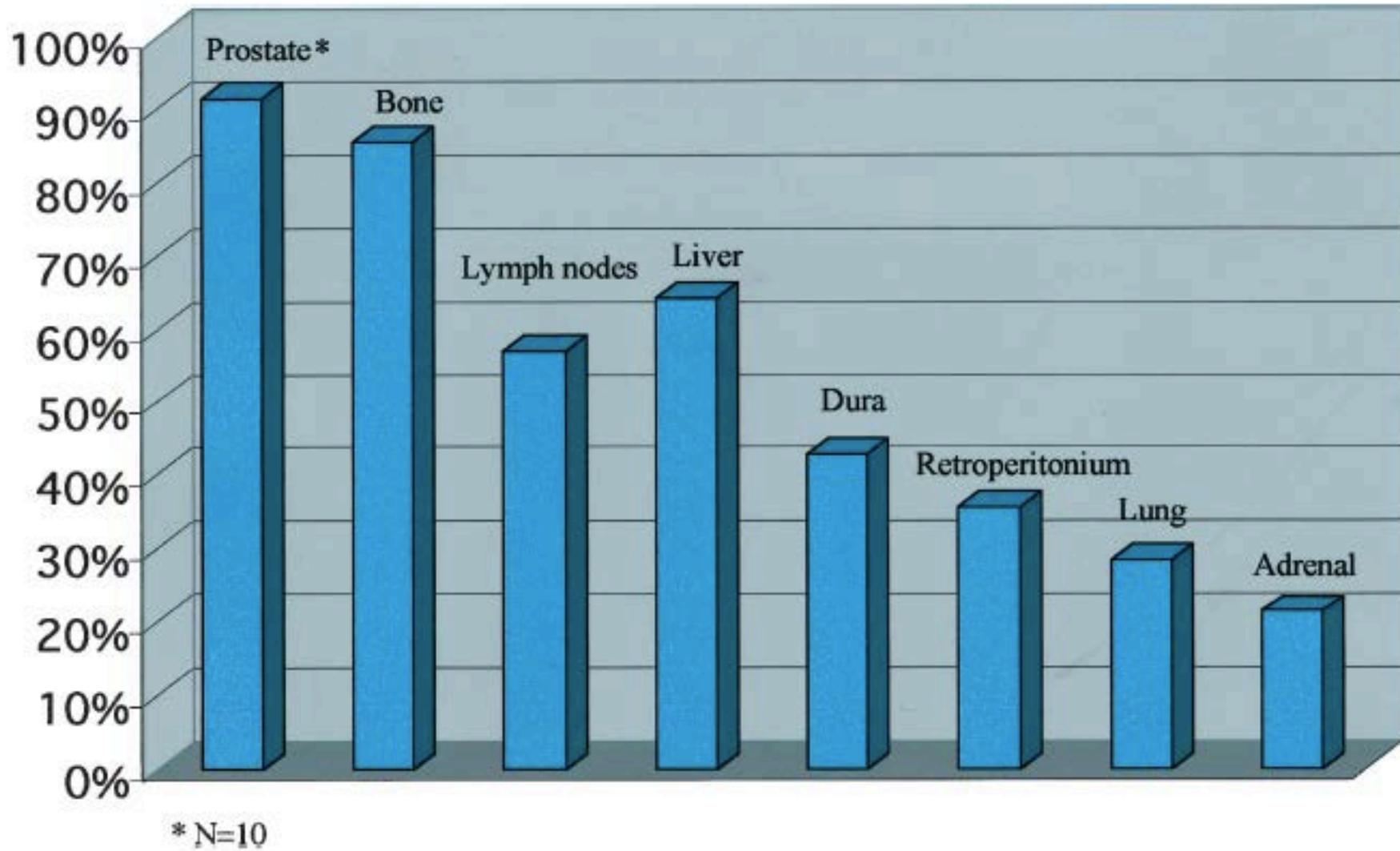
“warm” autopsy or tissue procurement program at the University of Michigan.

The term “warm” derives from the short interval between time of death and acquisition of tissue samples during the autopsy. The primary goal of this program was to develop a tumor donor program that would allow men with metastatic hormone-refractory prostate cancer to agree to an immediate autopsy shortly after death. This program would serve as an

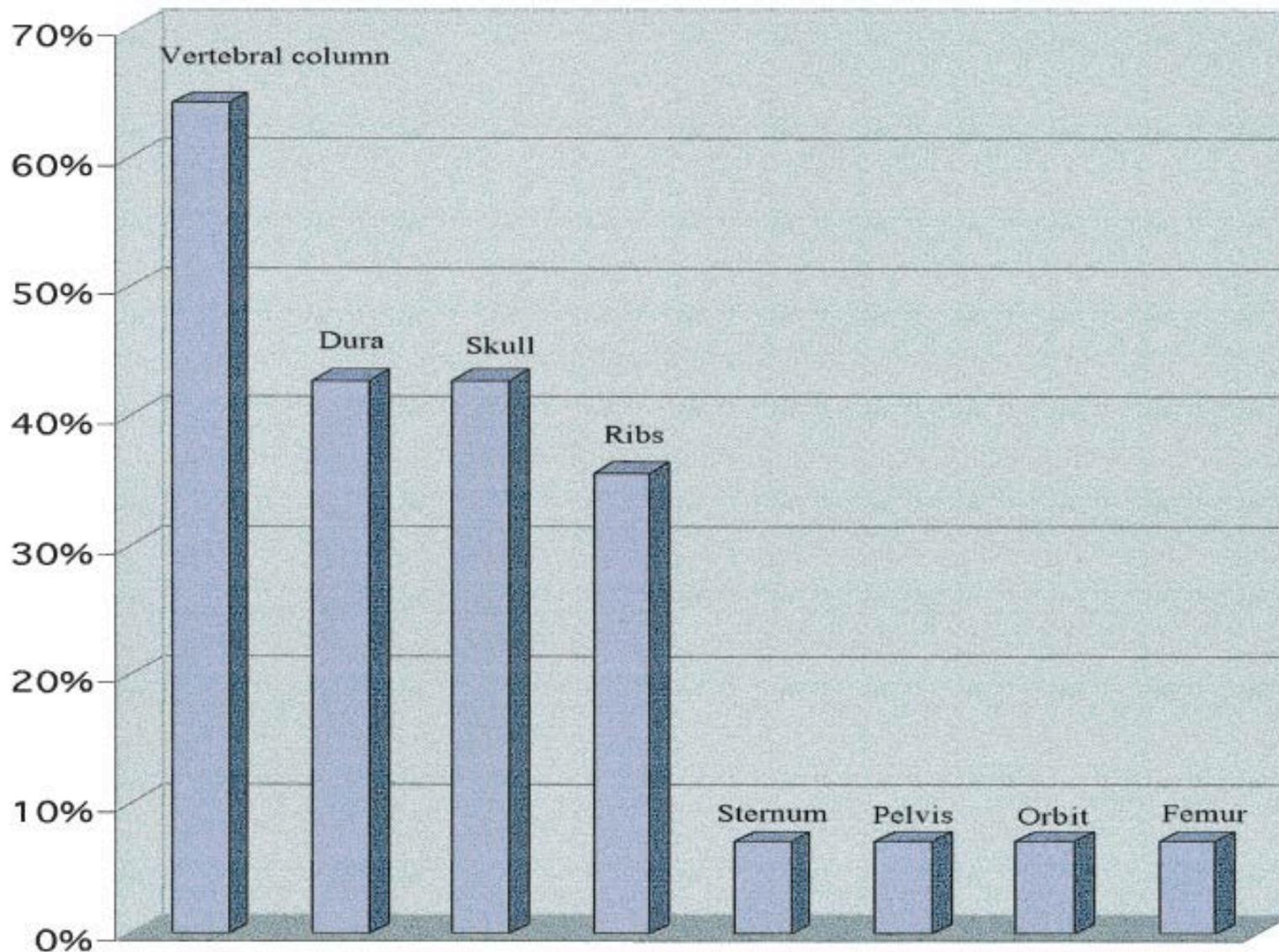
### **University of Michigan: Rapid Autopsy Study of Metastatic Prostate Cancer**

- Sept. 1996- Jan 1999: 14 autopsies performed.
- Median time to autopsy: 2.8 hours
- Delay beyond 2 hours was always because of transportation of the body from home or hospice to the hospital.

# Tissue types involved in hormone refractory prostate cancer



# Bony sites involved in hormone refractory prostate cancer *n=14 cases*



# A major goal of the Michigan rapid autopsy program:

Obtain high quality tumor tissue for prostate cancer research

- Bulky tumor metastases harvested and care to remove areas of necrosis.
- Good tumor histology
- Immunoreactivity for PSA
- Ability to develop xenografts

Essay

# Lessons from Our Patients: Development of a Warm Autopsy Program

Kathleen Oare Lindell, Judith A. Erlen, Naftali Kaminski\*

## Warm autopsy program at the Univ. of Pittsburgh: Interstitial Lung Disease

- .Lesson 1 - listen to the patient**
- .Lesson 2 - go to the people who have experience**
- .Lesson 3 - family members are often your best allies**
- .Lesson 4 - respect your patient's last wishes**
- .Lesson 5 - allow space for patient leadership**

## Ethics guidelines for research with the recently dead

Rebecca D Pentz, Cynthia B Cohen, Mark Wicclair, Michael A DeVita, Anne Lederman Flamm, Stuart J Youngner, Ann B Hamric, Mary S McCabe, Jacqueline J Glover, Winona J Kittiko, Kathy Kinlaw, James Keller, Adrienne Asch, John J Kavanagh & Wadih Arap

**Consensus Panel on Research with the Recently Dead (CPRRD)**

# **CPRRD guidelines** Nature Medicine Vol 11:1145-49

1. Receive scientific and ethical review and oversight
2. Involve the community of potential research subjects
3. Coordinate with organ procurement organizations
4. Not conflict with organ donation or required autopsy
5. Use procedures respectful of the dead
6. Be restricted to one procedure per day
7. Preferably be authorized by first person consent, though general advance directives and surrogate consent are acceptable
8. Protect confidentiality
9. Not impose costs on subject' estates or next of kin and not involve payment
10. Clearly explain ultimate disposition of the body.

# Metastatic castration-resistant prostate cancer reveals intrapatient similarity and interpatient heterogeneity of therapeutic kinase targets

Justin M. Drake<sup>a</sup>, Nicholas A. Graham<sup>b,c</sup>, John K. Lee<sup>d,e</sup>, Tanya Stoyanova<sup>a</sup>, Claire M. Faltermeier<sup>e</sup>, Sudha Sud<sup>f</sup>, Björn Titz<sup>b,c</sup>, Jiaoti Huang<sup>g,h,i</sup>, Kenneth J. Pienta<sup>f,j</sup>, Thomas G. Graeber<sup>b,c,g,k,l</sup>, and Owen N. Witte<sup>a,c,l,m,1</sup>

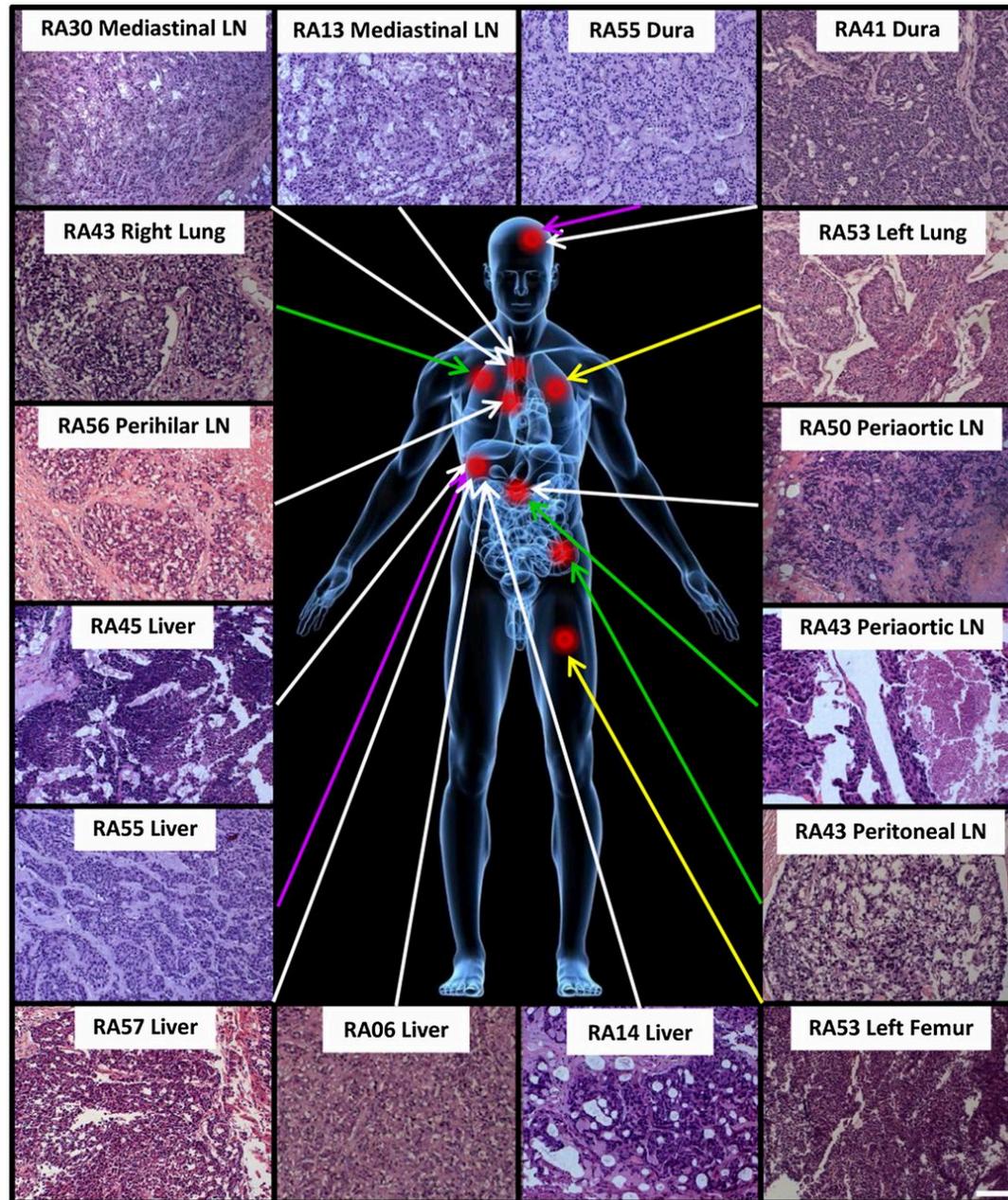
<sup>a</sup>Department of Microbiology, Immunology, and Molecular Genetics, <sup>b</sup>Crump Institute for Molecular Imaging, <sup>c</sup>Department of Molecular and Medical Pharmacology, <sup>d</sup>Division of Hematology and Oncology, Department of Medicine, <sup>e</sup>Molecular Biology Institute, <sup>g</sup>Jonsson Comprehensive Cancer Center, <sup>h</sup>Department of Pathology and Laboratory Medicine, <sup>i</sup>Eli and Edythe Broad Center of Regenerative Medicine and Stem Cell Research, <sup>k</sup>Institute for Molecular Medicine, <sup>l</sup>California NanoSystems Institute, and <sup>m</sup>Howard Hughes Medical Institute, David Geffen School of Medicine, University of California, Los Angeles, CA 90095; <sup>1</sup>The Brady Urological Institute, Johns Hopkins School of Medicine, Baltimore, MD 21231; and <sup>f</sup>Department of Internal Medicine, University of Michigan Medical School, Ann Arbor, MI 48109

Contributed by Owen N. Witte, October 23, 2013 (sent for review September 5, 2013)

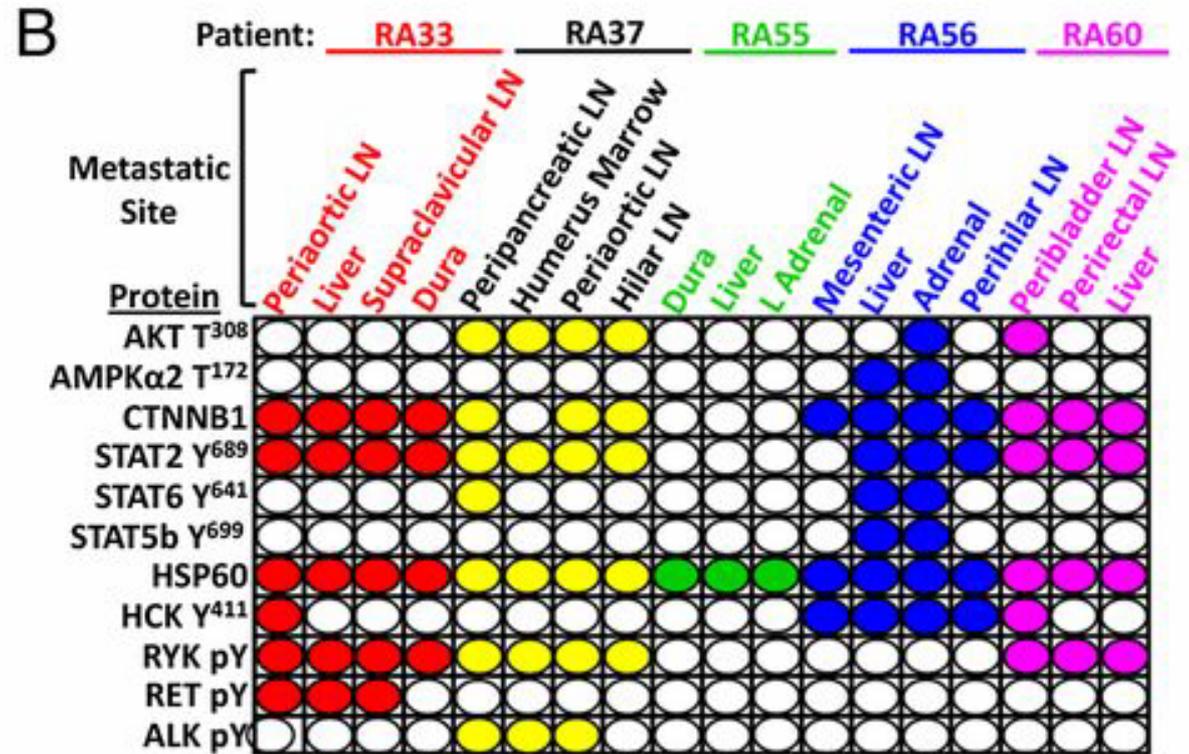
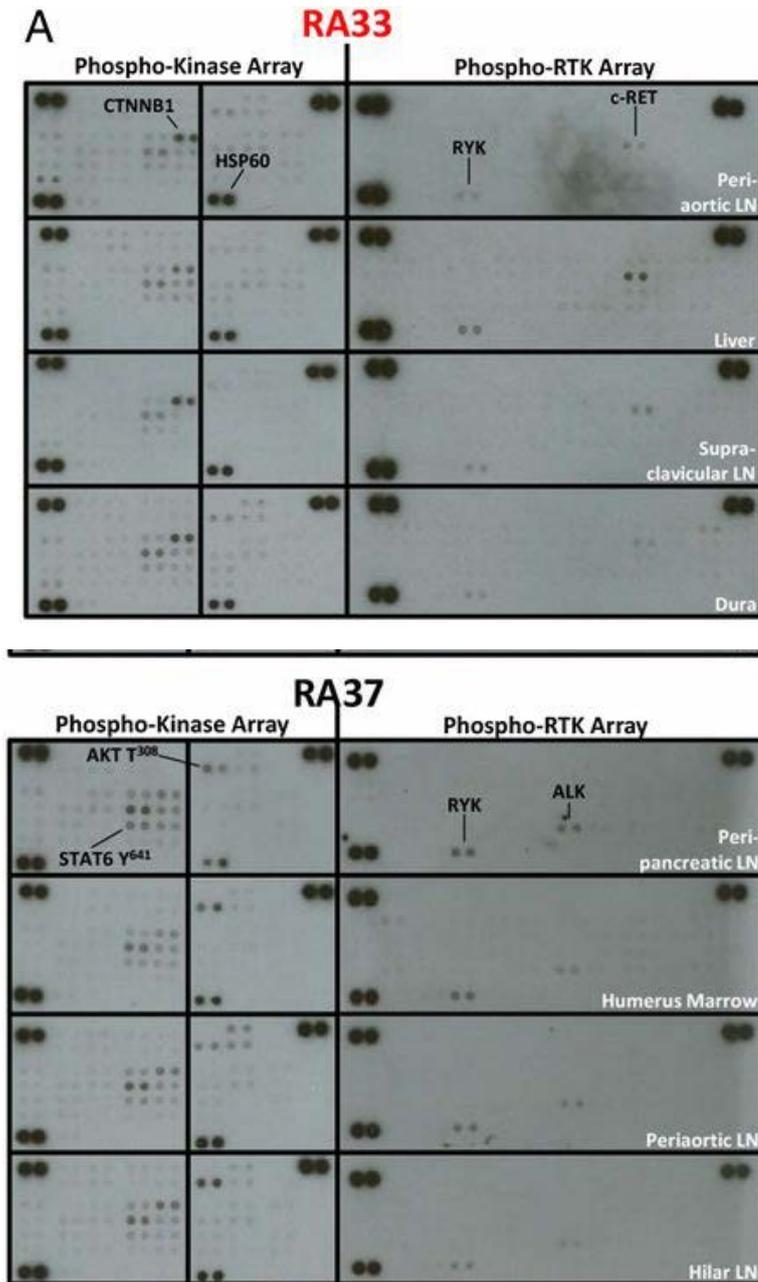
16 metastatic CRPC samples from 13 different patients obtained at rapid autopsy (Michigan program)

Quantitative phosphoproteomics (mass spec, antibody arrays, Western blots)  
Evaluated active kinases

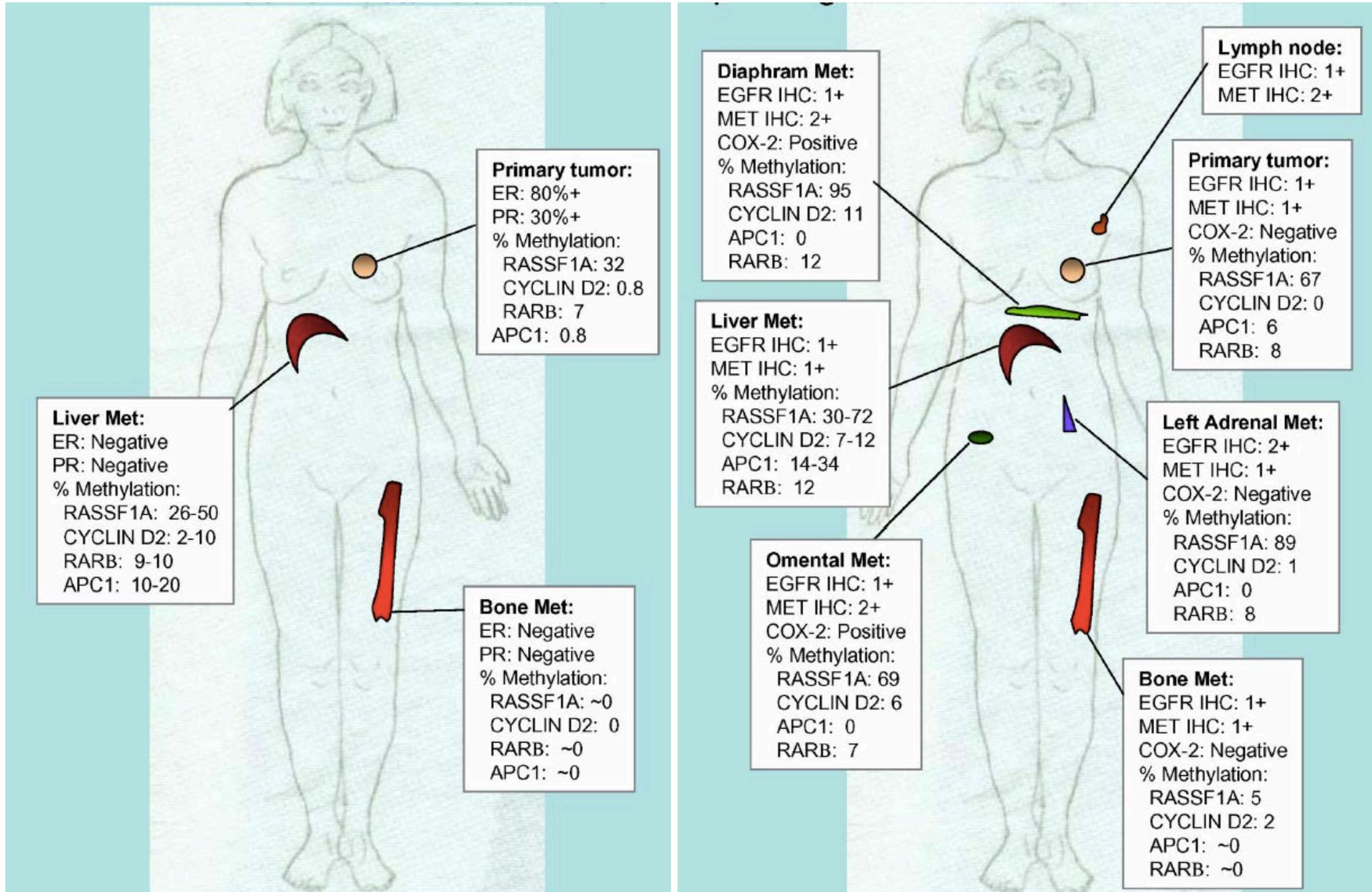
# Anatomical location and histological characterization of metastatic CRPC samples used for phosphoproteomics.



# Kinase activation patterns confirm intrapatient similarity across multiple, anatomically distinct metastases.



# Heterogeneity of breast cancer metastasis



End-of-life in-patient hospice and  
rapid autopsy upon death (within three hours)  
Collect multiple sites of disease and adjacent  
normal tissue

# The patient, family and a comprehensive team

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Pain and palliative

Social work

Home hospice

RAPID  
AUTOPSY

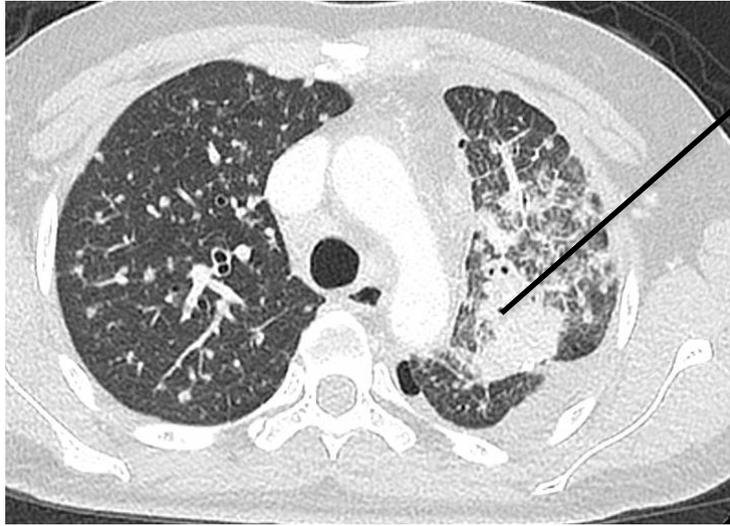
Nurses

Admission

Physicians

Pathologists

# The promise of EGFR tyrosine kinase inhibitors (TKIs)



L858R

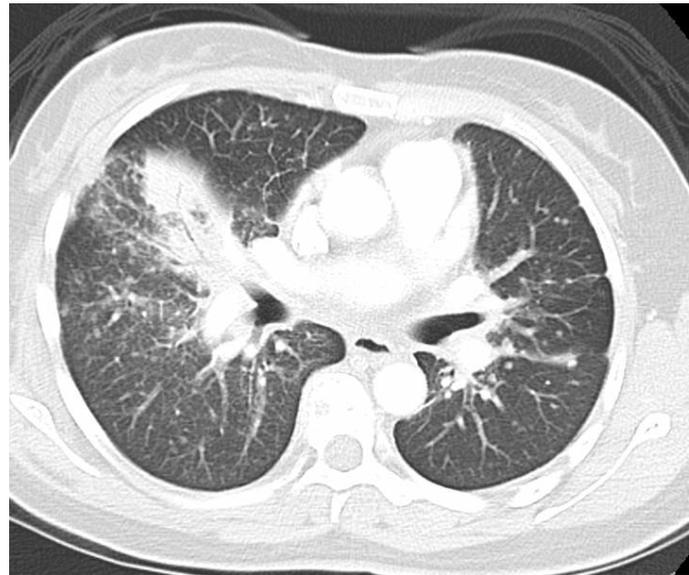
Erlotinib



6 weeks



And the inevitable problem.....

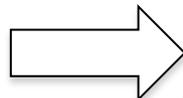


13 months

# Influence of tumor heterogeneity on EGFR TKI resistance



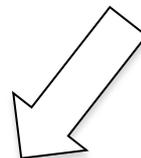
Erlotinib



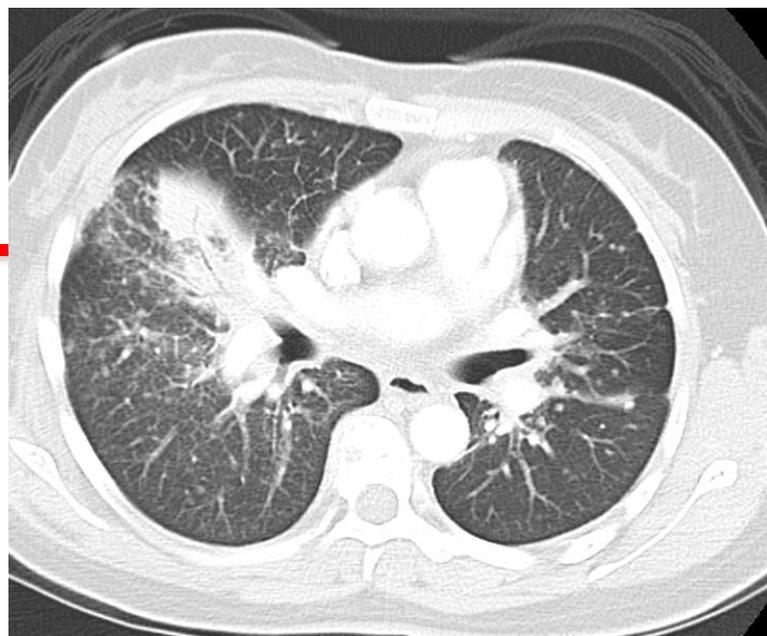
6 weeks



Resistance  
Mechanism:  
A



Resistance  
Mechanisms:  
A and  
"others"



What are  
Others ??

# **End-of-life in-patient hospice and rapid autopsy protocol for thoracic malignancies (NSCLC, SCLC, TET, neuroendocrine, mesothelioma)**

## **Hypothesis**

Clonal evolution and selection of tumor cells can be assessed by examining genomic and proteomic alterations of tumor samples obtained from multiple sites of primary and metastatic sites

## **Primary objective**

Procure tumor tissue from different sites shortly after death in order to study tumor heterogeneity- both intra tumor and between different metastatic sites  
Using integrated genomic and proteomic analysis.

## **Secondary objectives**

- end of life inpatient hospice care
- compare genetic alterations of autopsied tissue with archival tissue
- compare genomic alterations in tumor tissue with those identified in isolated circulating tumor cells.
- generate cell lines and xenografts from isolated tumor tissue

# Study design

**Screening evaluation**  
Screening consent  
Discussion of end-of-life directives  
Discussion of DNR and limited treatment preferences  
History and physical examination  
Social Work screen  
Pain and Palliative care consult

→ **Patient appropriate for inpatient hospice care at NIH** →

→ **No**

→ **Yes**

↑  
Patient continues palliative care received at home or another institution

↓  
Consent to participate in study  
CT scan of neck, chest, abdomen  
Identification of the patient's next of kin  
Designation of Durable Power of Attorney  
Completion of NIH Advance Directive for Health Care and Medical Research Participation

↓  
Follow up visits q 2weeks in OP12  
Review of previously established advance directives

↓  
Study investigator estimates an expected survival of less than two weeks

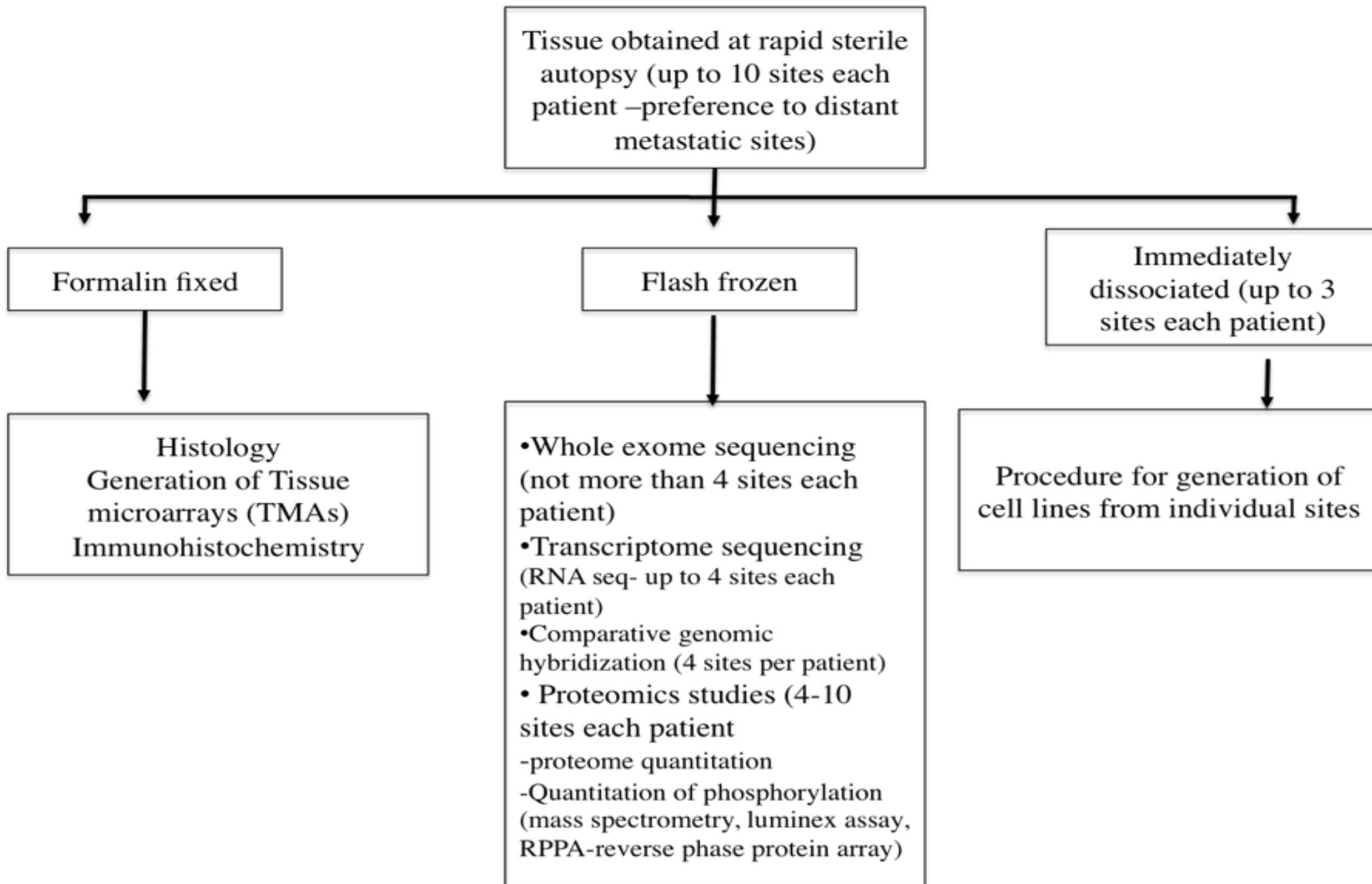
↓  
Admission to 3 NW

↓  
Death of patient

↓  
Notification of next of kin  
Obtain authorization for autopsy

↓  
Full Autopsy

# Proposed studies



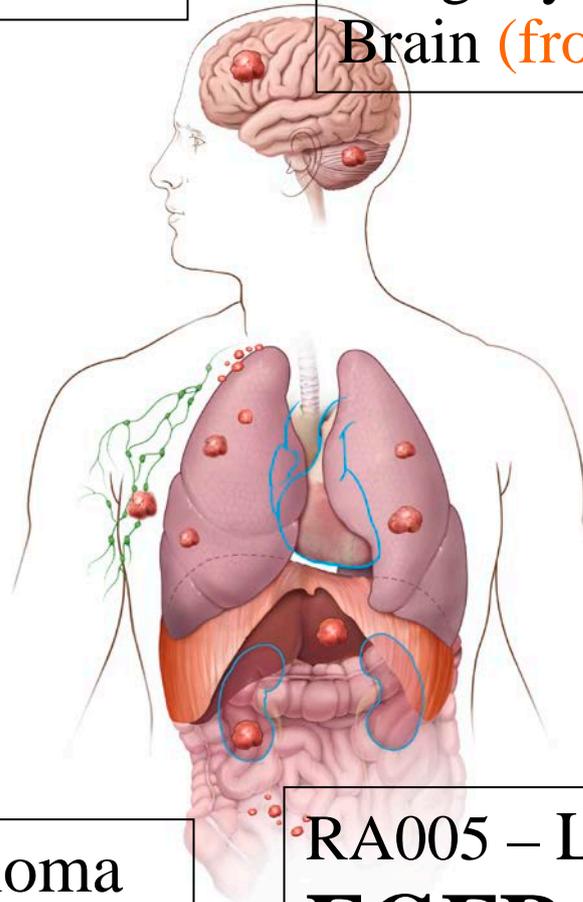
# Tissue collection from rapid autopsy

RA000 – Lung adenocarcinoma  
**KRAS mutation**, MEK inhibitor R<sub>x</sub>  
Lung, Liver (from home)

RA004 – Lung adenocarcinoma  
**KRAS mutation**, MEK inhibitor R<sub>x</sub>  
Lung, Lymph node, Liver, Kidney,  
Brain (from 3NW, Clinical Center)

RA002 – Mesothelioma  
(from ICU, Clinical Center)

*All possible sites of disease*



*Multiple cores from each site*

RA003 – Lung adenocarcinoma  
**HER2 amplification**, Lapatinib R<sub>x</sub>  
Lung, Brain, Pleural fluid  
(from home)

RA005 – Lung adenocarcinoma  
**EGFR mutation**, erlotinib R<sub>x</sub>  
Lung, Brain, Liver  
(from 3NW, Clinical Center)

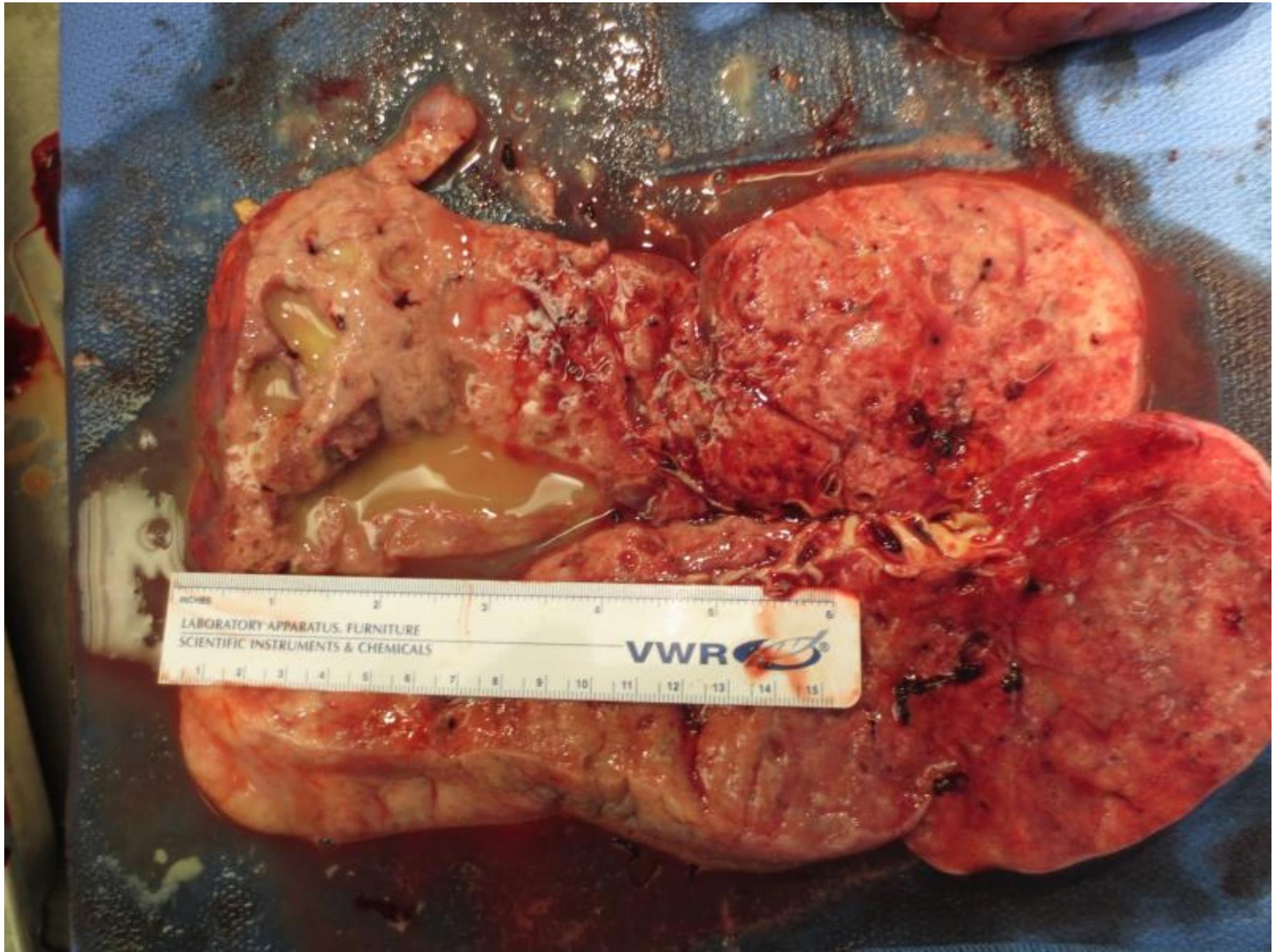
## Clinical Summary (RA005)

- 6/2009- 56yo male non-smoker with Stage IV lung adenocarcinoma s/p chemo referred to NIH
- 6/2009- started on sorafenib (brief holiday due to side effects)
- 2/2010- CT scan showed progression of disease; switched to erlotinib (presence of EGFR mutation)
- 3/2011- returned to NIH after care at WRNMMC and progression on erlotinib; started on pemetrexed and sirolimus
- 5/2011- returned to WRNMMC for care – again maintained on erlotinib or chemotherapy.

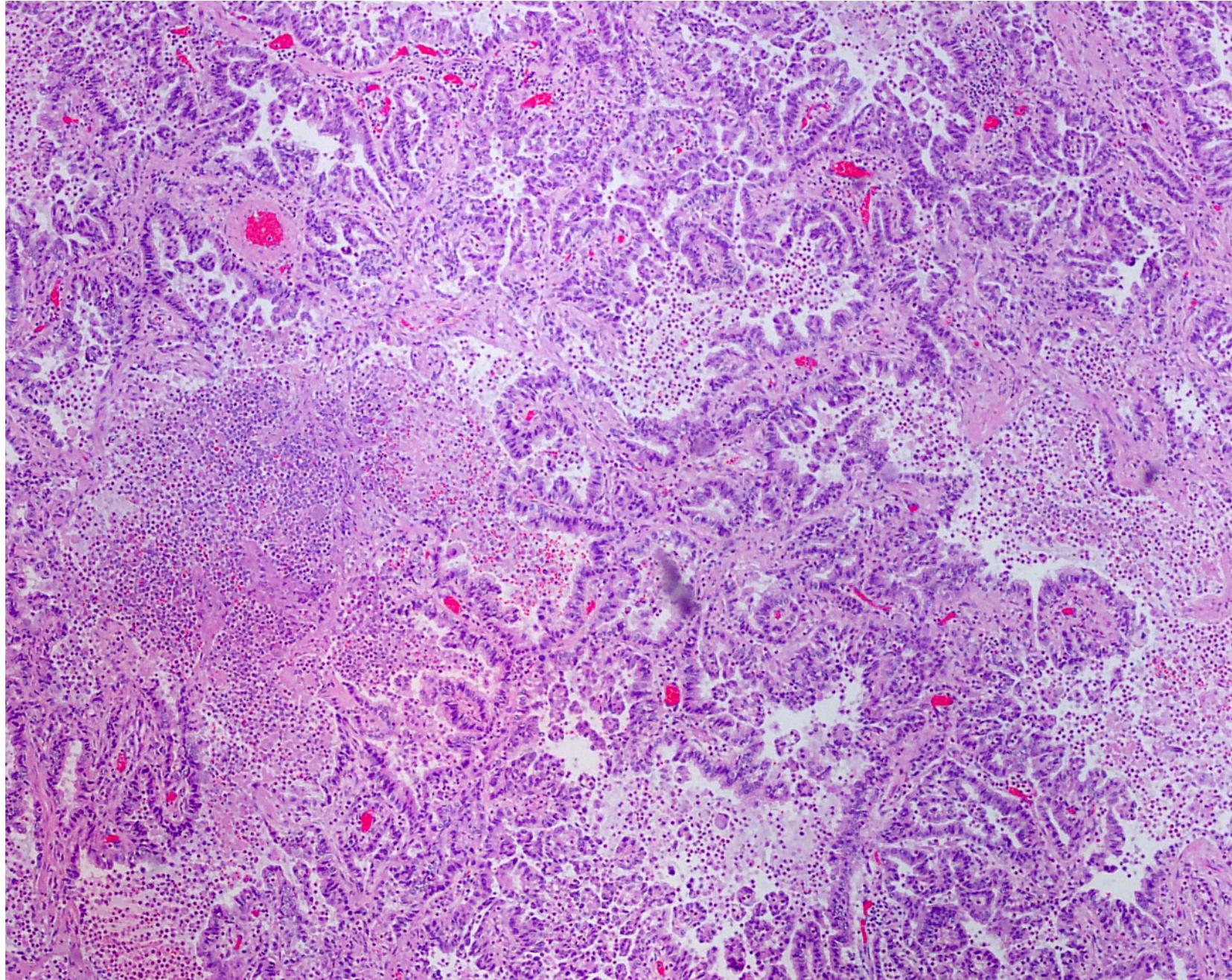
## Clinical summary (RA005)

- 3/2013- Returned to NIH for Hsp90 trial
- 5/2013- stopped Hsp90i due to side effects
- 5/2013- Returned to WRNMMC and transferred to home hospice at some point, but maintained on erlotinib
- 6/12/2014- Transferred to NIH for rapid autopsy protocol.
- Wife signed protocol consent (no DPA- ethics involved)
- He expired on 6/13/2014 at 10:49 AM
- Autopsy initiated at 3.5 hours.

**Lung –RA005 (R- 925g, L-1120g)**

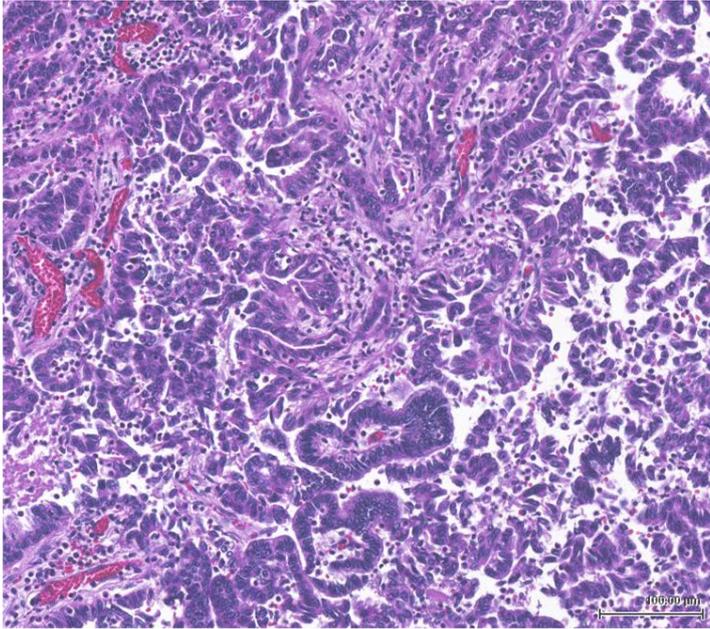


# Lungs, all lobes (RA005)

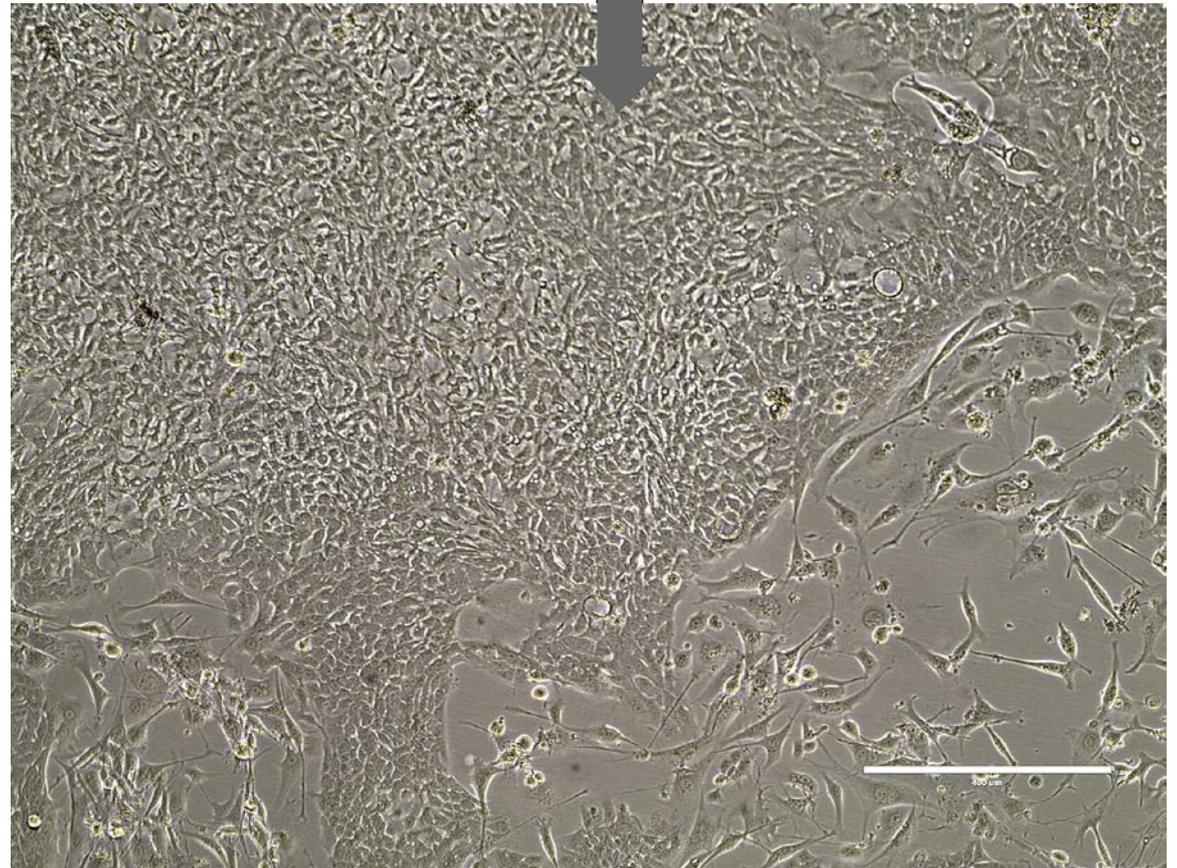


# RA005- Lung Adenocarcinoma- EGFR mutant

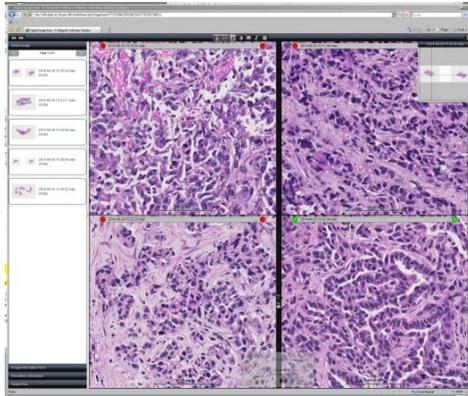
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Cell line generated (RA005)



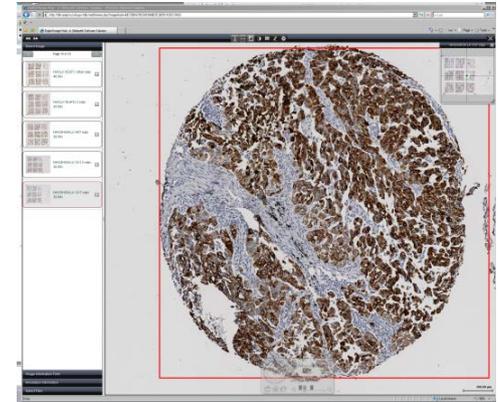
# TMA construction to validate targets



Selection Of Tumor  
From Different Sites



Tissue Microarray  
Construction



Immunohistochemistry  
On Tissue Microarray

## Proteo-genomics studies

### Mass spectrometry

- Protein estimation
- Phosphoproteomics

GUHA LAB

### Simple western assays

- Target validation
- Pathway specific probes

CPTR core facility

### Genomics (NGS)

- Whole exome
- Transcriptome

NCI Frederick core and  
Collaboration

(Javed Khan, CCR)

# Summary

Tumor heterogeneity - Science and Controversies

Branched tumor evolution - challenge for personalized medicine

A unique case report of unprecedented heterogeneity  
(the benefit of sequential biopsy protocols)

Less than 1% similarity of sequential biopsies from metastatic sites

A review of a couple of published rapid autopsy series

Michigan, Hopkins, Pittsburgh programs. Striking intra-patient similarity of metastatic sites and primary in prostate cancer

Ethics guidelines for conducting such studies

CPRRD guidelines

Thoracic Malignancies Rapid Autopsy at the NIH Clinical Center

5 rapid autopsies performed in less than a year

# Acknowledgements

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Christopher Albanese, Georgetown Univ.

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Javed Khan  
Stephen Hewitt  
David Kleiner

## *Pain and Palliative Service*

### *Social Work*

### *3NW Nursing team*

### *Admissions*