Best Practices in Oncology Personalized Medicine

November 29, 2018

"Oncology High-Value Best Practices" Webinar Series, Webinar #2

CQC
CALIFORNIA QUALITY COLLABORATIVE
Breakthroughs for Better Health Care

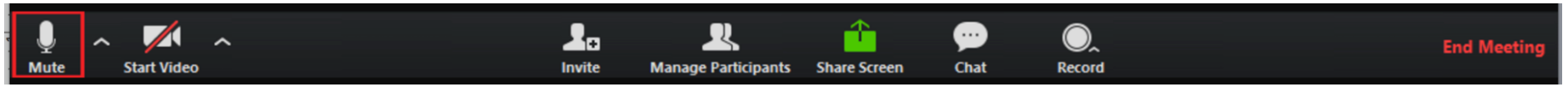
Tech Tips – Zoom Meetings

Attendees are automatically MUTED upon entry

Refrain from using the hold button

Use the chat box, raise your hand, or *unmute yourself and jump in* if you have questions or would like to participate

Direct messages to Jose if you have any technical issues



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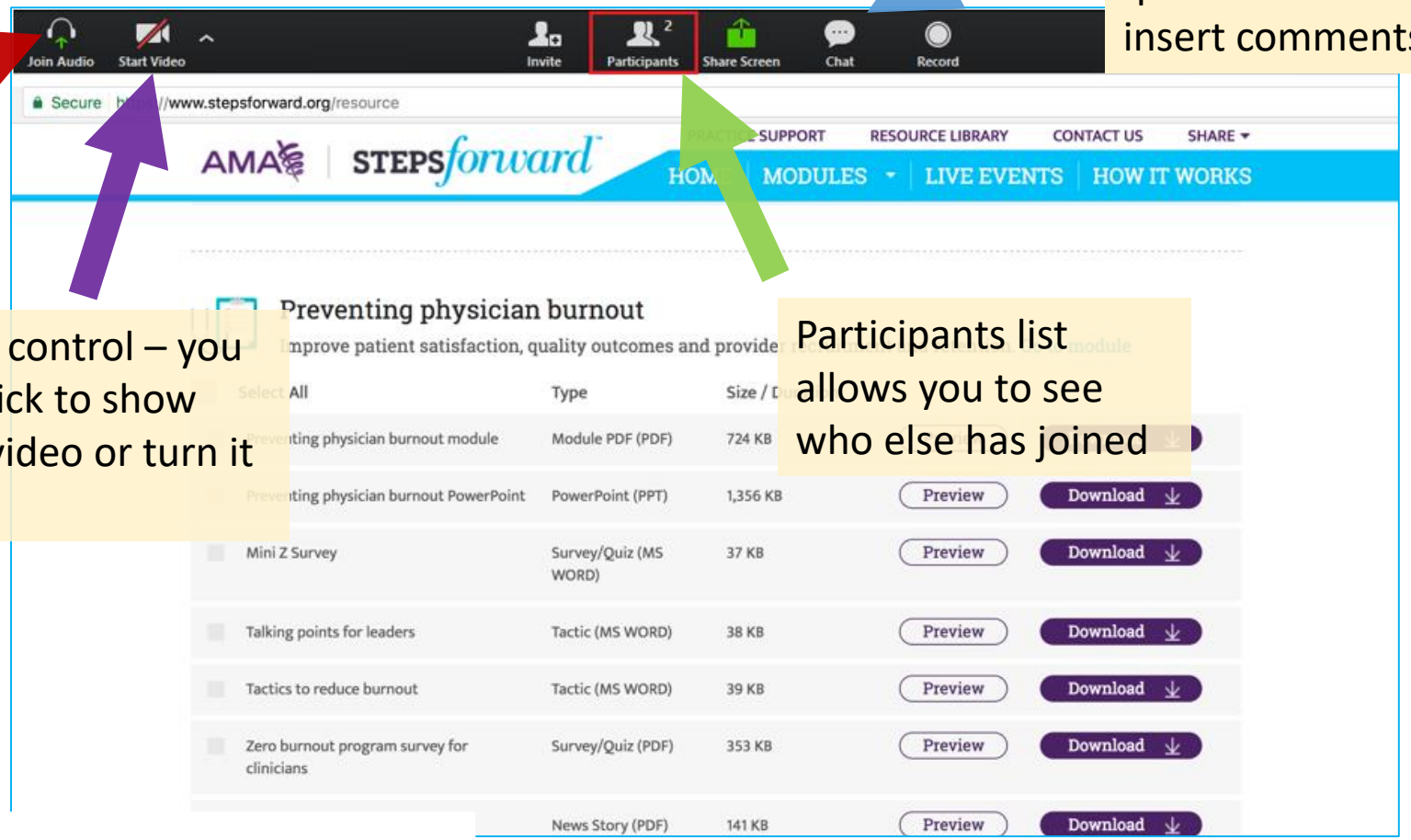
Zoom Tips & Tricks

Chat box so you can ask questions and insert comments

Click here to join audio



Video control – you can click to show your video or turn it off

Participants list allows you to see who else has joined

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Today's Speakers

- Bart Wald, MD
- Medical Director, California Quality Collaborative

- Mark Pegram, MD
- Associate Director for Clinical Research and Associate Dean for Clinical Research Quality for the Stanford School of Medicine

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Breakthroughs for Better Health Care

Who is the California Quality Collaborative (CQC)?

CQC is a health care improvement organization dedicated to advancing the quality and efficiency of the health care delivery system in California. CQC creates scalable, measurable improvement in the care delivery system important to patients, purchasers, providers, and health plans.

- Started in 2007
- Multi-stakeholder governance
  - Core funding from health plans sharing a delivery system
  - Administered by the Pacific Business Group on Health
- **Purpose:** Identify and spread best practices across outpatient delivery system in California
  - Trains 2,000 individuals from 250 organizations each year

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PBGH PACIFIC BUSINESS GROUP ON HEALTH
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Oncology Series
Webinar Dates

- **Benefits & Limitations of Oncology Guidelines** (Anthony Ciarolla, MD)
- **Personalized Medicine** (Mark Pegram, MD)

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Breakthroughs for Better Health Care

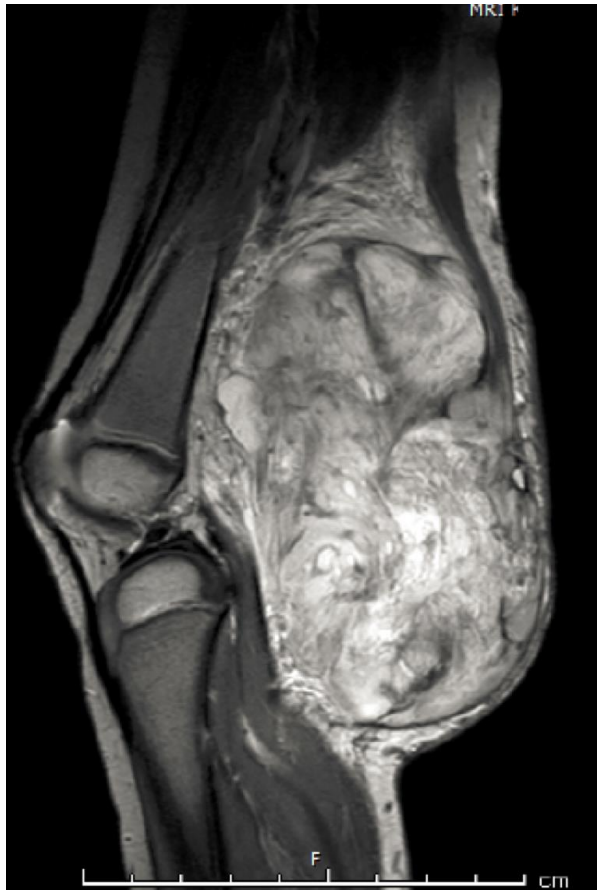
STANFORD
CANCER INSTITUTE

Understanding and rational use of personalized medicine for diagnostics and (or) treatment in oncology patients

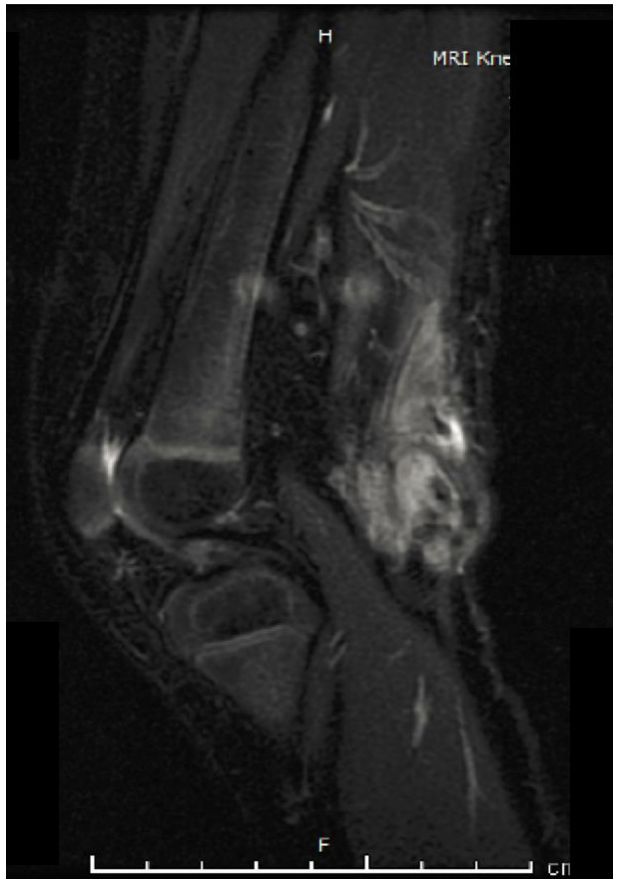
October 2018

Mark Pegram, M.D.
Susy Yuan-Huey Hung Professor of Oncology
Associate Director for Clinical Research
Director, Stanford Breast Oncology Program
Associate Dean for Clinical Research Quality
Stanford University School of Medicine

ETV6-NTRK3 infantile fibrosarcoma patient



Baseline



Cycle 3

2F infantile fibrosarcoma

2 cycles of vincristine/ actinomycin-D/ cyclophosphamide → progression → leg amputation was only alternative option

4 cycles larotrectinib → referred for surgery

Pathologic complete response with clear margins

No functional deficit post-surgery

Hyman, LBA2501

The Hope and Promise of Personalized Medicine

Nov. 26, 2018: STAMFORD, Conn. and WHIPPANY, N.J.

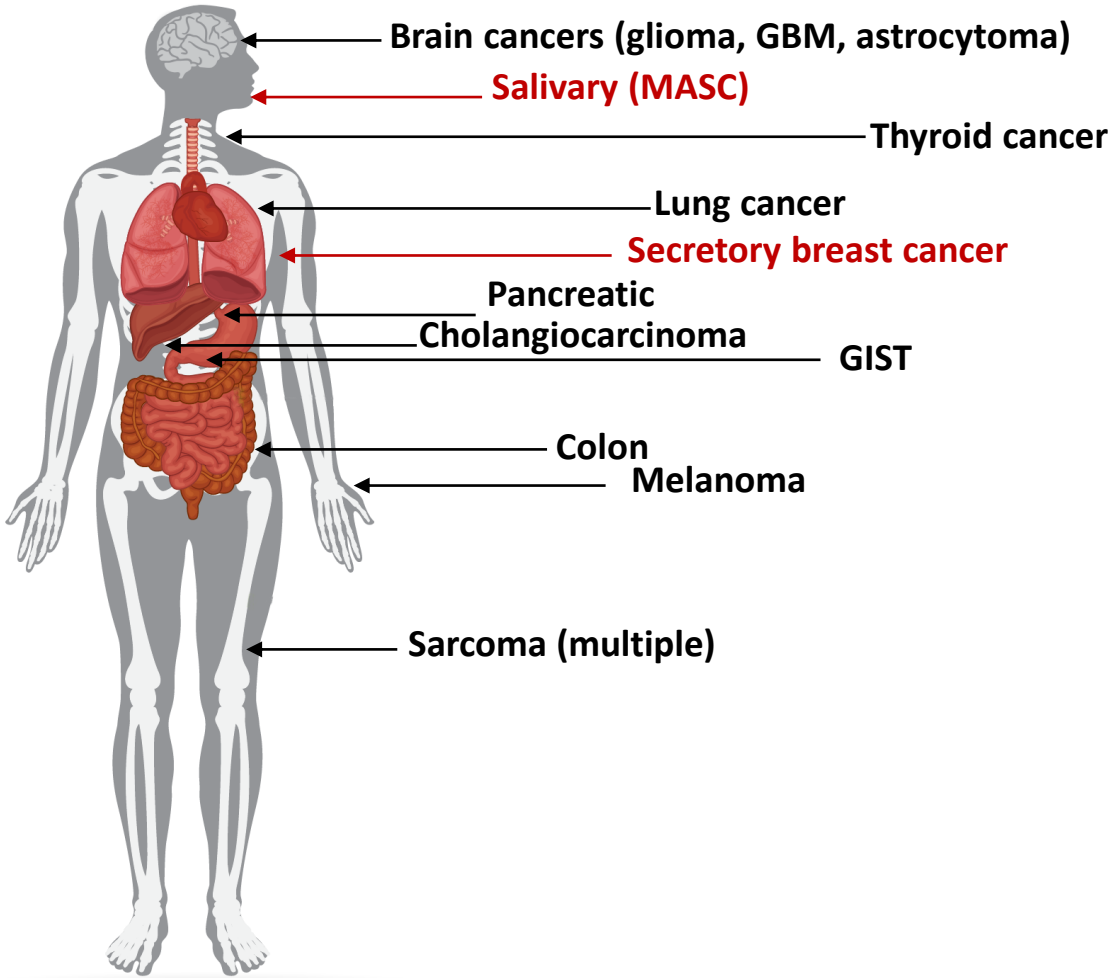
FDA Approves Vitrakvi® (larotrectinib), the First Ever TRK Inhibitor, for Patients with Advanced Solid Tumors Harboring an NTRK Gene Fusion

- First treatment with a tumor-agnostic indication at the time of initial FDA approval

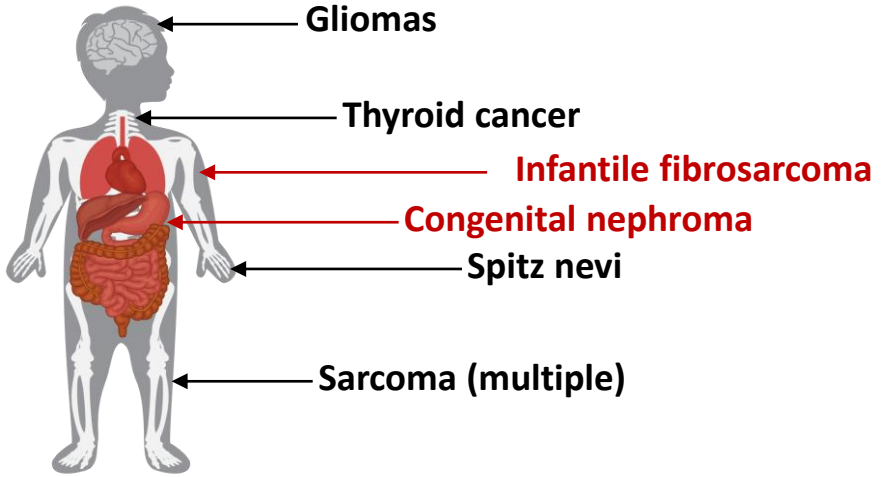
- 75% overall response rate [22% complete response and 53% partial response] across various solid tumors in adults and children

- Adverse events of any grade observed in 20% or more of patients, regardless of attribution, included increased AST/ALT (45%), anemia (42%), fatigue (37%), nausea (29%), dizziness (28%), cough (26%), vomiting (26%), constipation (23%), and diarrhea (22%)

TRK gene rearrangements (fusions) found in diverse cancer types

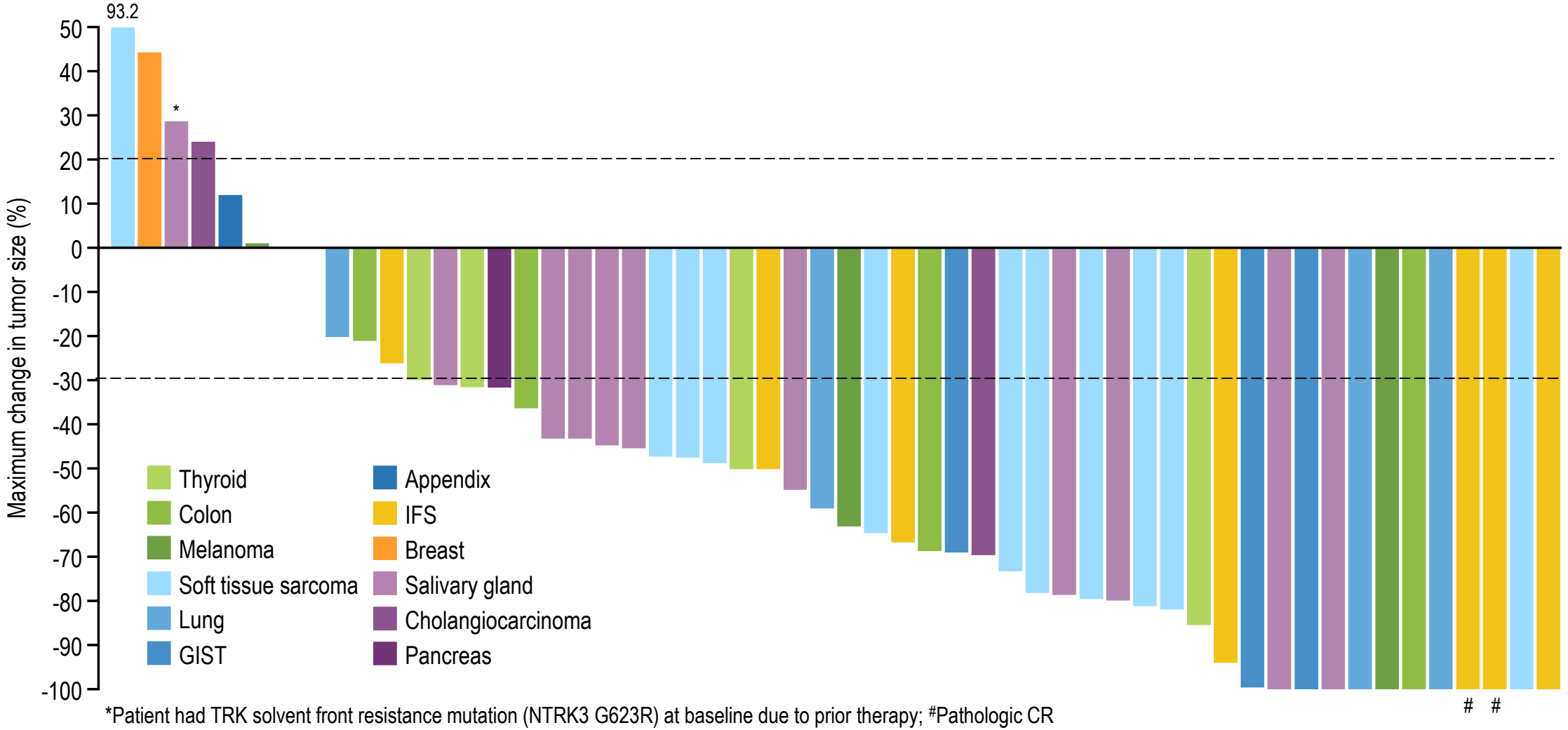


- Common cancer with low TRK fusion frequency
- Rare cancer with high TRK fusion frequency



Efficacy irrespective of tumor type*

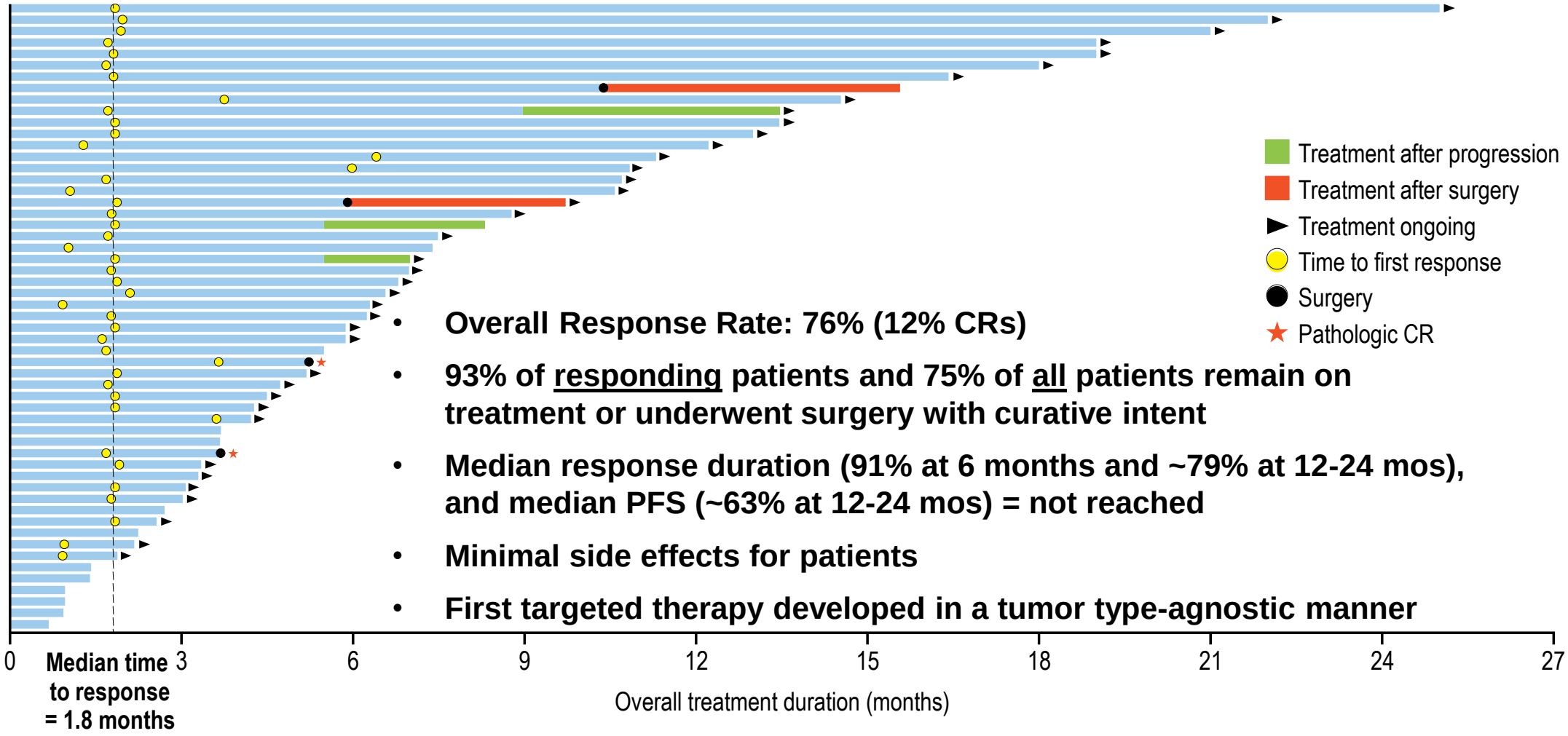
*Efficacy regardless of age, NTRK gene, or fusion partner



*Patient had TRK solvent front resistance mutation (NTRK3 G623R) at baseline due to prior therapy; #Pathologic CR

Note: One patient not shown here. Patient experienced clinical progression and no post-baseline tumor measurements were recorded.

Duration of larotrectinib therapy



- **Overall Response Rate: 76% (12% CRs)**
- **93% of <u>responding</u> patients and 75% of <u>all</u> patients remain on treatment or underwent surgery with curative intent**
- **Median response duration (91% at 6 months and ~79% at 12-24 mos), and median PFS (~63% at 12-24 mos) = not reached**
- **Minimal side effects for patients**
- **First targeted therapy developed in a tumor type-agnostic manner**

FOUNDATION MEDICINE DIAGNOSTIC PORTFOLIO

Simultaneous detection of all four classes of genomic alterations

ANALYTICAL VALIDATION: DEMONSTRATED ACCURACY AND REPRODUCIBILITY FOR CLINICAL USE

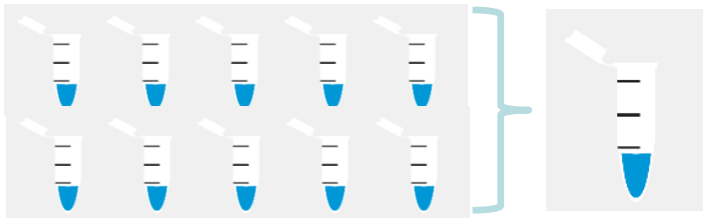
nature biotechnology

Development and validation of a clinical cancer genomic profiling test based on massively parallel DNA sequencing

Controlled validation

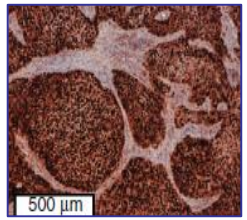
Cell-line pools with known alterations:

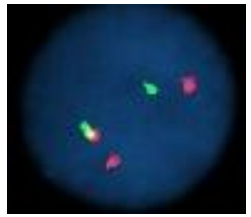
- 2056 subs 227 indels
- 210 CNAs 32 fusions



Clinical concordance with existing platforms :

- 118 subs/indels: Sequenom, PCR
- 185 CNAs: FISH, IHC
- 43 fusions: break-apart FISH





Frampton et al., *Nat Biotech.* 2013

BASE SUBSTITUTIONS

(MAF 5-100%)
Sensitivity: >99.9%
PPV: >99.9%

INSERTIONS/DELETIONS

(1-40bp, MAF 10-100%)
Sensitivity: 98%
PPV: >99%

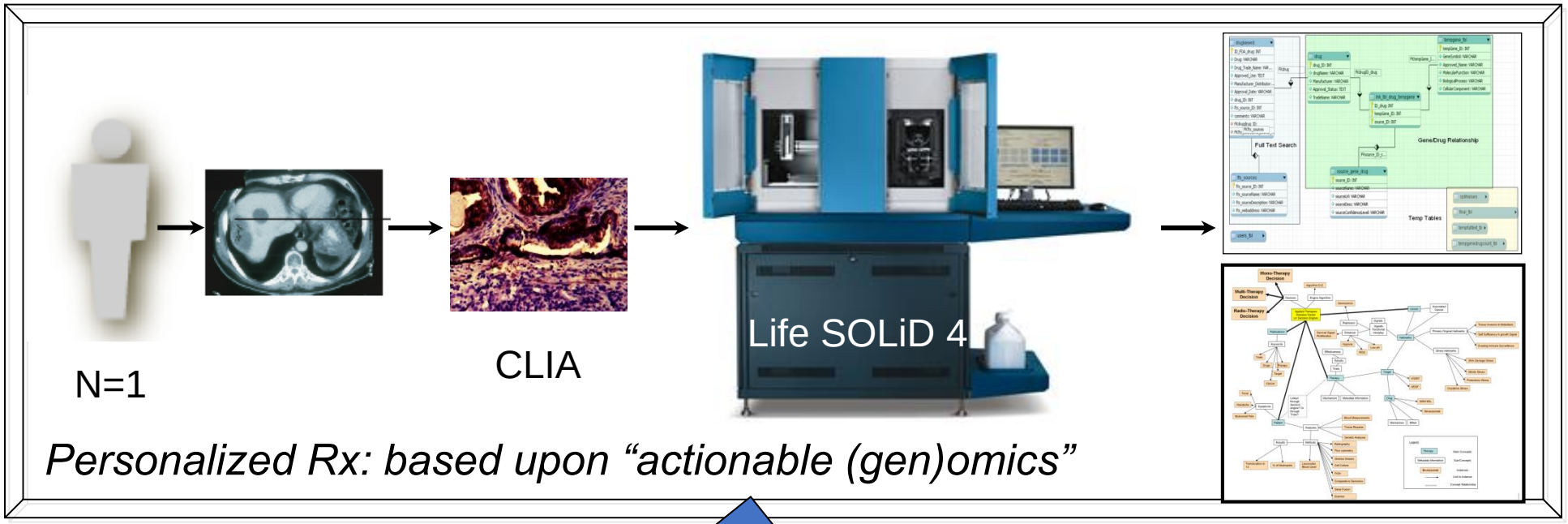
GENE FUSIONS

(>20% tumor content, select introns)
Sensitivity: >95%
PPV: >99%

COPY NUMBER ALTERATIONS

(>20% tumor content, zero or ≥8 copies)
Sensitivity: >95%
PPV: >99%

Identifying Therapeutic Targets on Next-generation DNA Sequencing of Cancer



Molecular Pathway Knowledge Mining

Integrated Analysis Tumor DNA/RNA and germline DNA

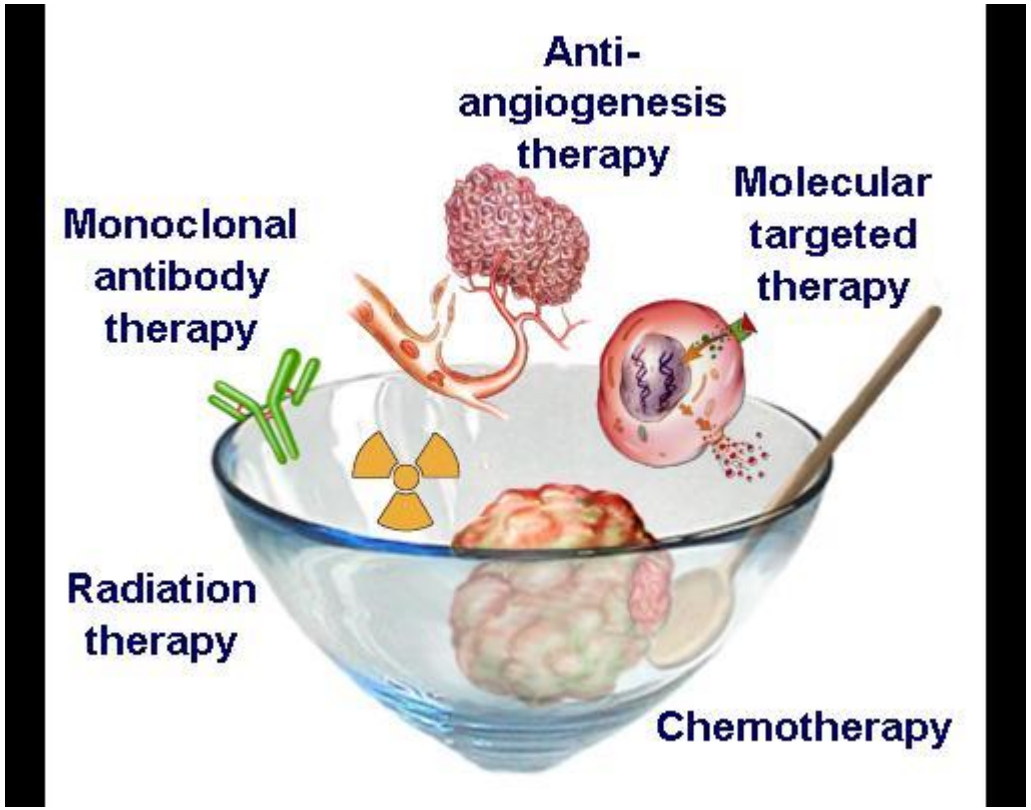
Individualized Therapy Decision Support System

CLIA validation

Clinically and Molecularly Appropriate Therapy

Multidisciplinary Genomics Rounds, Courtesy Dr. J. O’Shaughnessy

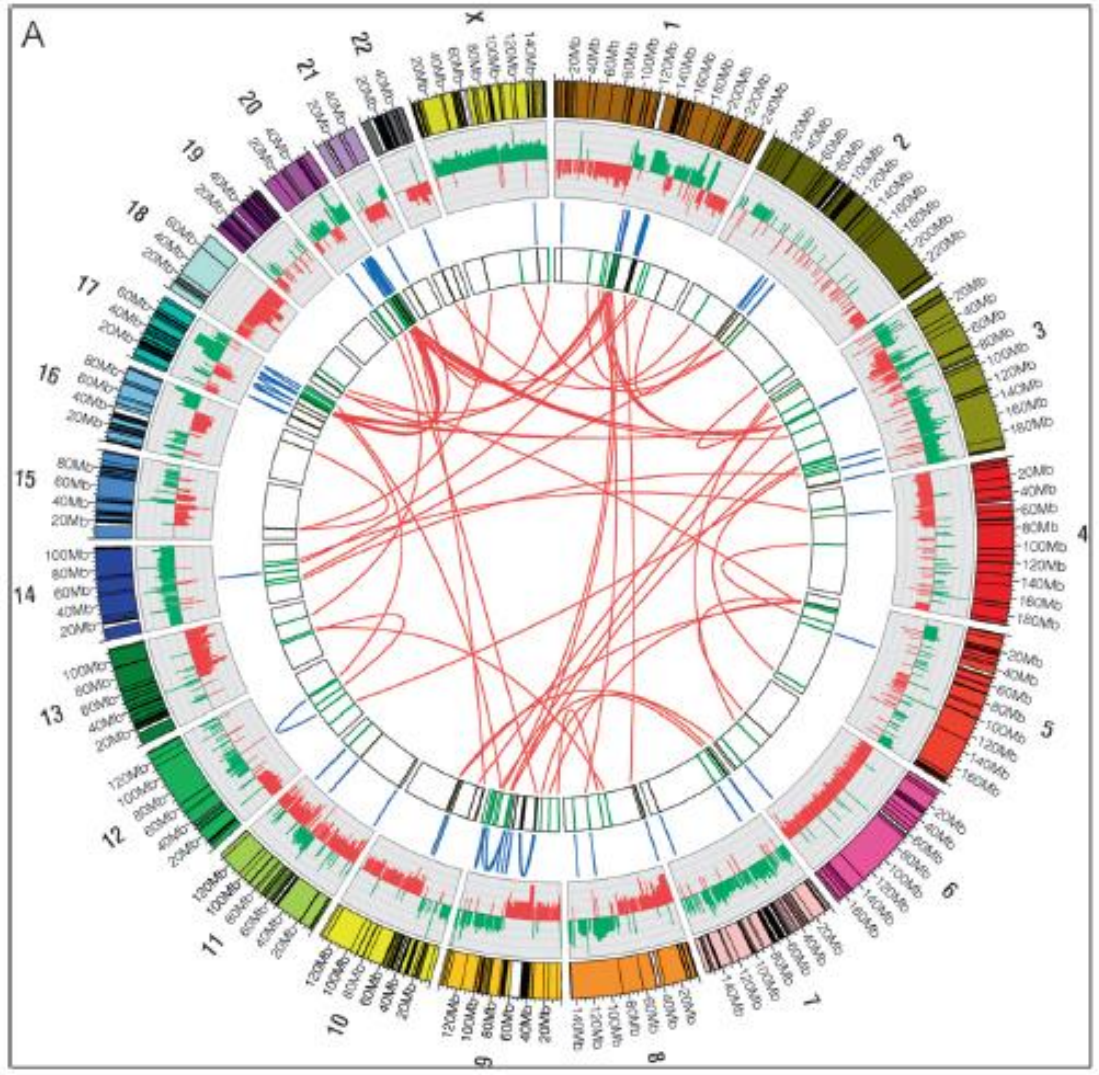
Targeted Therapy Cocktail



- Molecular diversity of tumors may require a combination of agents to maximize therapeutic benefit
- Future research should address best use of multi-targeted therapeutic approaches

Circos Plot of genomic chaos in a human breast cancer cell line

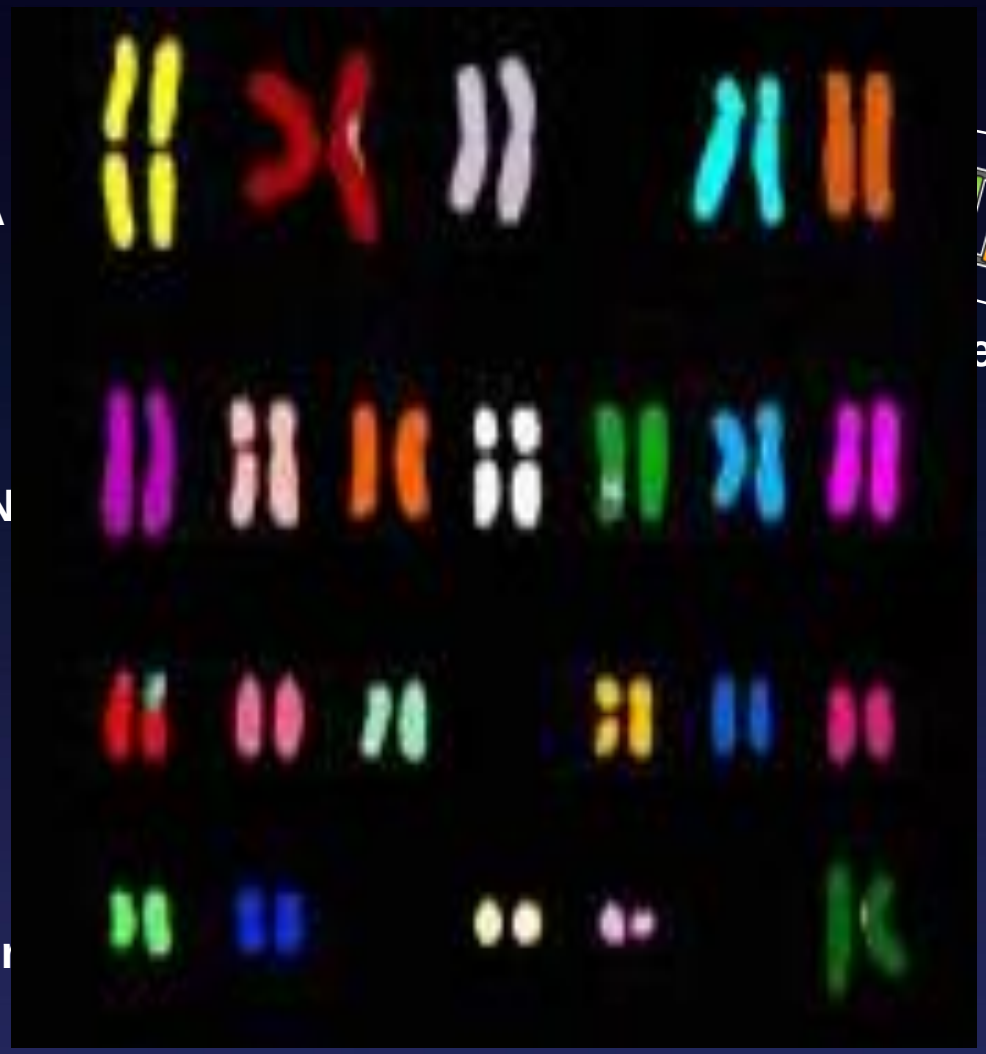
A sequence-level map of (MCF-7) human breast cancer cells reveals 157 different chromosomal breakpoints in a single breast cancer cell line!



Hampton, et al., Genome Res (29 Jan 2009)

The human genome is complex, yet highly organized

DNA



exon

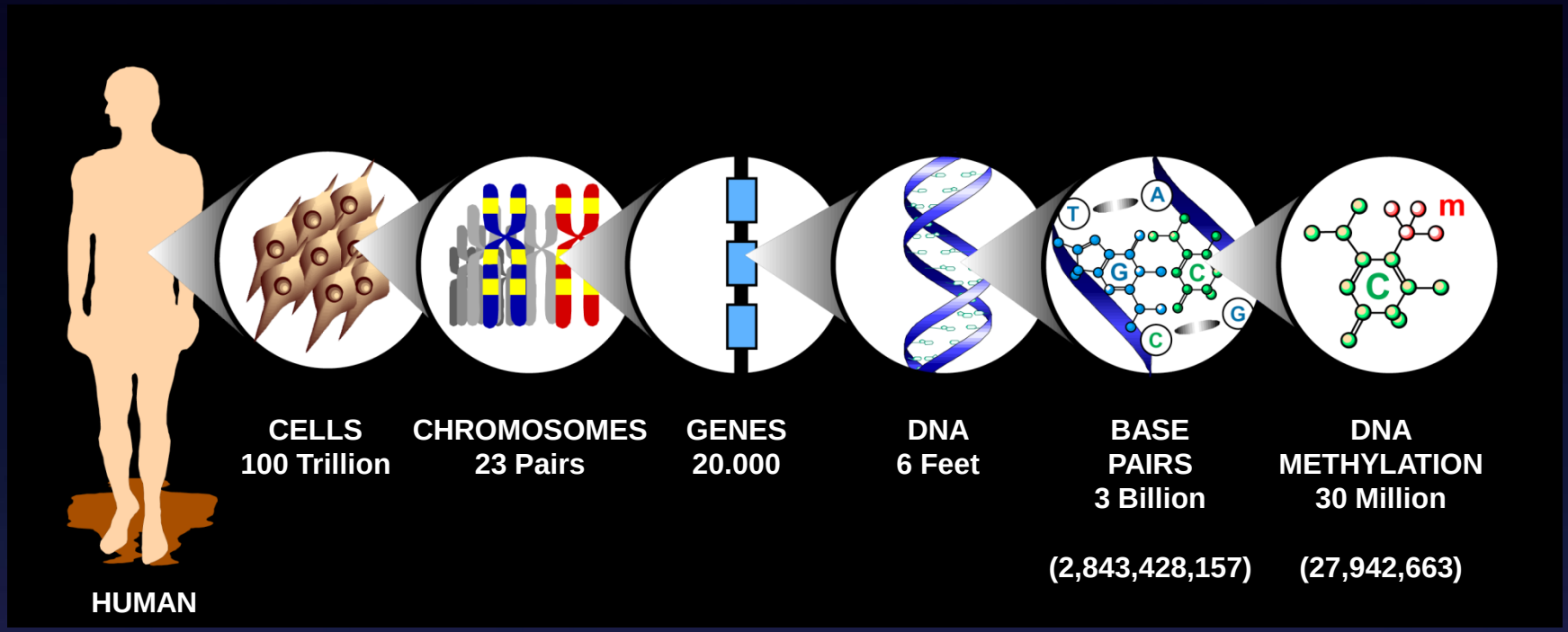
N

Chr

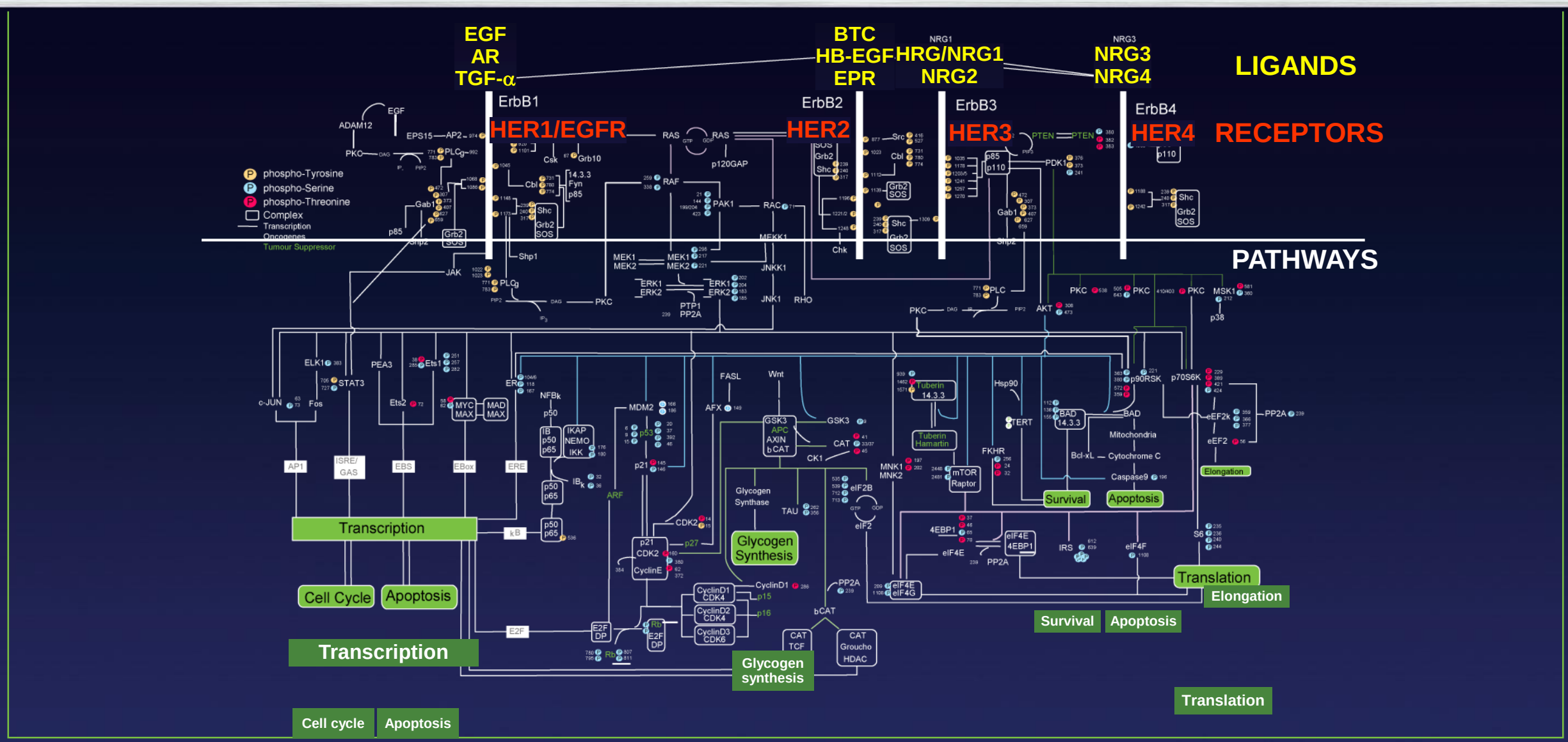
Normal human karyotype 46,XX

National Human Genome Research Institute. The National Institute of Health. 2007. Available at: http://www.genome.gov//Pages/Hyperion//DIR/VIP/Glossary/Illustration/sky.cfm. Accessed August 7, 2007.

Cells and Genes

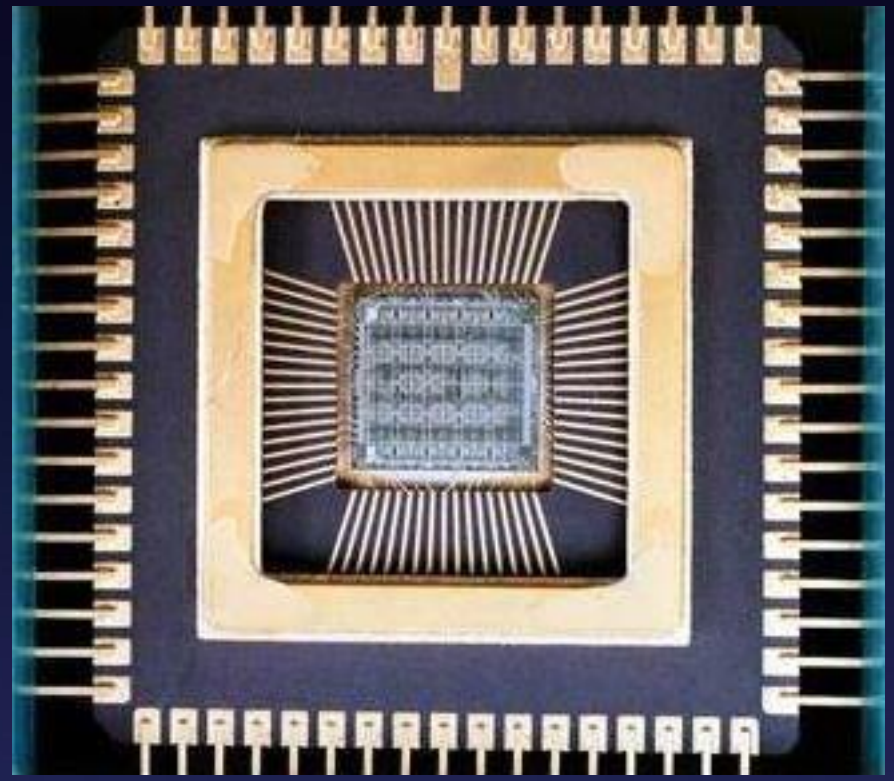


A clinical example: The Human Epidermal Growth Factor Receptor (HER) signaling network in breast cancer

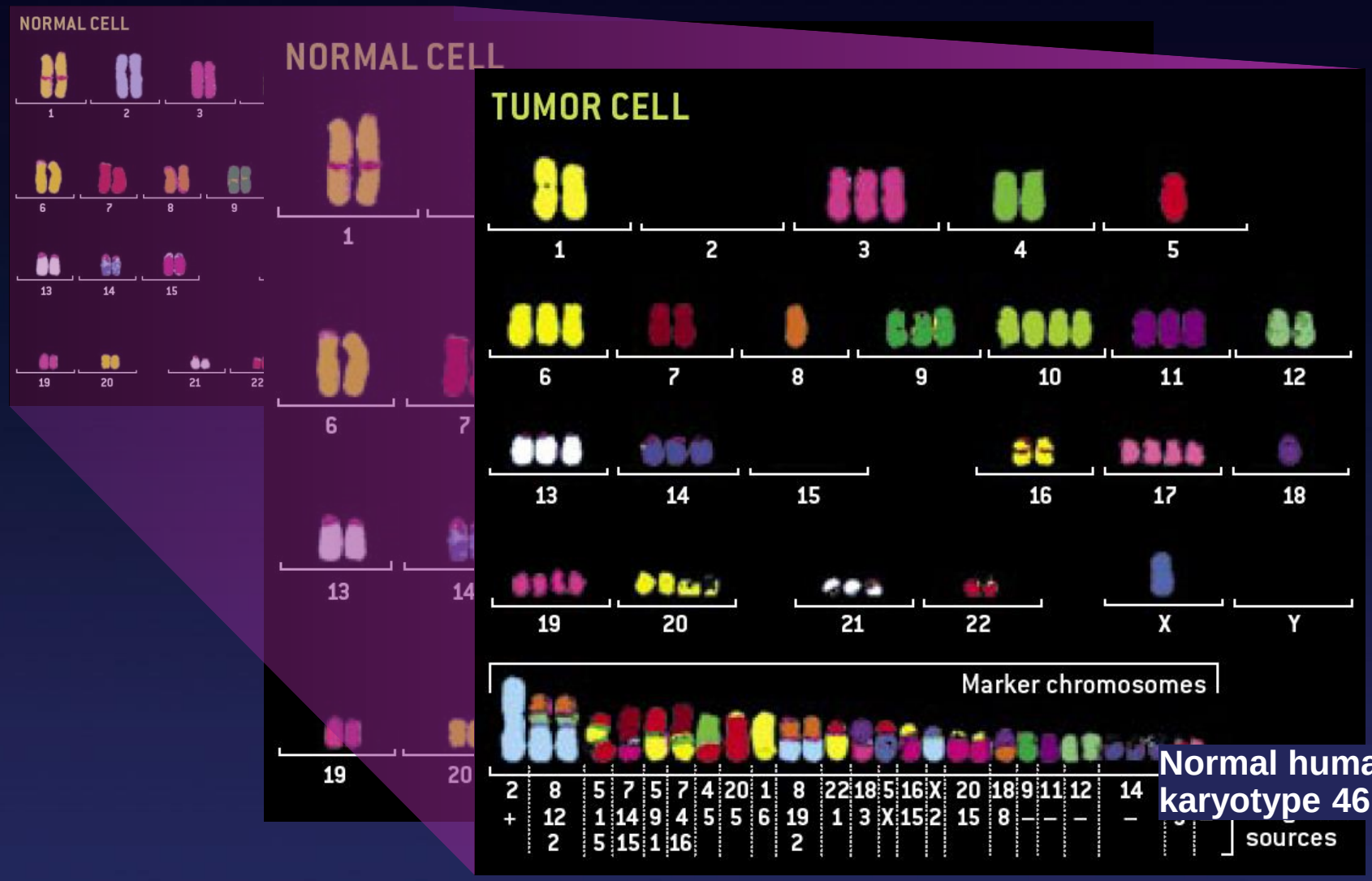


Adapted with permission from Richard Neve, M.D.
Citri A, Yosef Y. *Nat Rev Mol Cell Biol.* 2006;7:505-516.

Advantage of Signaling Networks in Biological Systems



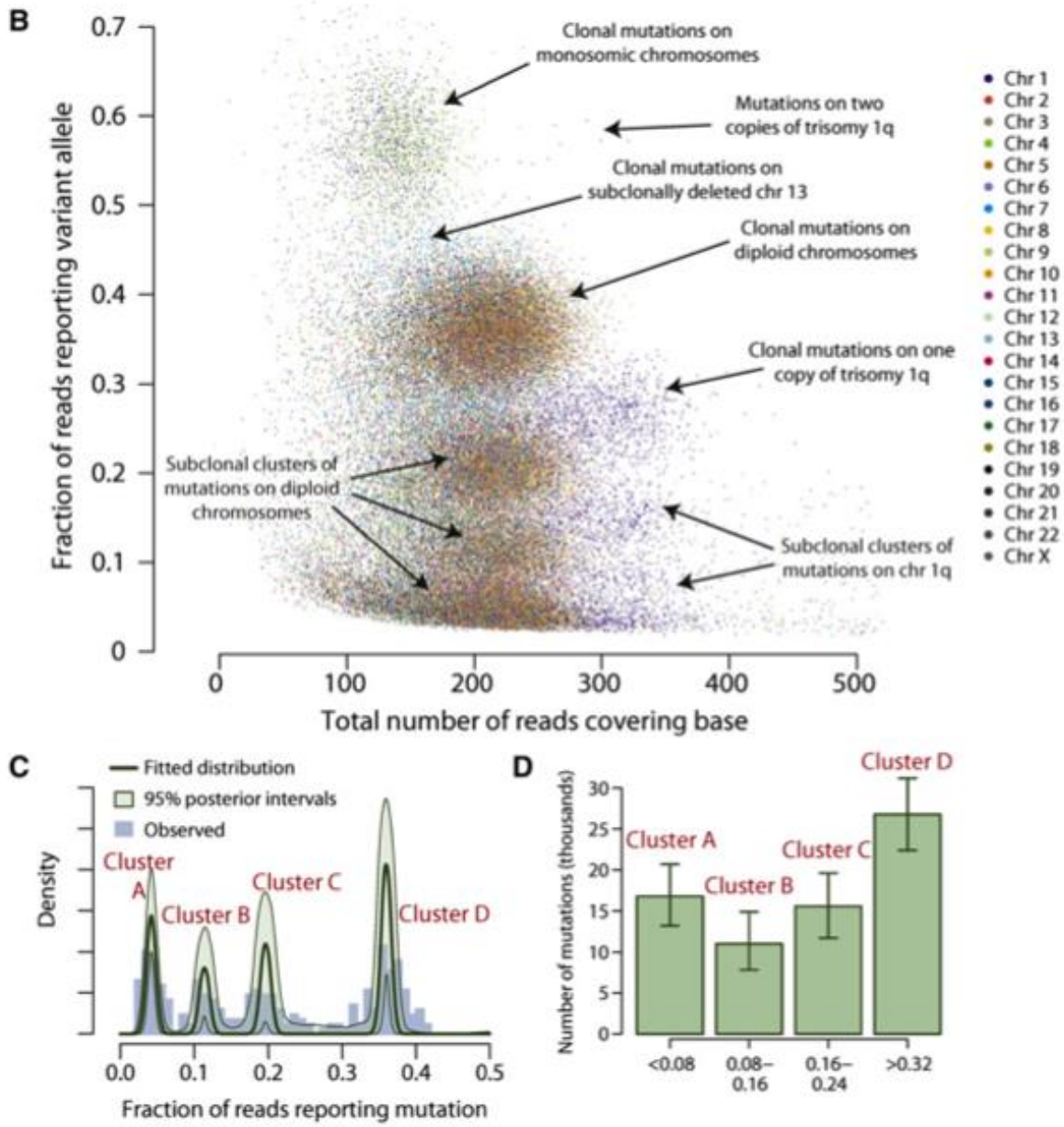
Certain genetic insults (mutations) generate oncogenes and loss of tumor suppressor genes



Duesberg P. *Sci Am*. 2007;296:52-59.

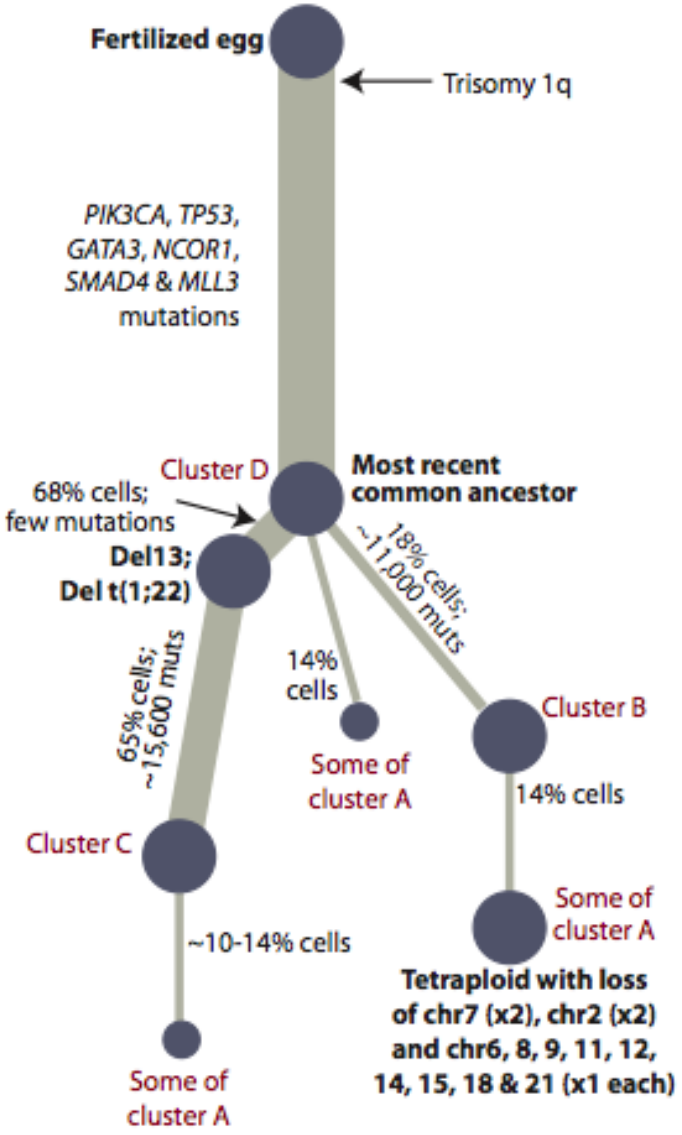

ATM

Genomic Architecture of PD4120a, a Breast Cancer Genome Sequenced to 188-Fold Coverage



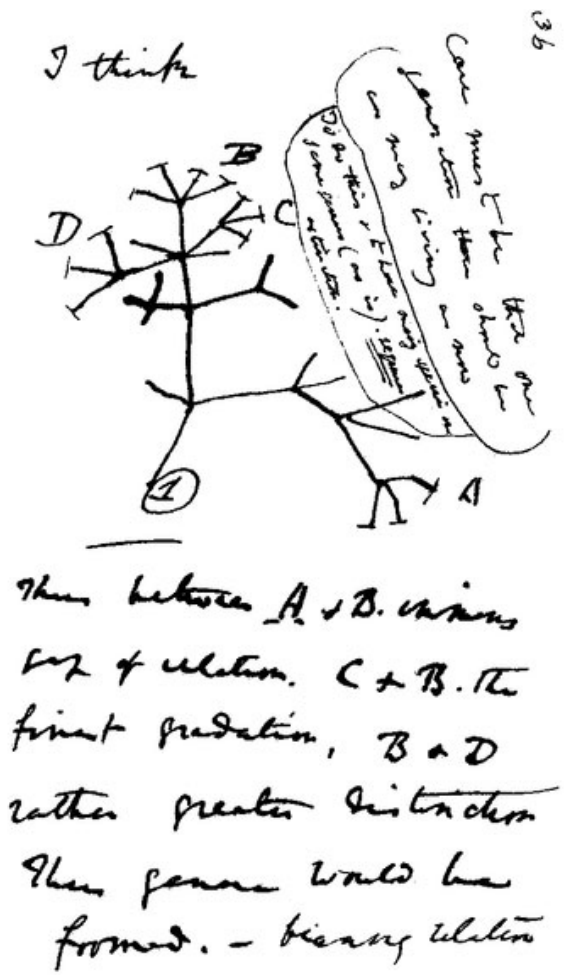
Nik-Zainal, et al., Cell *149,* 994–1007, May 25, 2012

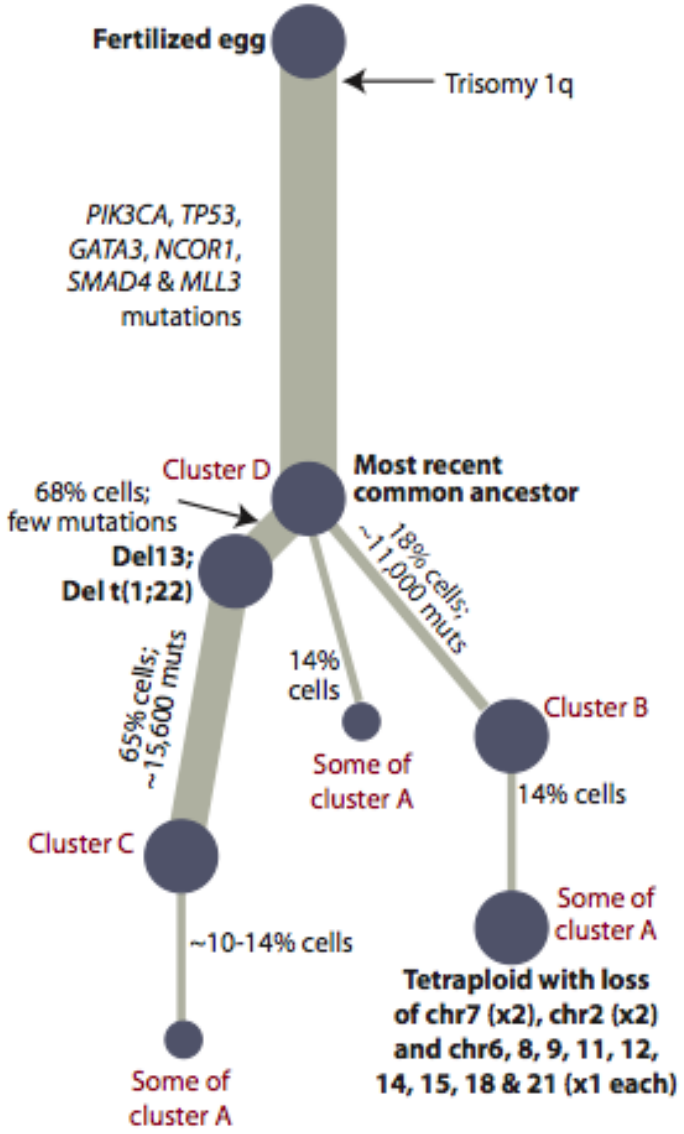
Genomic Architecture of PD4120a, a Breast Cancer Genome Sequenced to 188-Fold Coverage

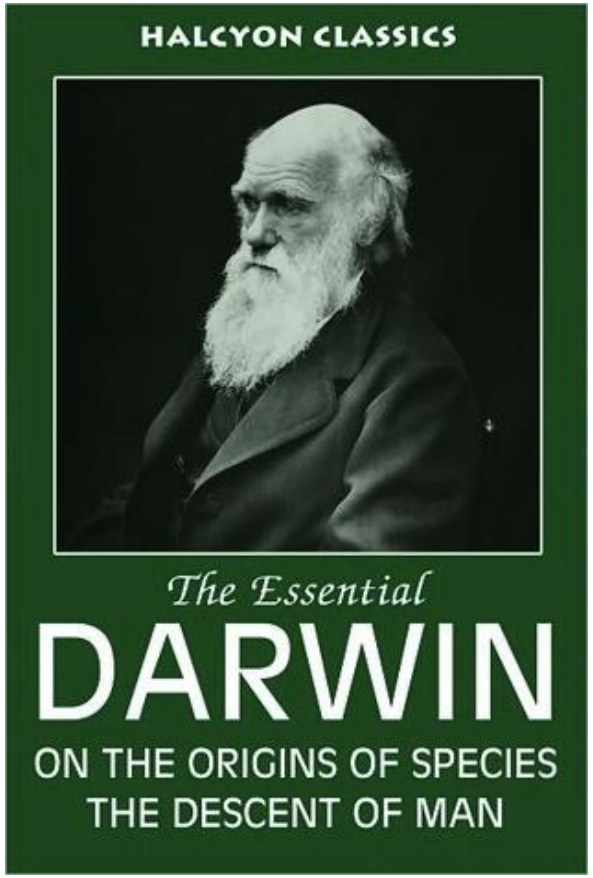


Nik-Zainal, et al.,
Cell *149,* 994–1007,
May 25, 2012

Genomic Architecture of PD4120a, a Breast Cancer Genome Sequenced to 188-Fold Coverage

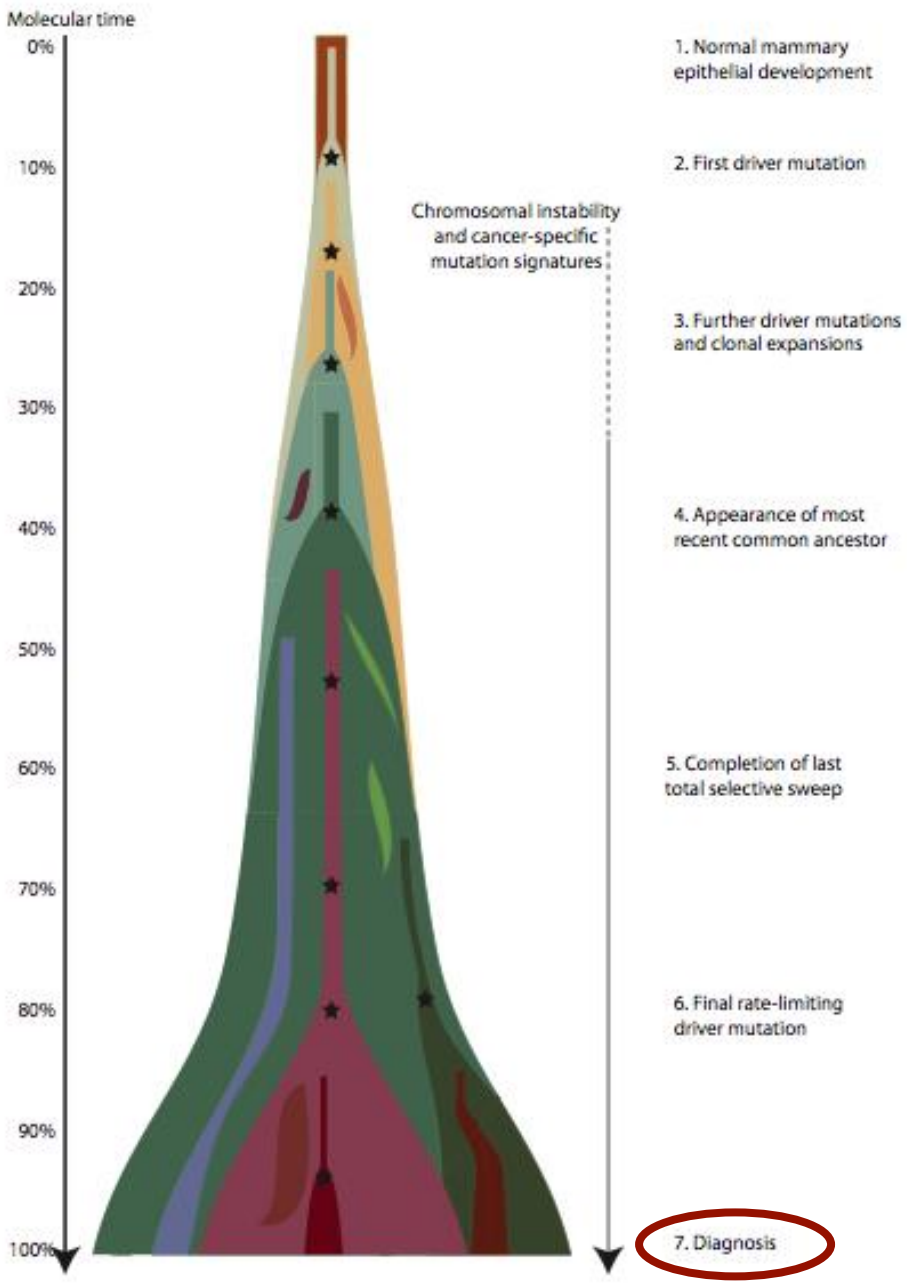




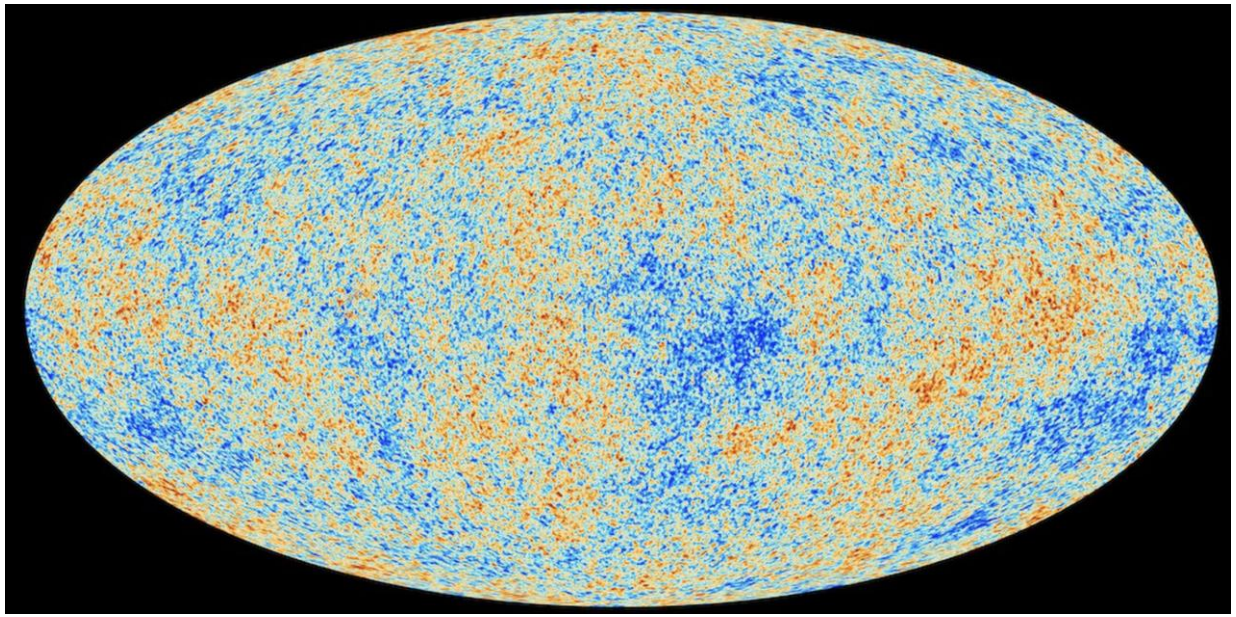


Nik-Zainal, et al.,
Cell *149,* 994–1007,
May 25, 2012

A Model for Breast Cancer Development over Molecular Time



The “Big Bang” Model of Tumor Evolution

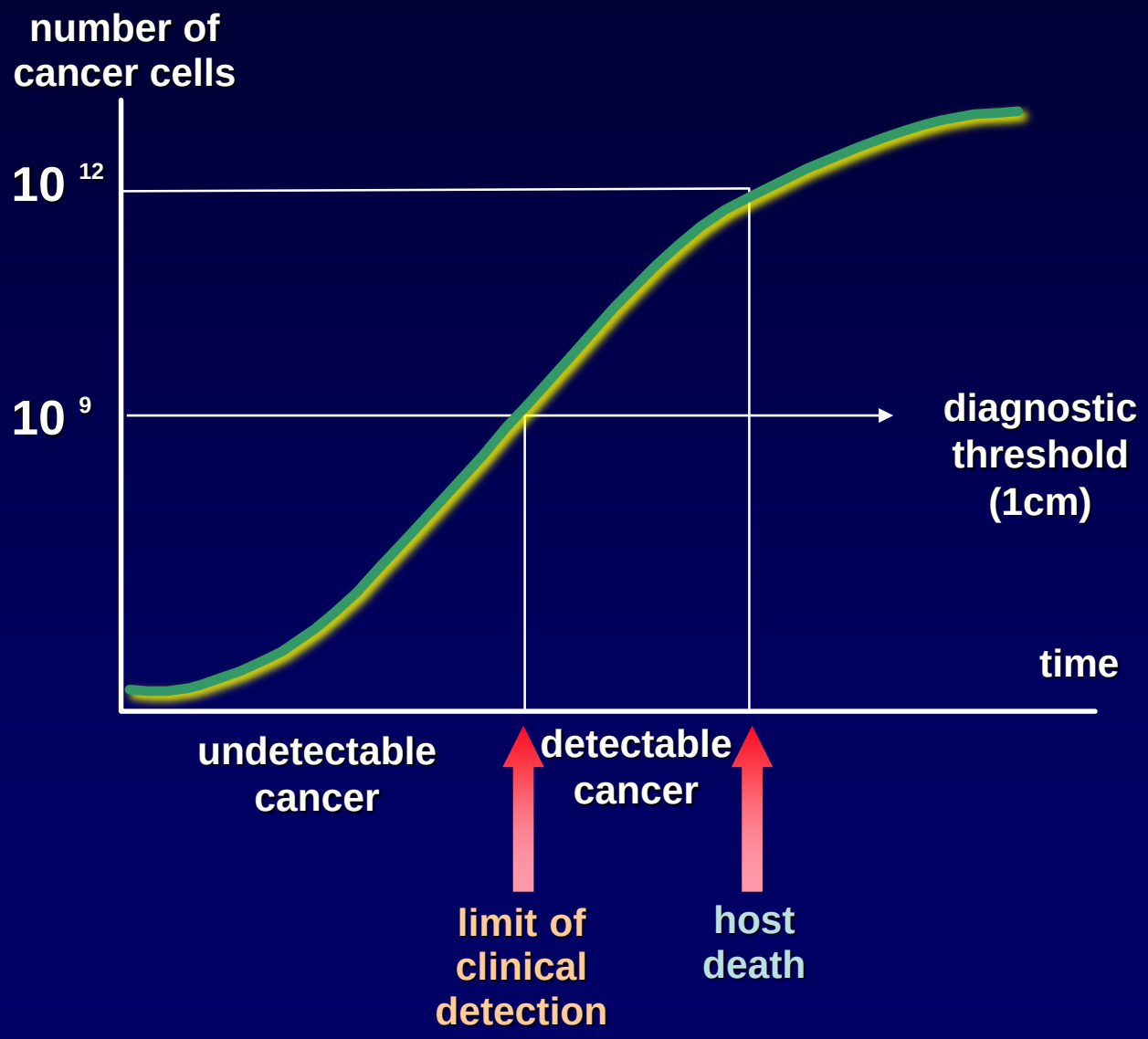


2013 map of cosmic background radiation left over from the Big Bang (discovered by accident in 1964 by American radio astronomers Arno Penzias and Robert Wilson, earning them the 1978 Nobel Prize in Physics)

-- *Taken by the ESA's Planck spacecraft, capturing the oldest light in the universe.*

Nik-Zainal, et al., Cell *149,* 994–1007, May 25, 2012

TUMOR GROWTH

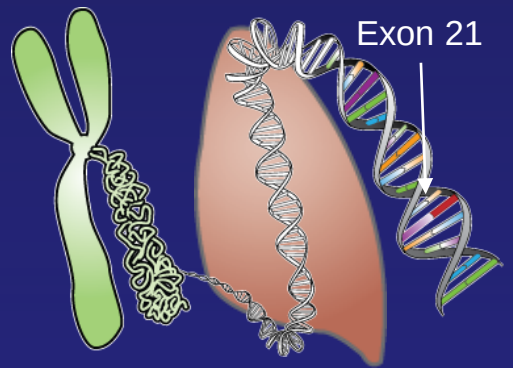


THEOREM: Gene mutations that drive carcinogenesis can be structurally classified and molecularly targeted with therapeutics

Targeted
Therapeutic
Drug = erlotinib

Lung cancer — single base pair mutation

Chromosome 7



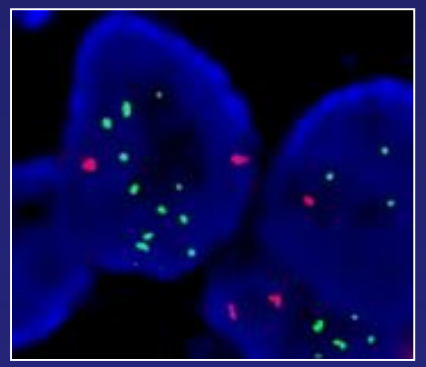
- Deletions
- Insertions
- Translocations

CML — translocation

Imatinib Targets
Abl kinase

Trastuzumab
(Herceptin)
Targets HER2
Gene amplification

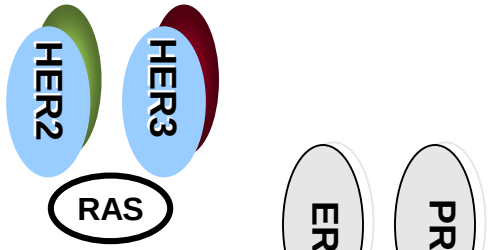
HER2 amplification: Chromosome 17



The Cancer Genome Atlas (TCGA). The National Cancer Institute. 2007.
Available at: http://cancergenome.nih.gov/media/images.asp. Accessed July 18, 2007.

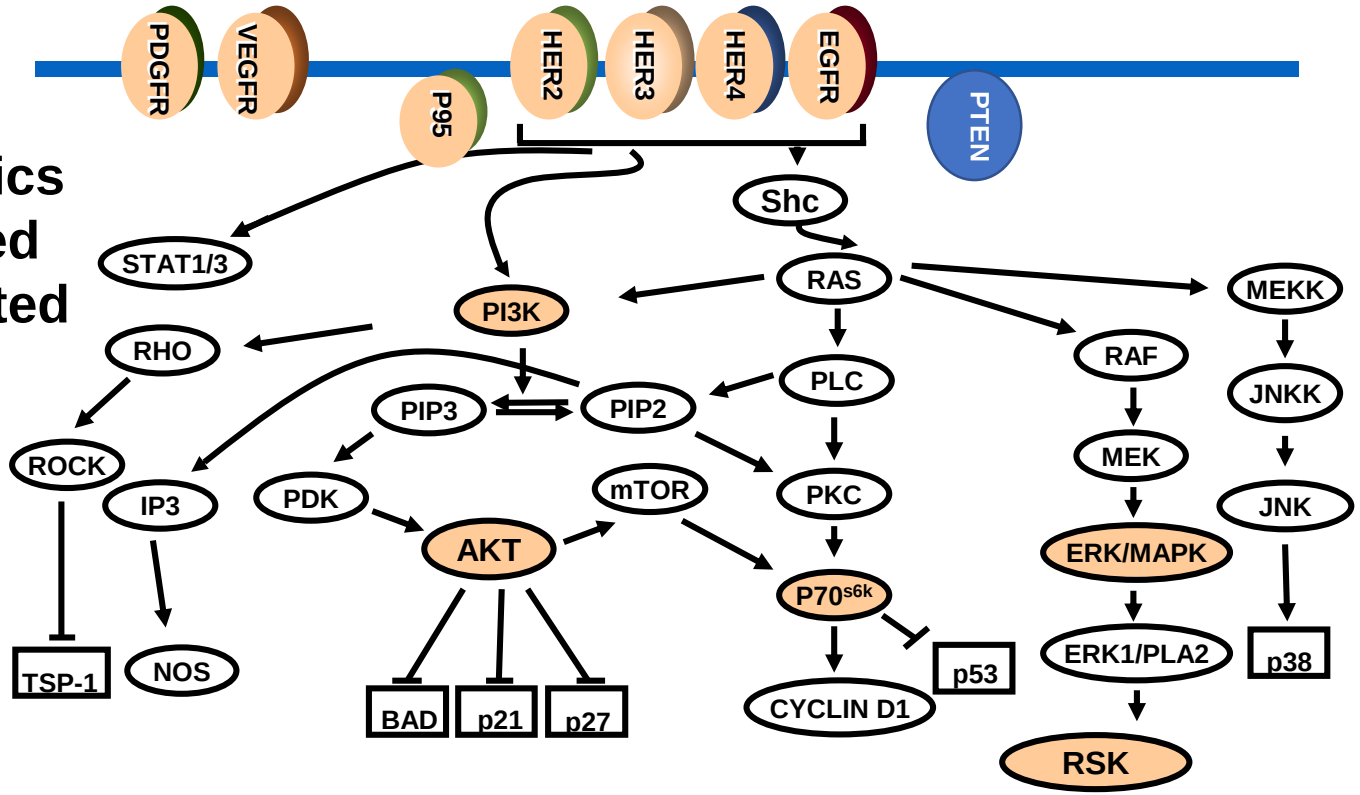
Challenge of "Relevant" Information

What we know today:

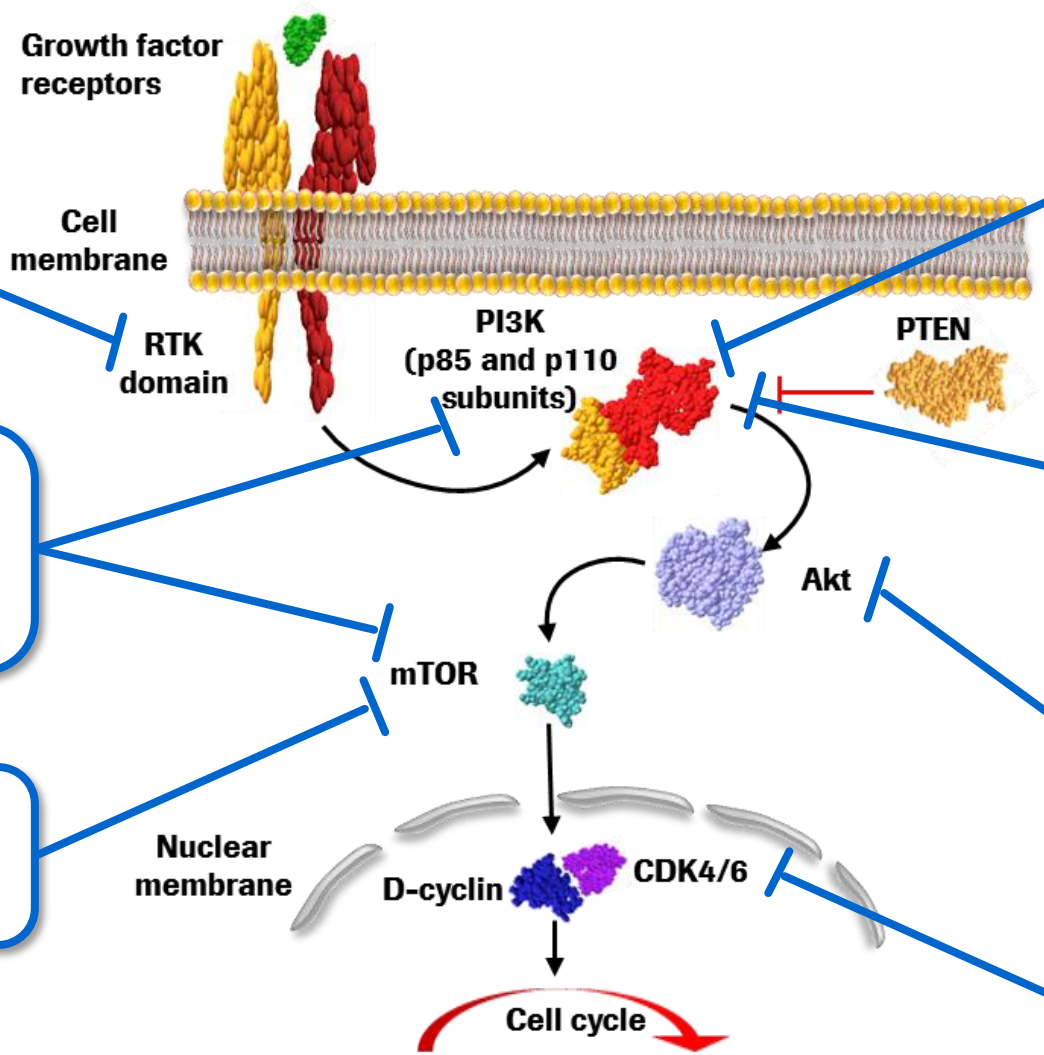


What we should know:

COROLLARY:
Companion diagnostics are frequently required for molecularly-targeted therapeutics



Example: The PI3K-AKT-mTOR Pathway is Under Investigation as a Potential Target



Lapatinib
Trastuzumab
Pertuzumab

PI3K/mTOR inhibitors[1–3]
Apitolisib
LY3023414
Gedatolisib

mTOR inhibitor[1,2]
Everolimus
Vistusertib

Pan-PI3K inhibitors[1]
Buparlisib
Pictilisib
Pilaralisib
PX-866

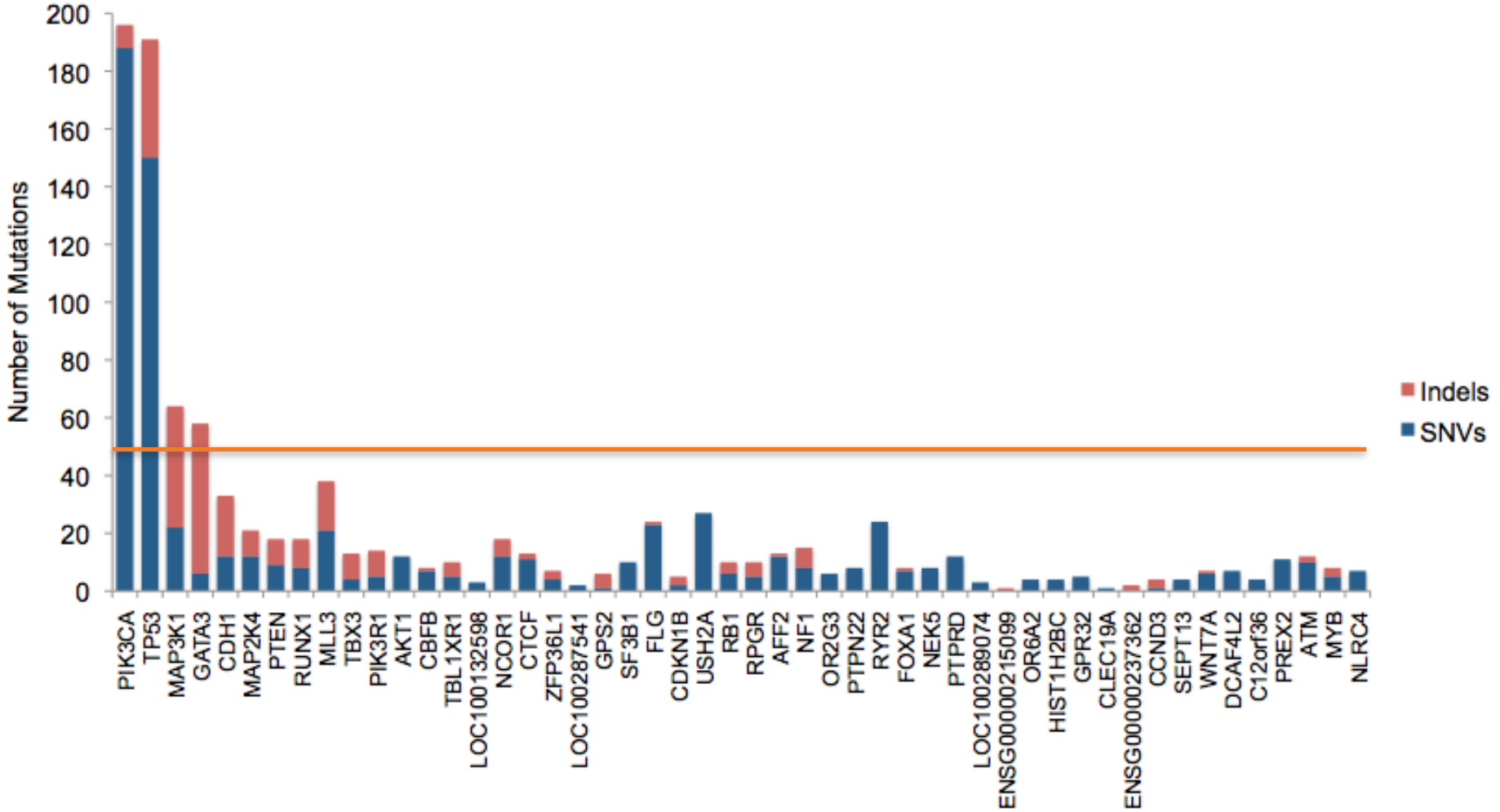
Selective PI3K inhibitors[1]
Alpelisib (α-specific)
Taselisib (β-sparing)
GDC-007 (α-specific)
MLN01117 (α-specific)
GSK2636771 (b-specific)
AZD8186 (b-specific)
IPI-549 (g-specific)

Akt inhibitors[1–3,5]
MK-2206
Ipatasertib
AZD5363

CDK4/6 inhibitors[1,3]
Palbociclib
Abemaciclib
Ribociclib

1. Janku F. Can Treat Rev. 2017; 2. Rodon J, et al. Nat Rev Clin Oncol 2013;
3. Ciruelos Gil EM. Cancer Treat Rev 2014; 4. National Cancer Institute;
5. Addie M, et al. J Med Chem 2013; 6. Martini M, et al. Front Oncol 2013.

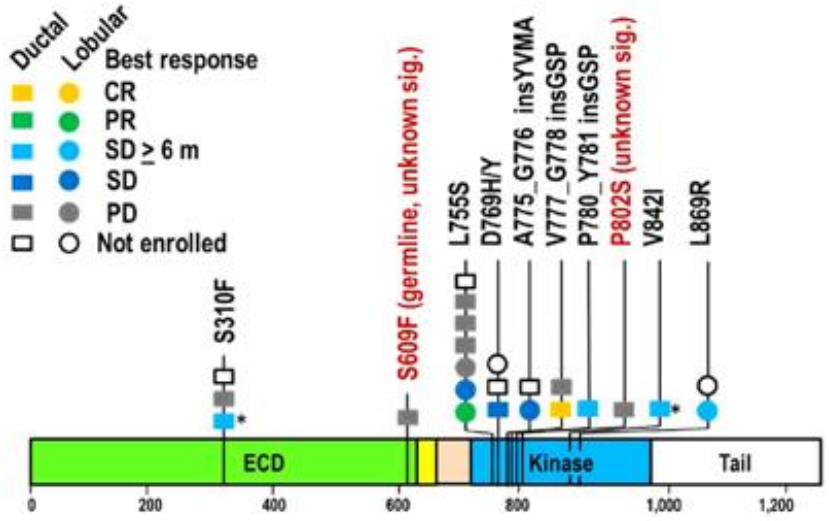
TCGA Significantly Mutated Genes in Breast Cancer (First 507 Cases)



SMGs with FDR<0.15 by at least two tests (Fisher's, LR, or Convolution)

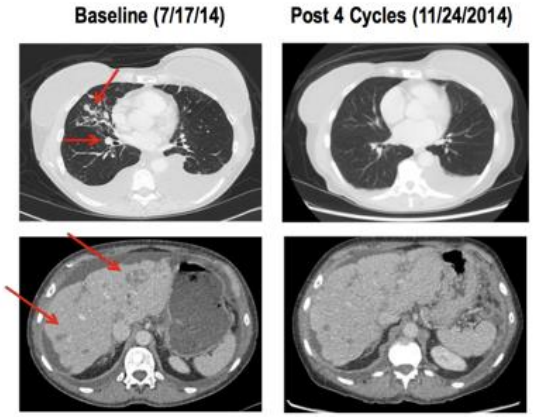
Cancer Genome Atlas Network. Nature. 2012 Oct 4;490(7418):61-70.

Neratinib Efficacy and Circulating Tumor DNA Detection of HER2 Mutations* in HER2 Non-amplified Metastatic Breast Cancer



*Concurrent in the same patient

Example: *HER2* Mutations in *HER2* non-amplified breast cancer (5/309 = 1.6%)



Cynthia X. Ma et al. Clin Cancer Res 2017;23:5687-5695

Number Needed to Study (NNS): HER2 Mutation

- NNS = $\frac{1}{(\%\ \text{biomarker-positive} \times \text{fraction trial-eligible} \times \text{fraction giving informed consent})}$

Example:

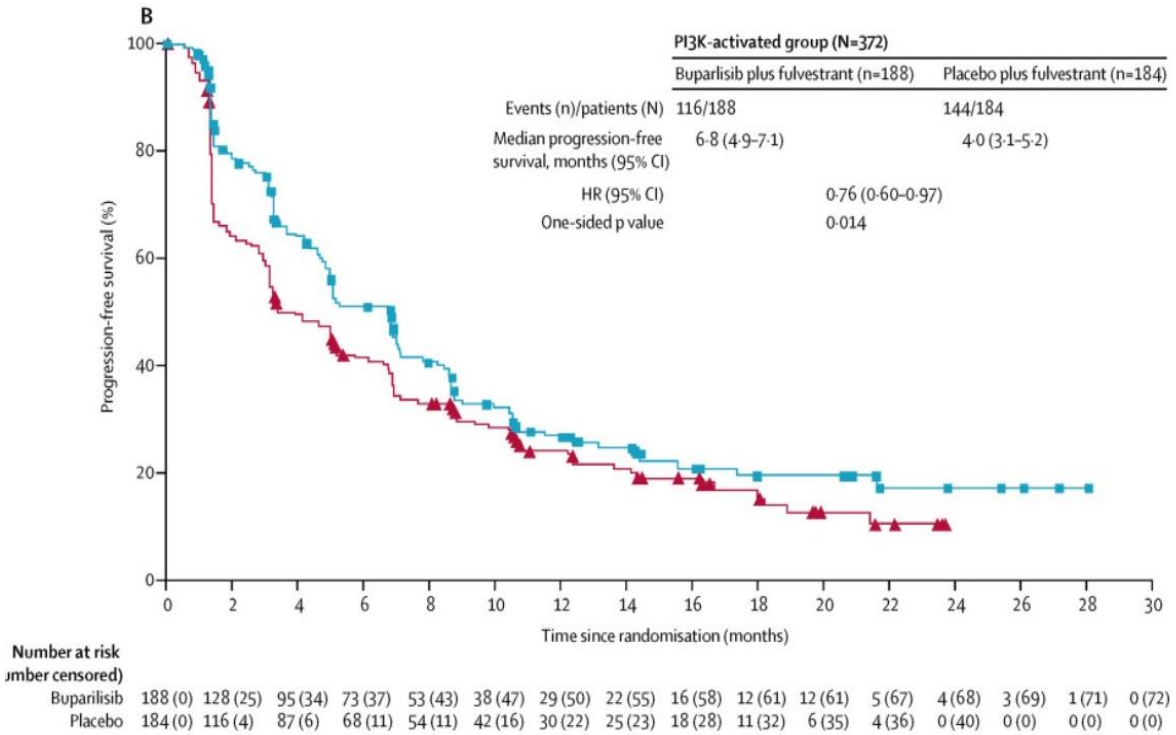
HER2 = 1/(0.02 X 0.5 X 0.8) = .008

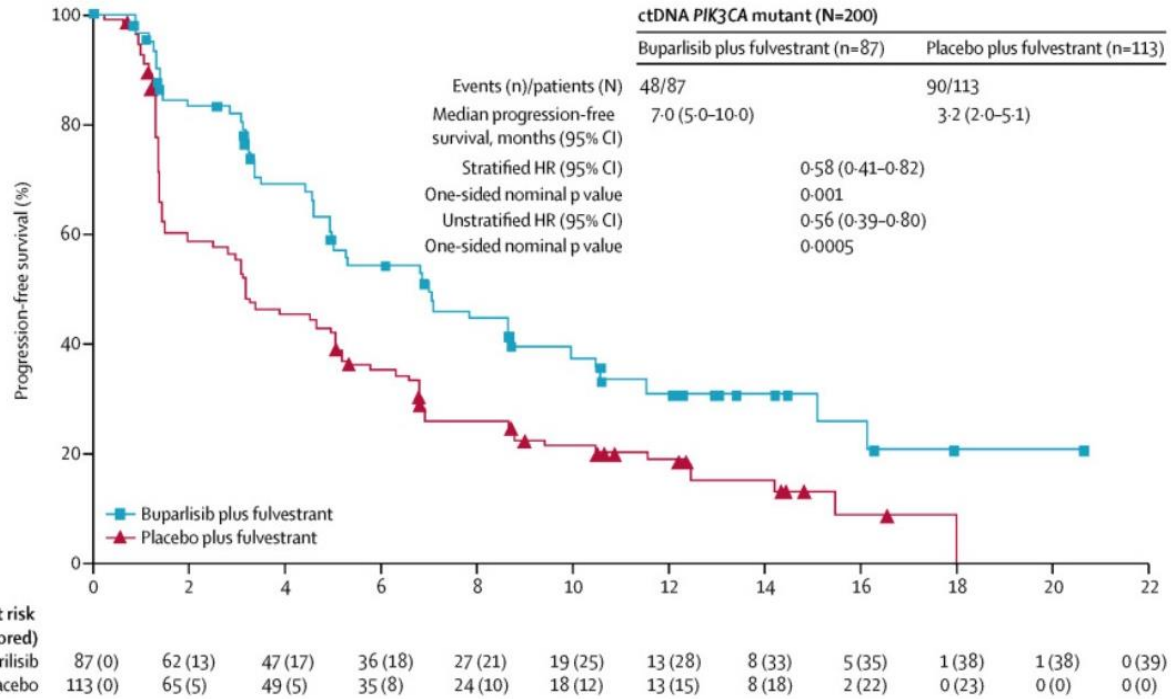
= ~125 patients screened/patient studied

G Sledge, personal communication, 2013

ctDNA Analysis of PI3K Status May be More Predictive than Archival Tissue

Overall concordance of PIK3CA status in tumour tissue and ctDNA was 342 (77%) of 446*



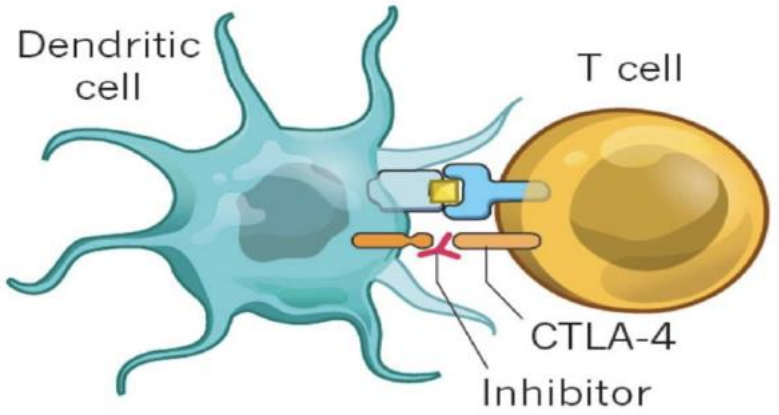


***In 307 patients with PIK3CA wild-type tumour tissue, 243 (79%) had non-mutant ctDNA, and 64 (21%) had PIK3CA mutant ctDNA, potentially indicating tumour evolution between initial diagnosis and treatment.**

Baselga J, et al. *Lancet Oncol*. 2017

The Nobel Prize in Physiology or Medicine 2018: Releasing the CTLA-4 brake on T-cells

Jim Allison
M.D. Anderson

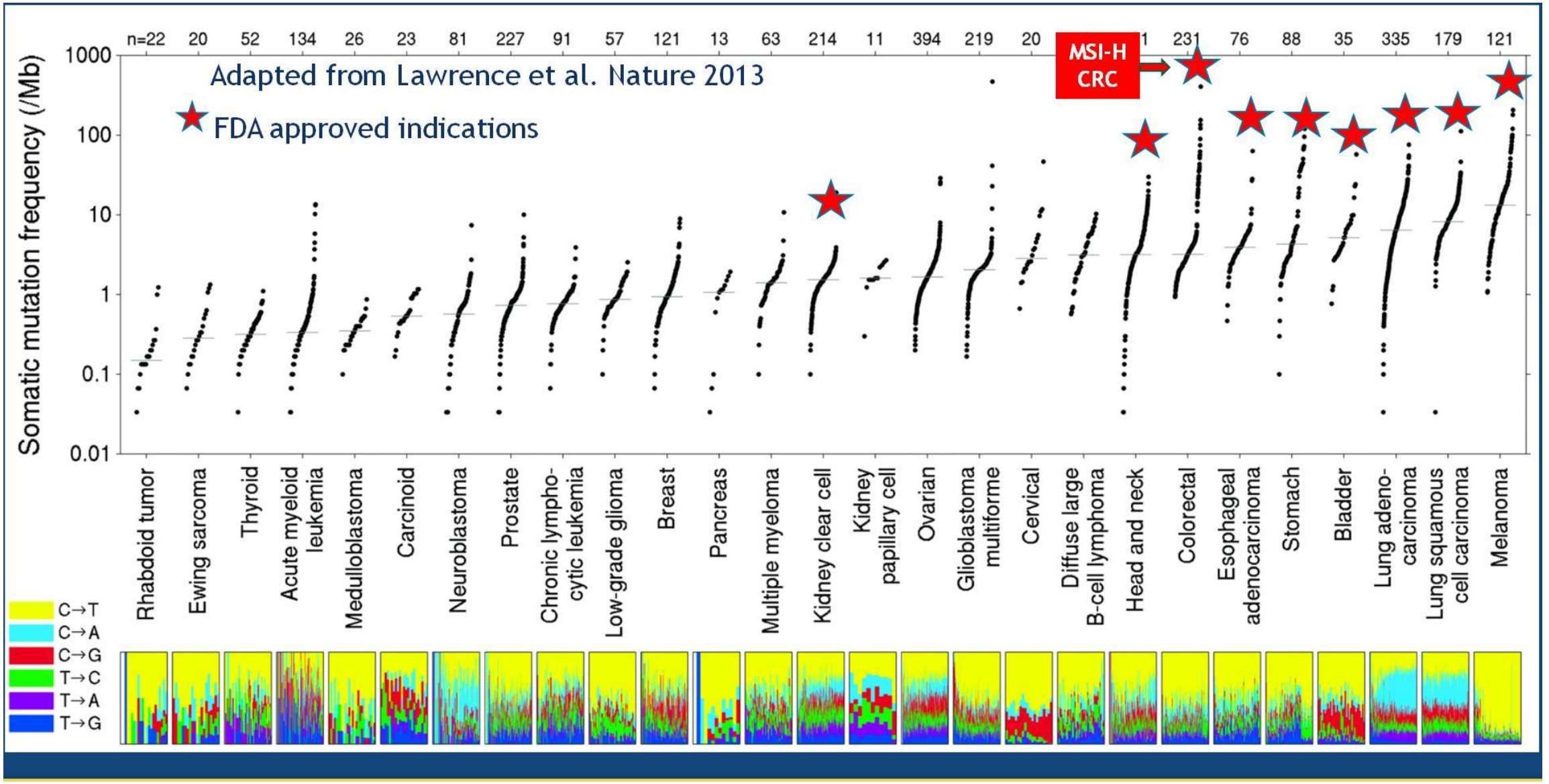


The CTLA-4 checkpoint protein prevents dendritic cells from priming T cells to recognize tumours. Inhibitor drugs block the checkpoint.

Brunet , ..., Golstein, Nature 1978:
A new member of the immunoglobulin superfamily – CTLA-4

Ledford H. Nature. 2014;508(7494):24-6.

MSI and TMB in FDA-Approved Indications for Immune Checkpoint Inhibitors



Who is a Candidate for Personalized Oncology?

Key questions….

- **What is the probability of finding “actionable” mutations for the patient’s cancer? (But remember, "actionable” does not guarantee tumor response!)**
- **What is the allele frequency of the mutation? (100%?, <10%?)**
- **Is there a publication (or abstract presentation) track record?**
- **Is there a drug source for expected mutations? (commercial, approved? experimental? compassionate use?)**
- **Are there other effective treatment options already available?**
- **Are the patient’s medical condition and laboratory parameters consistent with proposed treatment?**
- **What is the patient’s performance status?**

Table 1. The ECOG scoring system versus the Karnofsky scoring system

ECOG/WHO/Zubrod score		Karnofsky score	
Fully active, no restrictions	0	Normal, no evidence of disease Able to perform normal activity with only minor symptoms	100 90
Restricted in strenuous activity Ambulatory, can carry out work	1	Normal activity with effort Able to care for self but unable to do normal activities	80 70
Ambulatory >50% of the time Capable of self-care Unable to work/usual activities	2	Requires occasional assistance, cares for most needs Requires considerable assistance	60 50
Ambulatory ≤50% of the time Capable of limited self-care only	3	Disabled, requires special assistance Severely disabled	40 30
Disabled, no self-care Confined to bed or chair	4	Very sick, requires active support Moribund	20 10

ECOG = Eastern Cooperative Oncology Group; WHO = World Health Organization

Conventional Diagnostics

Molecular/Genomic Diagnostics

very sophisticated, ultra sensitive/specific, expensive $$

How do we get there?…

Conclusions

- Cancer is a disease of the genes, resulting from acquired sporadic mutation(s), leading to highly heterogeneous tumors at diagnosis.
- Therapeutic strategies targeting driver mutations can result in clinically meaningful and durable responses – even cure
- Identification of new molecular targets in clinical practice requires a major shift in focus to large diagnostic *screening* campaigns
- Complexity, heterogeneity and genomic chaos are actually *favorable* characteristics for response to immunotherapeutic approaches
- The marrying of clinical and genomic data will drive a new wave of discovery and improve outcomes for patients with cancer
- There is no more exciting time than now to be involved in cancer genomics and translational research

Questions/Comments
Discussion

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Stanford Bio-X Program:
Biology, Medicine, Chemistry,
Physics and Engineering