Next-Generation Sequencing in Personalized Medicine

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Senior Manager, Medical Affairs
In vitro Diagnostics (IVD), Illumina, Inc.

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Disclosures

- I am an employee of Illumina, Inc. and declare stock ownership in the company.
- Some of the genomic testing applications mentioned herein are not available as commercial products and/or do not have marketing authorization in all countries.

Our Background

Leading Innovation Regionally and Around the Globe

- Founded Fall 1998
  - IPO July 27, 2000
- Headquartered in San Diego, CA
  - 1.2M square ft. in 7 countries
  - >3,200 employees
  - 13 offices around the world
  - 65% of employee base in California

AWARDS

MIT Technology Review

50 Disruptive Companies
2010, 2013

Smartest Company
2014

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Dawn of the Genomic Medicine Era

First FDA Clearance of a Next-Gen Sequencing Platform (Nov, 2013)

U.S. Food and Drug Administration
Protecting and Promoting *Your* Health

The FDA's review of the MiSeqDx… provides clinical laboratories with information about the expected performance of the device and the quality of the results. This information was not previously available for next generation sequencers. With this platform, labs can develop tests for clinical use with greater confidence.

Alberto Gutierrez, FDA (OIVD)

The NEW ENGLAND JOURNAL of MEDICINE

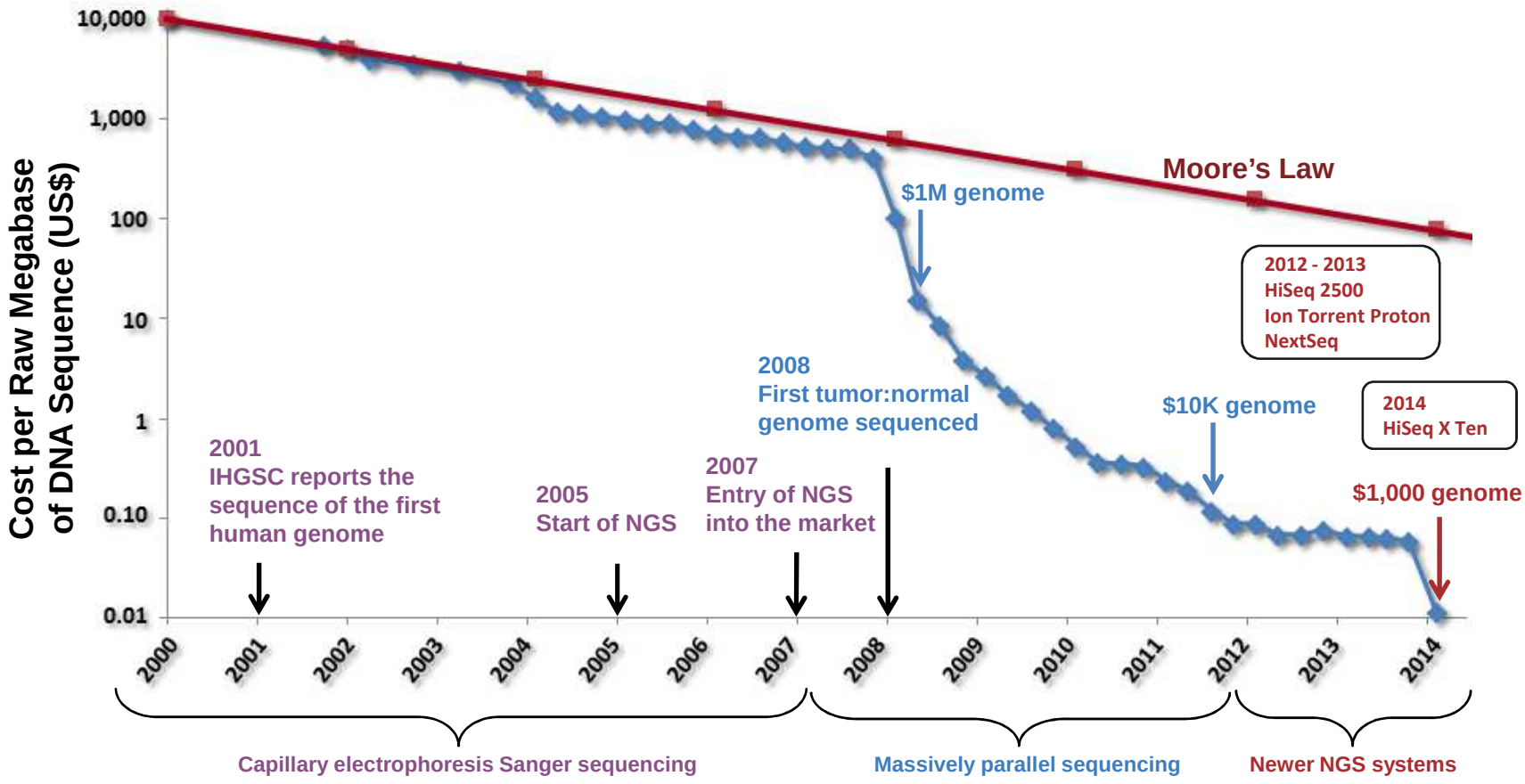
The marketing authorization for the first next-gen genome sequencer represents a significant step forward in the ability to generate genomic information that will ultimately improve patient care... this marketing authorization of a non-disease-specific platform will allow any lab to test any sequence for any purpose.

Francis Collins, NIH Director & Margaret Hamburg, FDA Commissioner

Gutierrez, A. FDA clears next-generation sequencer for routine medical care. NHGRI. Nov 20, 2013.
Hamburg, M. & Collins, F. S. First FDA Authorization for Next-Generation Sequencer. N. Engl. J. Med. 1–3 (2013).

Genomic Era of Medicine

NGS continues to drive down the cost of sequencing



2005	2006	2007	2008	2009	2010	2011
454 pyrosequencing GS-20	Solexa/Illumina sequencer	ABI/SOLiD sequencer	Helicos BioSciences	Illumina GAIIX, SOLiD 3.0	Illumina HiSeq 2000 Oxford Nanopore	Ion Torrent PGM PacBio RS Illumina MiSeq

Adapted from: MacConaill LE. Existing and emerging technologies for tumor genomic profiling. *Journal of Clinical Oncology*, 31(15), 1815-1824 (2013).

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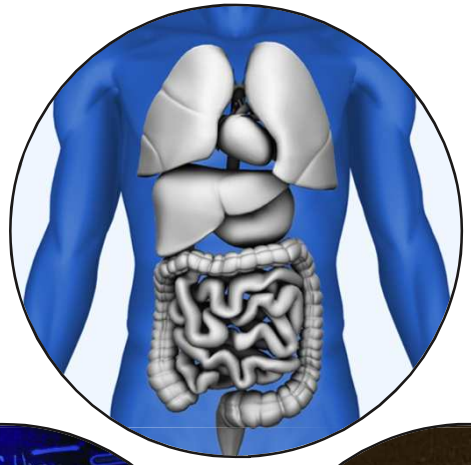
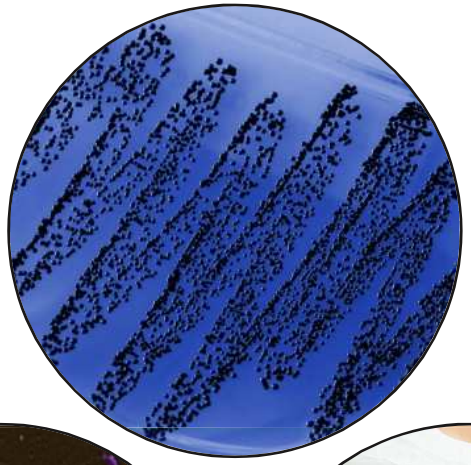
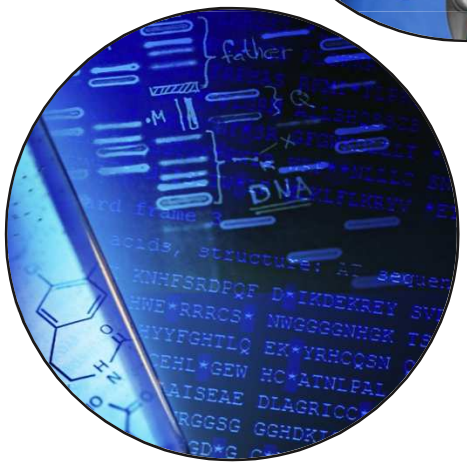
Applications of Genomic Testing in Medicine

Transplant Medicine

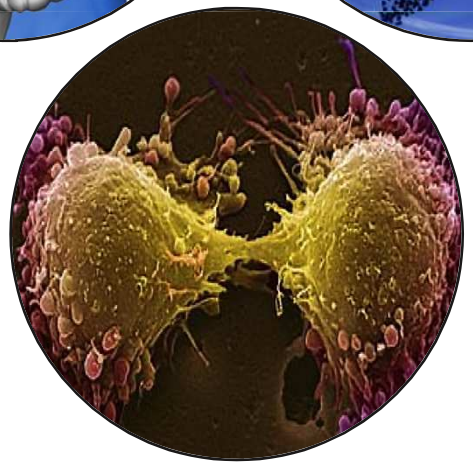


Microbiology





Inherited Disease



Cancer

Reproductive Health

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Applications of Genomic Testing in Medicine

Cancer

A New Taxonomy of Cancer

From organs to molecules

→ Genomics and the Future of Cancer Treatment

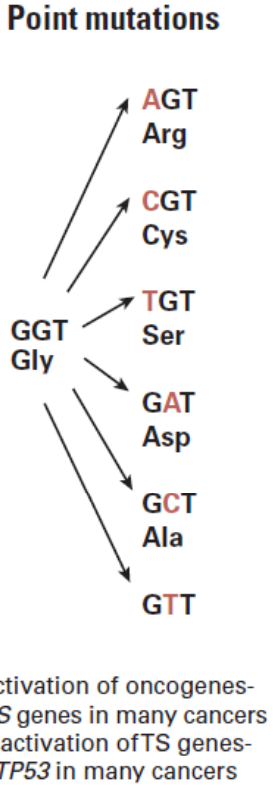
According to the President of the Dana Farber Cancer Institute, we may soon look at the concept of "organ-based" cancer types as ancient history.

- For more than a century, cancers have been **classified by the organ or tissue** – *with therapies geared to those specific areas*
- As more is learned about the basic biological processes in cancers, a new perspective has emerged
- The shift from an organ-focused to a ***gene-focused approach*** to cancer is already having a profound effect on the way cancer is treated

Interview with Edward J. Benz, Jr., MD
www.standup2cancer.org/innovations_in_science/view/genomics_and_the_future_of_cancer_treatment

Genomic Alterations in Cancer

Major classes



Activation of oncogenes-
RAS genes in many cancers
Inactivation ofTS genes-
TP53 in many cancers

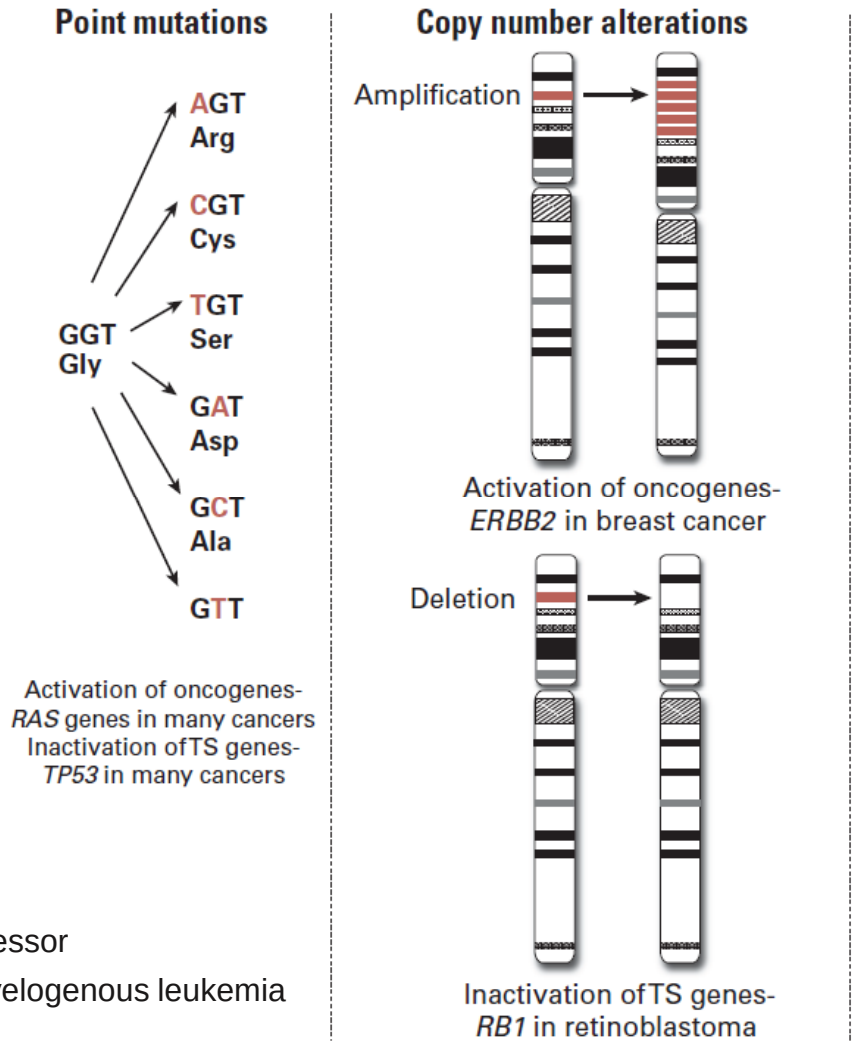
TS, tumor suppressor

CML, chronic myelogenous leukemia

Macconaill LE, Garraway LA. Clinical implications of the cancer genome. Journal of Clinical Oncology, 28(35), 5219-5228 (2010).

Genomic Alterations in Cancer

Major classes



TS, tumor suppressor

CML, chronic myelogenous leukemia

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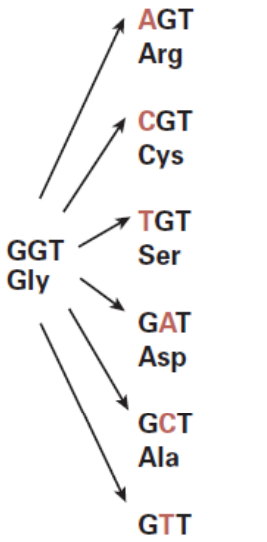
Genomic Alterations in Cancer

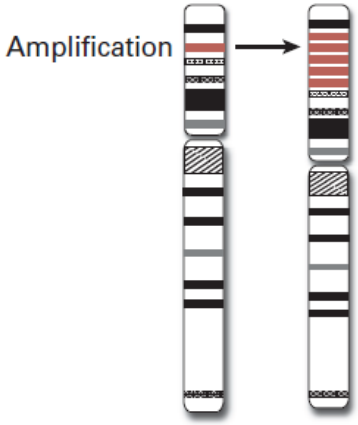
Major classes

Point mutations

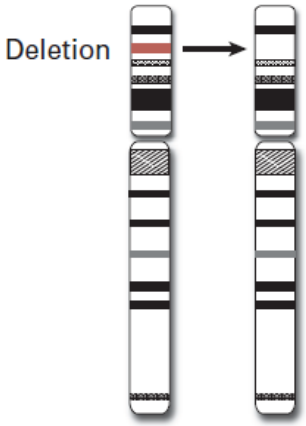


Activation of oncogenes-
RAS genes in many cancers
Inactivation ofTS genes-
TP53 in many cancers

Copy number alterations

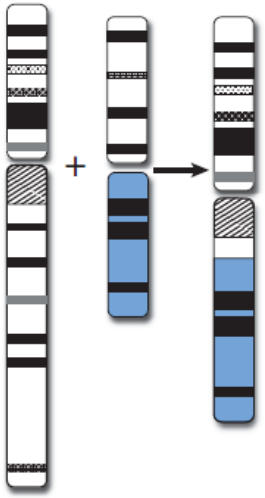


Activation of oncogenes-
ERBB2 in breast cancer



Inactivation ofTS genes-
RB1 in retinoblastoma

Translocations



Activation of many genes-
BCR-ABL in CML

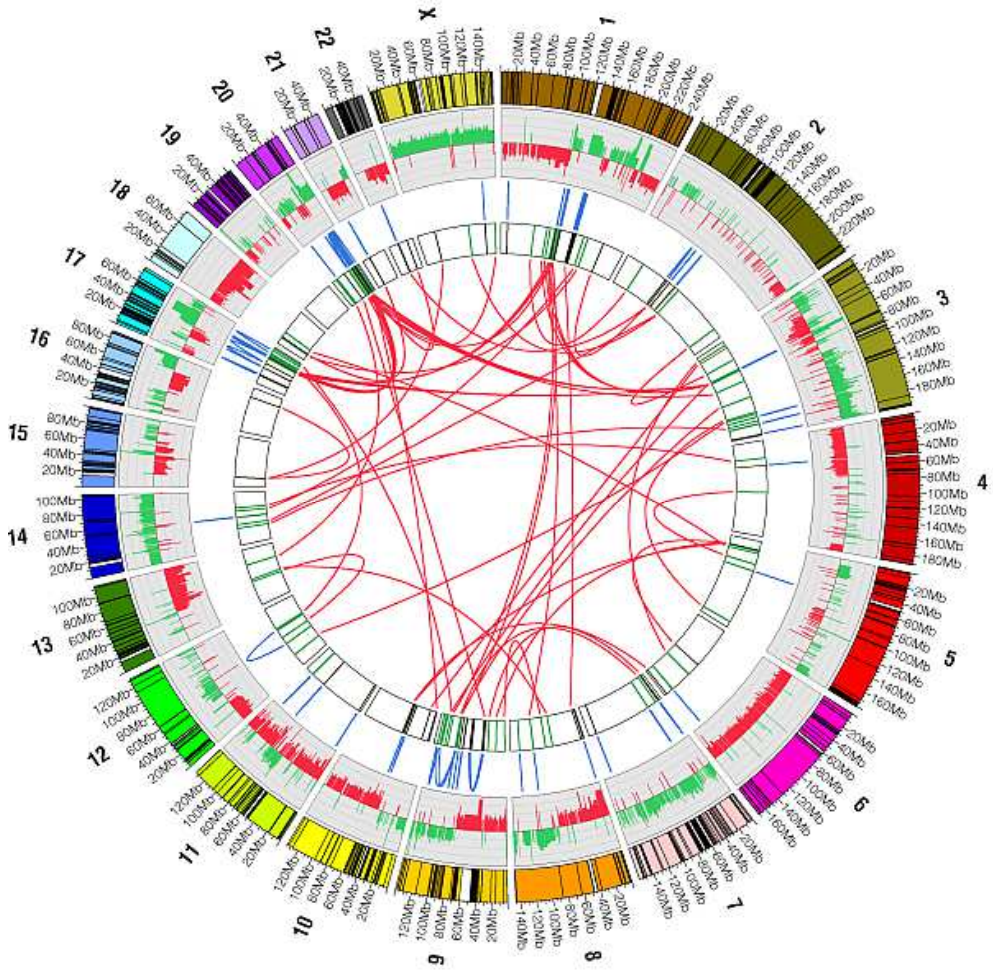
TS, tumor suppressor

CML, chronic myelogenous leukemia

Macconaill LE, Garraway LA. Clinical implications of the cancer genome. Journal of Clinical Oncology, 28(35), 5219-5228 (2010).

Breast Cancer

Genomic analysis

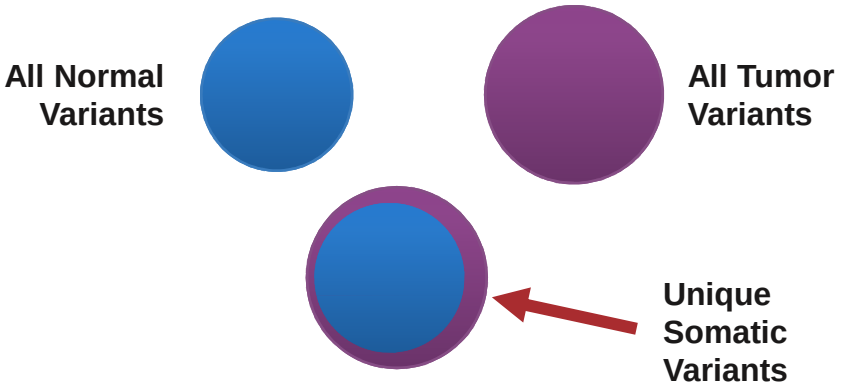


Hampton OA, Den Hollander P, Miller CA *et al.* A sequence-level map of chromosomal breakpoints in the MCF-7 breast cancer cell line yields insights into the evolution of a cancer genome. *Genome Research*, 19(2), 167-177 (2009).

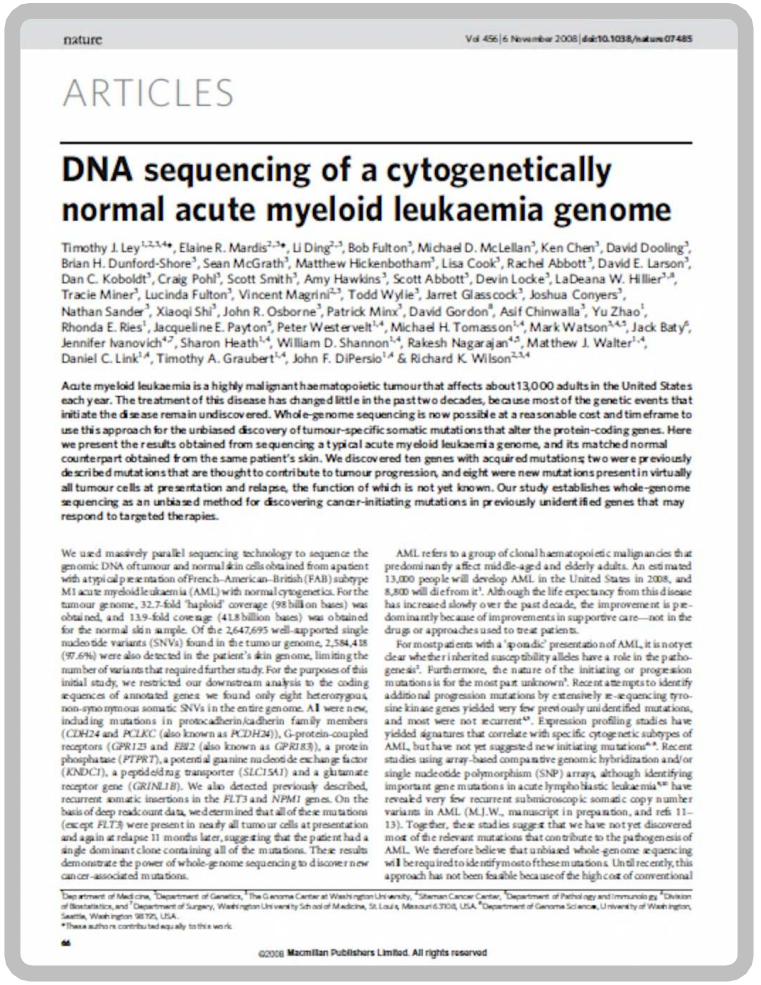
WGS

A new era in cancer genomics

- Sequenced leukemia genome vs. matched normal (skin) genome



- 8 new mutations discovered in AML
  - *Most in coding genes*
  - *Out of millions of total SNPs!*
- "Most of these genes would not have been candidates for directed sequencing on the basis of current understanding of cancer."



nature Vol 456 | 6 November 2008 | doi:10.1038/nature07485

ARTICLES

DNA sequencing of a cytogenetically normal acute myeloid leukaemia genome

Timothy J. Ley[1,2,3,4*], Elaine R. Mardis[2,3*], Li Ding[2,3], Bob Fulton[3], Michael D. McLellan[3], Ken Chen[3], David Dooling[3], Brian H. Dunford-Shore[3], Sean McGrath[3], Matthew Hickenbotham[3], Lisa Cook[3], Rachel Abbott[3], David E. Larson[3], Dan C. Koboldt[3], Craig Pohl[3], Scott Smith[3], Amy Hawkins[3], Scott Abbott[3], Devin Locke[3], LaDeana W. Hillier[3,4], Tracie Miner[3], Lucinda Fulton[3], Vincent Magrini[2,3], Todd Wylie[3], Jarret Glasscock[3], Joshua Conyers[3], Nathan Sander[3], Xiaoqi Shi[3], John R. Osborne[3], Patrick Minx[3], David Gordon[3], Asif Chinwalla[3], Yu Zhao[1], Rhonda E. Ries[1], Jacqueline E. Payton[5], Peter Westervelt[1,4], Michael H. Tomasson[1,4], Mark Watson[3,4,5], Jack Baty[6], Jennifer Ivanovich[4,7], Sharon Heath[1,4], William D. Shannon[1,4], Rakesh Nagarajan[4,5], Matthew J. Walter[1,4], Daniel C. Link[1,4], Timothy A. Graubert[1,4], John F. DiPersio[1,4] & Richard K. Wilson[2,3,4]

Acute myeloid leukaemia is a highly malignant haematopoietic tumour that affects about 13,000 adults in the United States each year. The treatment of this disease has changed little in the past two decades, because most of the genetic events that initiate the disease remain undiscovered. Whole-genome sequencing is now possible at a reasonable cost and timeframe to use this approach for the unbiased discovery of tumour-specific somatic mutations that alter the protein-coding genes. Here we present the results obtained from sequencing a typical acute myeloid leukaemia genome, and its matched normal counterpart obtained from the same patient's skin. We discovered ten genes with acquired mutations; two were previously described mutations that are thought to contribute to tumour progression, and eight were new mutations present in virtually all tumour cells at presentation and relapse, the function of which is not yet known. Our study establishes whole-genome sequencing as an unbiased method for discovering cancer-initiating mutations in previously unidentified genes that may respond to targeted therapies.

We used massively parallel sequencing technology to sequence the genomic DNA of tumour and normal skin cells obtained from a patient with atypical presentation of French–American–British (FAB) subtype M1 acute myeloid leukaemia (AML) with normal cytogenetics. For the tumour genome, 32.7-fold 'haploid' coverage (98 billion bases) was obtained, and 13.9-fold coverage (41.8 billion bases) was obtained for the normal skin sample. Of the 2,647,695 well-supported single nucleotide variants (SNVs) found in the tumour genome, 2,584,418 (97.6%) were also detected in the patient's skin genome, limiting the number of variants that required further study. For the purposes of this initial study, we restricted our downstream analysis to the coding sequences of annotated genes: we found only eight heterozygous, non-synonymous somatic SNVs in the entire genome. All were new, including mutations in protocadherin/cadherin family members (*CDH24* and *PCLKC* (also known as *PCDH24*)), G-protein-coupled receptors (*GPR123* and *EBI2* (also known as *GPR183*)), a protein phosphatase (*PTPRT*), a potential guanine nucleotide exchange factor (*KNDC1*), a peptide/drug transporter (*SLC15A1*) and a glutamate receptor gene (*GRIN1L1B*). We also detected previously described, recurrent somatic insertions in the *FLT3* and *NPM1* genes. On the basis of deep read-count data, we determined that all of these mutations (except *FLT3*) were present in nearly all tumour cells at presentation and again at relapse 11 months later, suggesting that the patient had a single dominant clone containing all of the mutations. These results demonstrate the power of whole-genome sequencing to discover new cancer-associated mutations.

AML refers to a group of clonal haematopoietic malignancies that predominantly affect middle-aged and elderly adults. An estimated 13,000 people will develop AML in the United States in 2008, and 8,800 will die from it[1]. Although the life expectancy from this disease has increased slowly over the past decade, the improvement is predominantly because of improvements in supportive care—not in the drugs or approaches used to treat patients.

For most patients with a 'sporadic' presentation of AML, it is not yet clear whether inherited susceptibility alleles have a role in the pathogenesis[2]. Furthermore, the nature of the initiating or progression mutations is for the most part unknown[3]. Recent attempts to identify additional progression mutations by extensively re-sequencing tyrosine kinase genes yielded very few previously unidentified mutations, and most were not recurrent[4,5]. Expression profiling studies have yielded signatures that correlate with specific cytogenetic subtypes of AML, but have not yet suggested new initiating mutations[6–8]. Recent studies using array-based comparative genomic hybridization and/or single nucleotide polymorphism (SNP) arrays, although identifying important gene mutations in acute lymphoblastic leukaemia[9,10] have revealed very few recurrent submicroscopic somatic copy number variants in AML (M.J.W., manuscript in preparation, and refs 11–13). Together, these studies suggest that we have not yet discovered most of the relevant mutations that contribute to the pathogenesis of AML. We therefore believe that unbiased whole-genome sequencing will be required to identify most of these mutations. Until recently, this approach has not been feasible because of the high cost of conventional

[1]Department of Medicine, [2]Department of Genetics, [3]The Genome Center at Washington University, [4]Siteman Cancer Center, [5]Department of Pathology and Immunology, [6]Division of Biostatistics, and [7]Department of Surgery, Washington University School of Medicine, St Louis, Missouri 63108, USA. [8]Department of Genome Science, University of Washington, Seattle, Washington 98195, USA.
*These authors contributed equally to this work.

Ley TJ, Mardis ER, Ding L *et al.* DNA sequencing of a cytogenetically normal acute myeloid leukaemia genome. *Nature*, 456(7218), 66-72 (2008)

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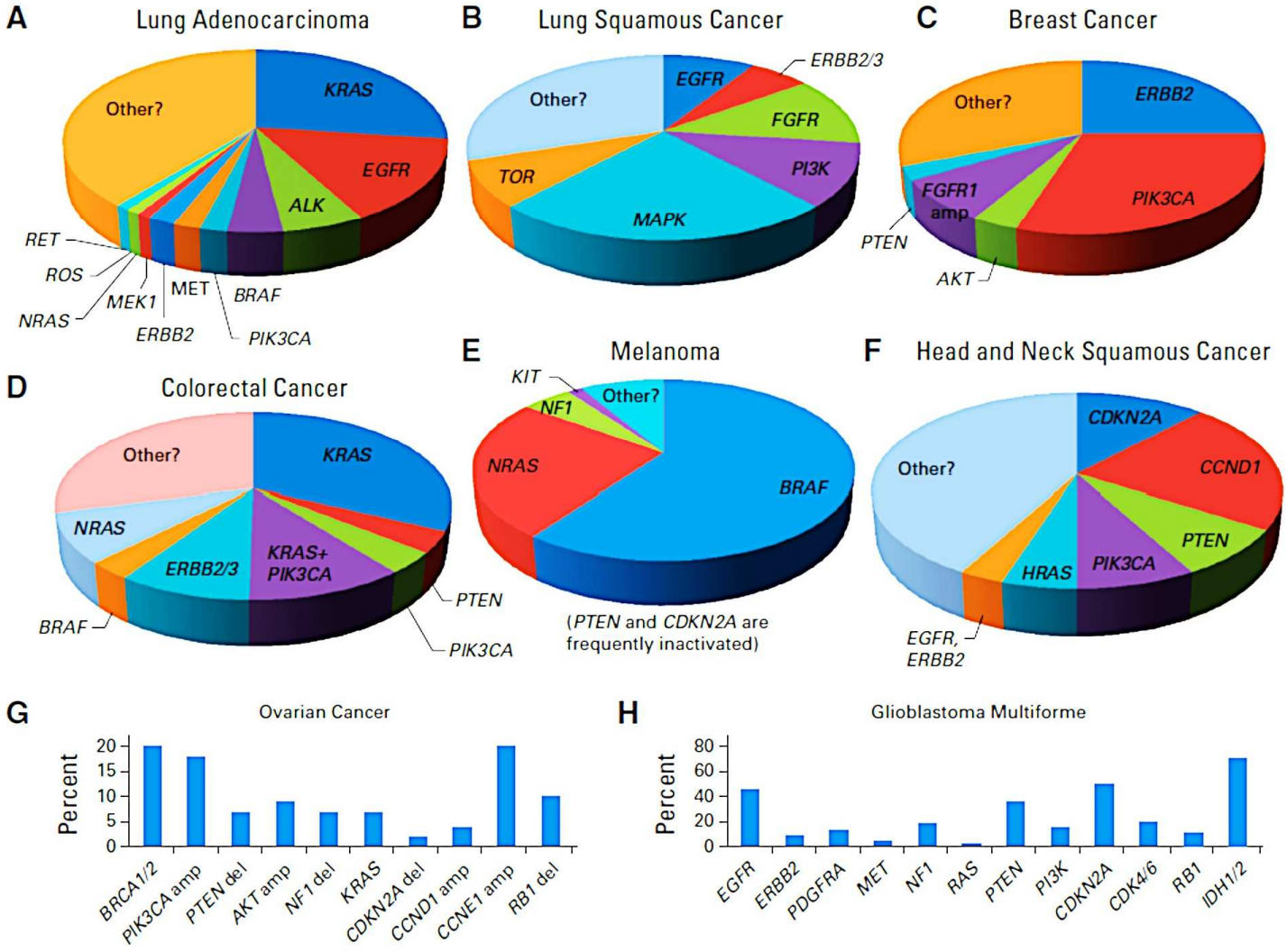
A New Taxonomy of Cancer

From organs to molecules



Garraway LA. Genomics-driven oncology: framework for an emerging paradigm. Journal of Clinical Oncology, 31(15), 1806-1814 (2013).

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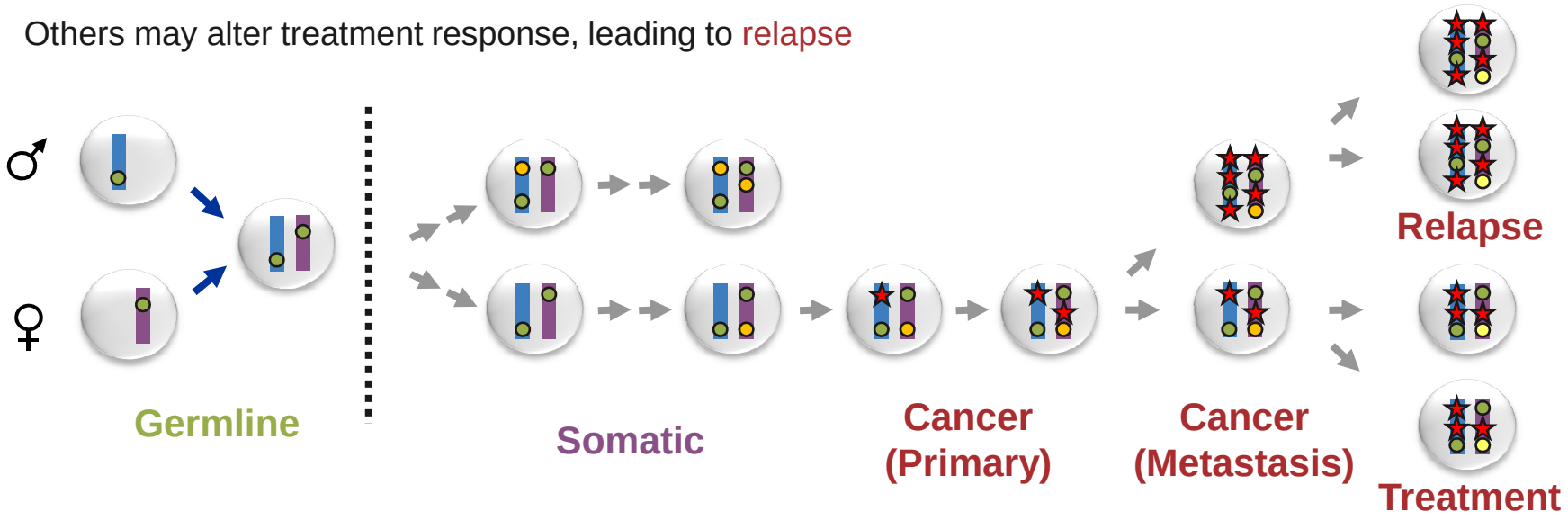
Cancer Genomes Are Dynamic

- WGS is a snapshot
- Certain mutations reflect paternal and/or maternal germline variation
- Additional somatic mutations accumulate through life
- "Driver" mutations cause cancer, "*passenger" mutations* are carried along
- Additional drivers evolve and diversify the cancer
- Some alter aggressiveness…
- …which may be treatable
- Others may alter treatment response, leading to relapse

Cancer genomes are not static.

In cancer, one snapshot is not enough.



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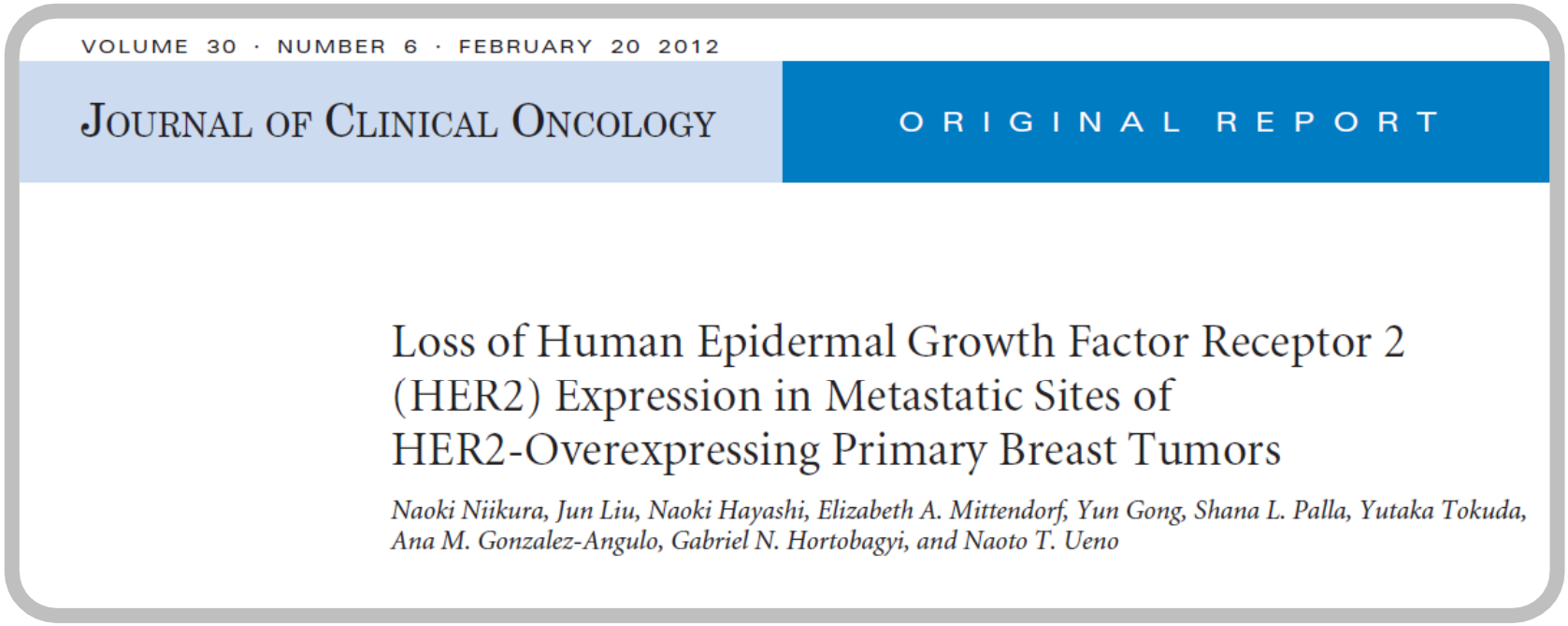
Evolution of Cancer Genomes

Primary vs. metastatic tumors



VOLUME 30 · NUMBER 6 · FEBRUARY 20 2012

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Loss of Human Epidermal Growth Factor Receptor 2 (HER2) Expression in Metastatic Sites of HER2-Overexpressing Primary Breast Tumors

Naoki Niikura, Jun Liu, Naoki Hayashi, Elizabeth A. Mittendorf, Yun Gong, Shana L. Palla, Yutaka Tokuda, Ana M. Gonzalez-Angulo, Gabriel N. Hortobagyi, and Naoto T. Ueno

24% of patients with *HER2*-positive primary breast tumors had *HER2*-negative metastatic tumors

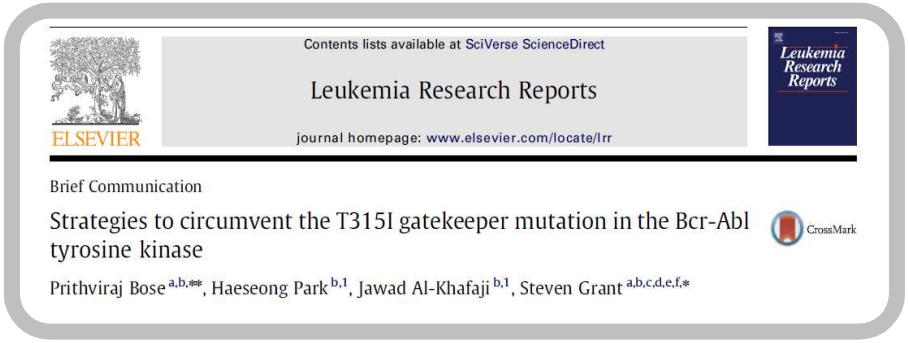
Niikura N, Liu J, Hayashi N *et al.* Loss of human epidermal growth factor receptor 2 (HER2) expression in metastatic sites of HER2-overexpressing primary breast tumors. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*, 30(6), 593-599 (2012).

Evolution of Cancer Genomes

Tumors change in response to treatment

Example #1

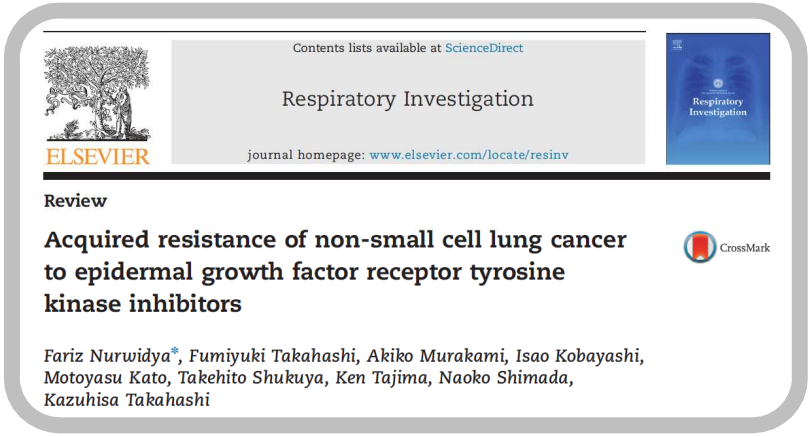
Chronic Myelogenous Leukemia (CML)



- **T315I** "gatekeeper mutation" leads to acquired BCR-ABL tyrosine kinase inhibitor resistance

Example #2

Non-Small Cell Lung Cancer (NSCLC)

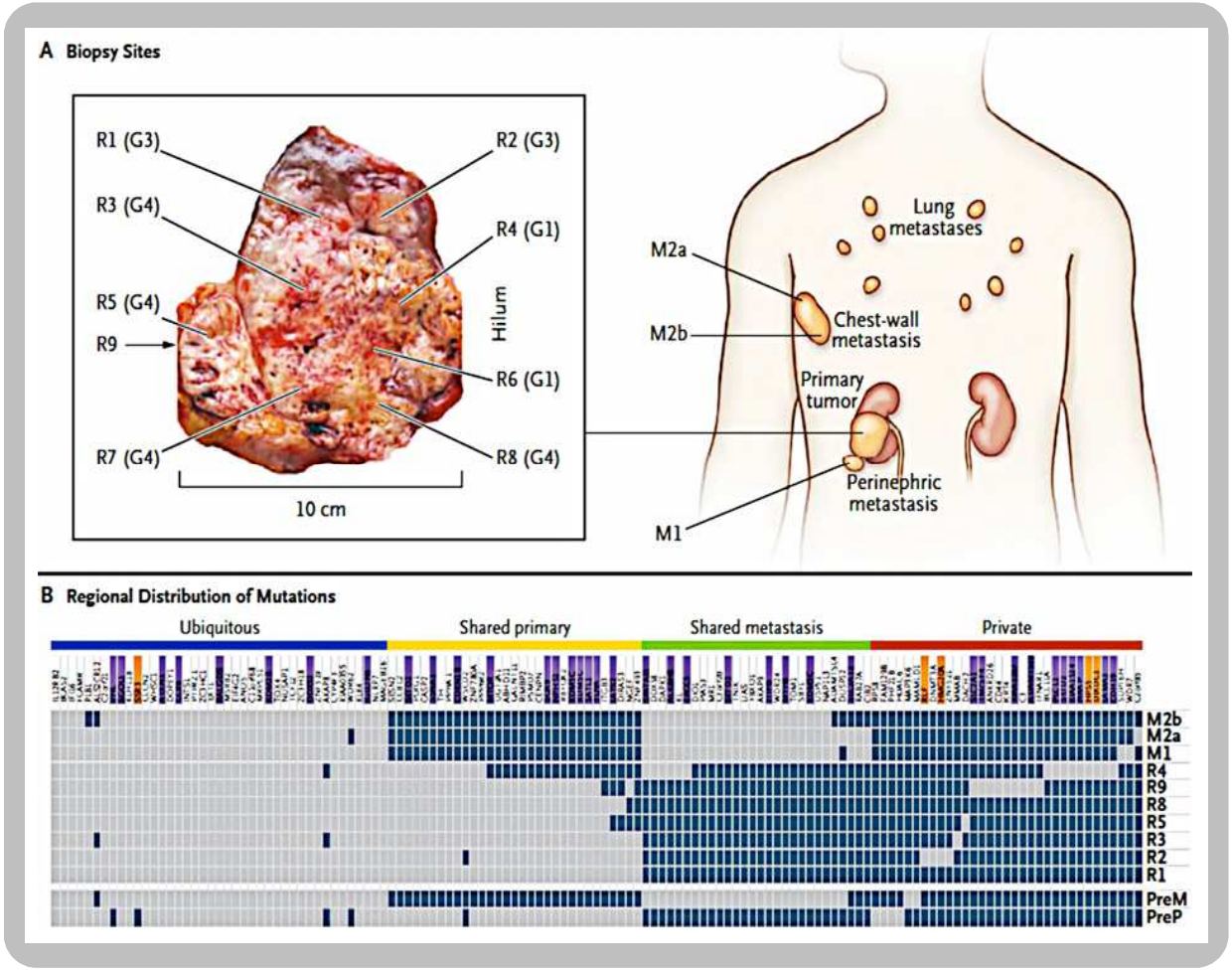


- **T790M** mutation leads to acquired EGFR tyrosine kinase inhibitor resistance

1. Bose P, Park H, Al-Khafaji J, Grant S. Strategies to circumvent the T315I gatekeeper mutation in the Bcr-Abl tyrosine kinase. *Leukemia research reports*, 2(1), 18-20 (2013).
2. Nurwidya F, Takahashi F, Murakami A *et al.* Acquired resistance of non-small cell lung cancer to epidermal growth factor receptor tyrosine kinase inhibitors. *Respiratory investigation*, 52(2), 82-91 (2014).

Intratumoral & Intermetastatic Clonal Heterogeneity

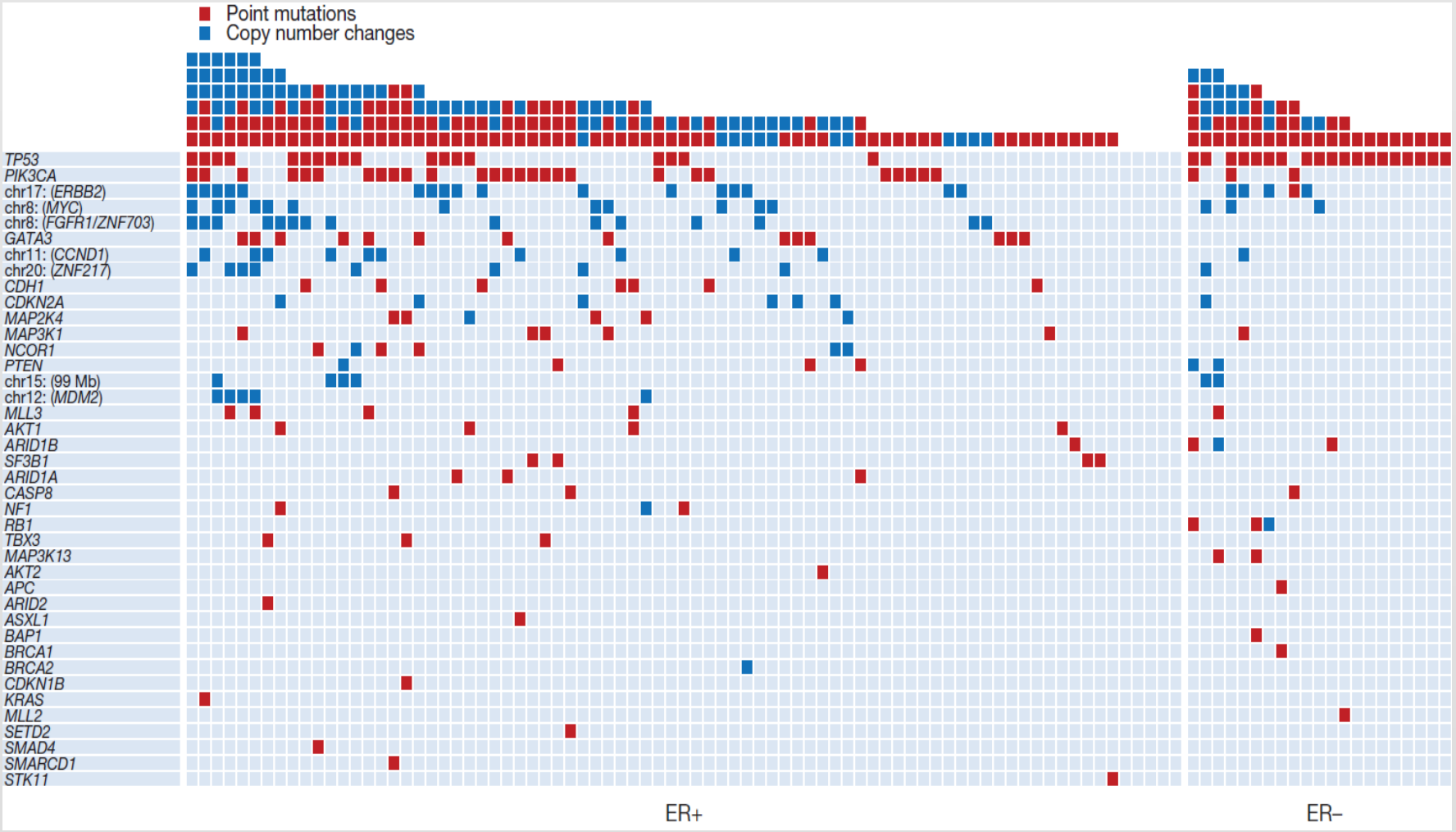
Heterogeneity within single patient



Gerlinger M, Rowan AJ, Horswell S *et al.* Intratumor heterogeneity and branched evolution revealed by multiregion sequencing. *The New England Journal of Medicine*, 366(10), 883-892 (2012).

Interpatient Genetic Heterogeneity

Breast Cancer – 40 Cancer Genes Across 100 Tumors



Stephens et al, Nature 2012; Shah et al. Nature 2012; Ellis et al. Nature 2012; Banerji et al. Nature 2012

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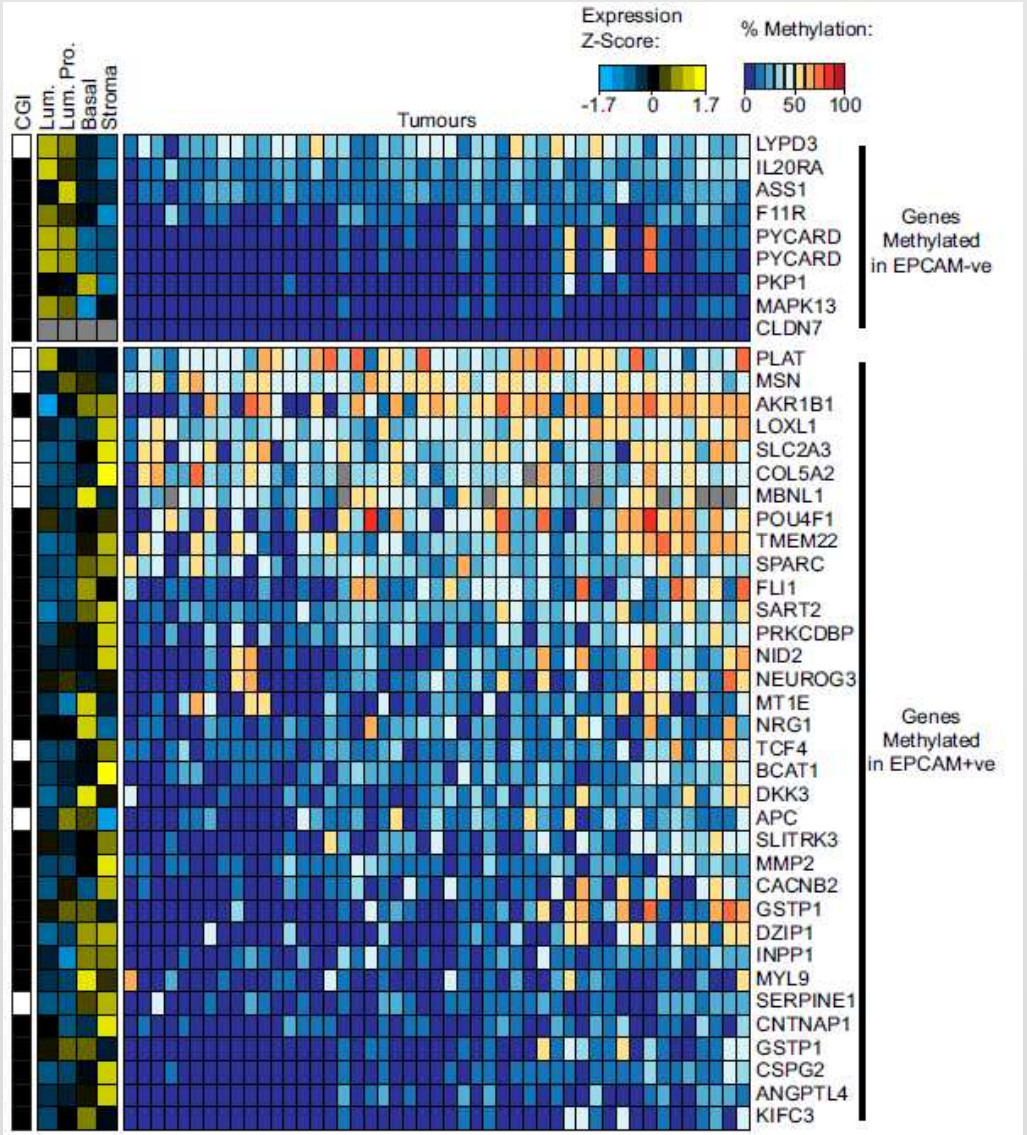
Interpatient Epigenetic Heterogeneity

Breast Cancer



PNAS March 15, 2011 vol. 108 no. 11 4364-4369

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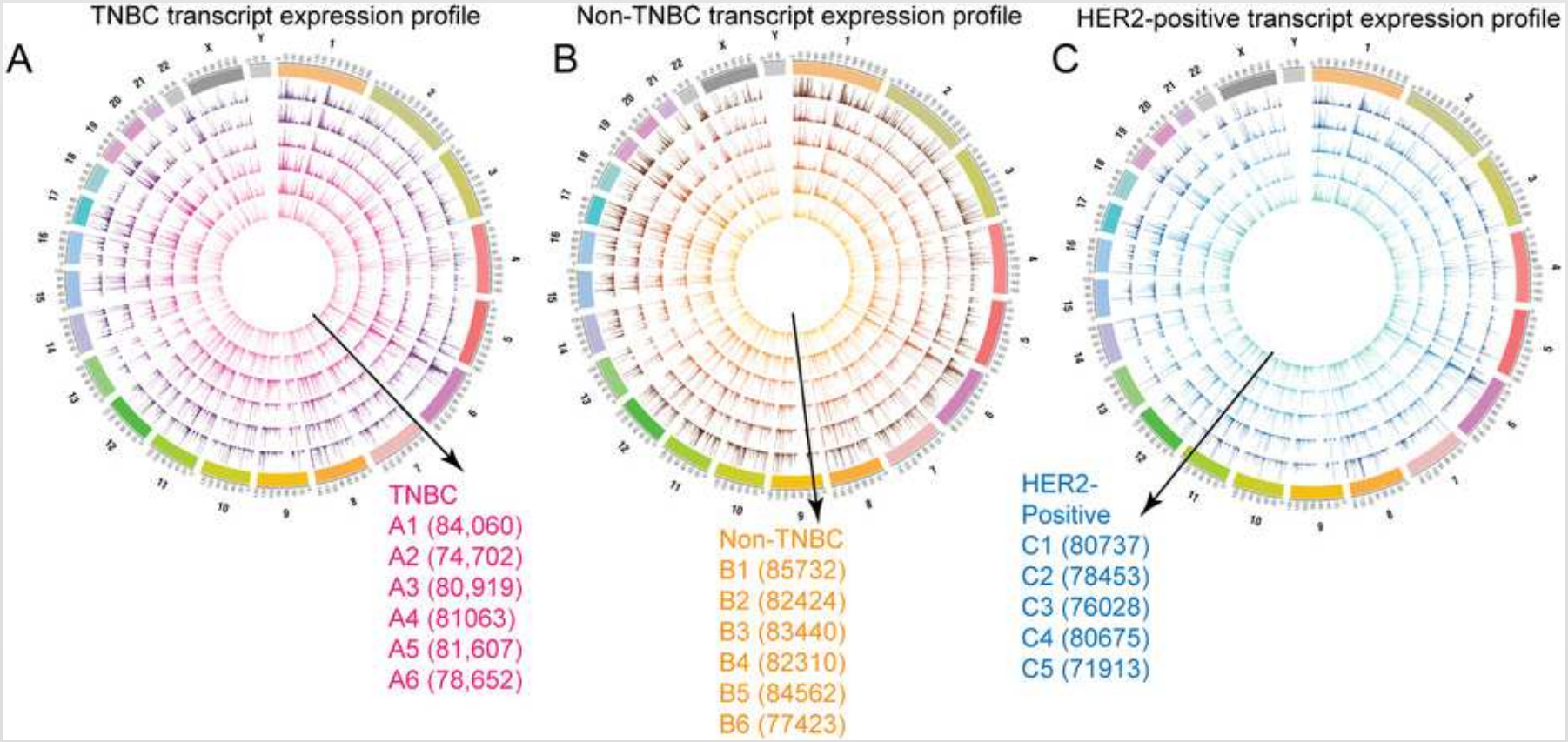
Interpatient Transcriptomic Heterogeneity

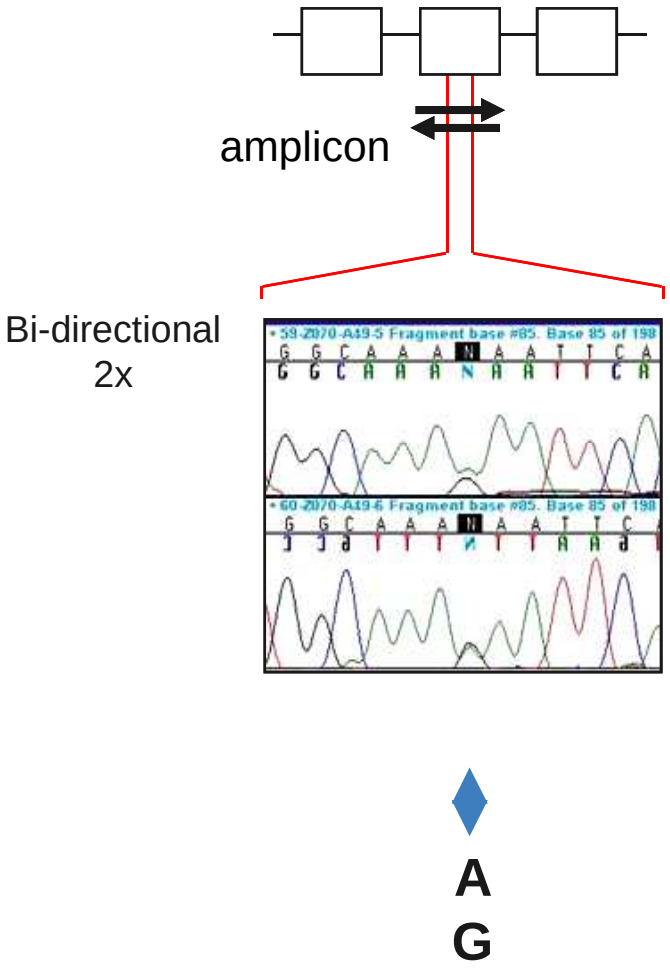
Breast Cancer



Transcriptomic landscape of breast cancers through mRNA sequencing. Scientific Reports 2, Article number: 264. 14 February 2012

NGS vs. Sanger

A. Capillary sequencing

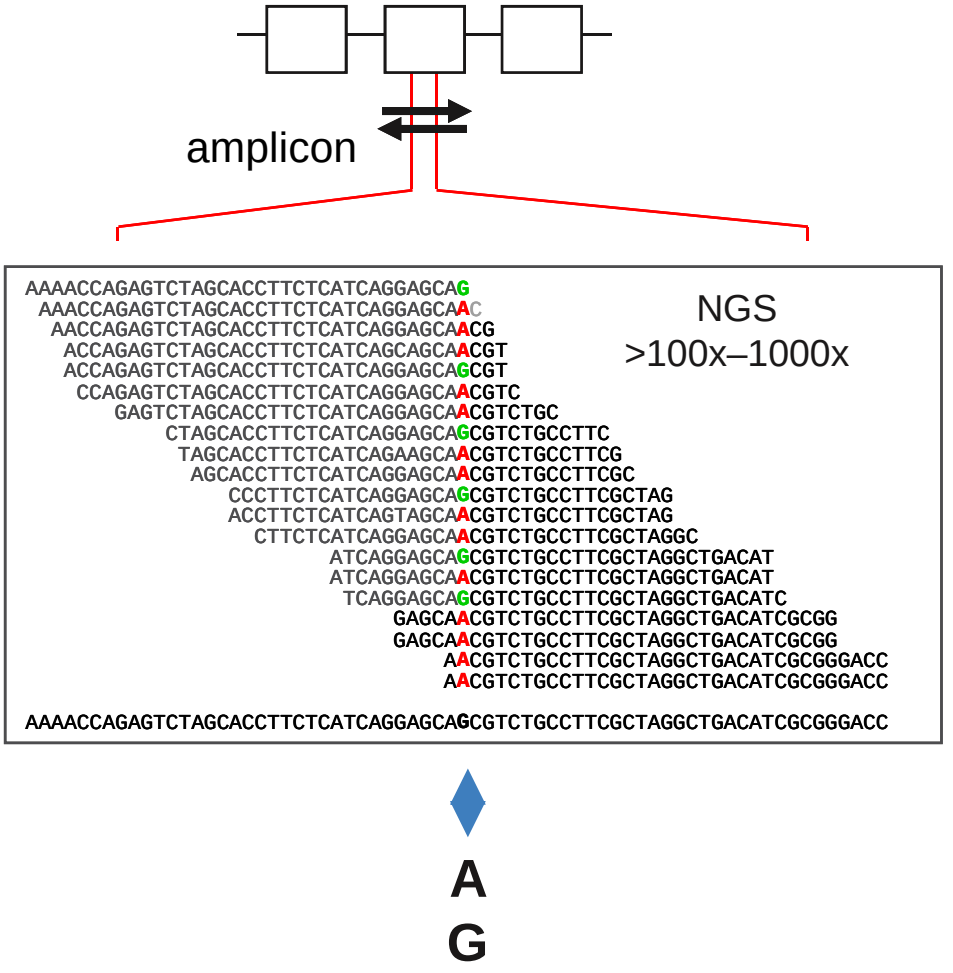


GENE

SEQUENCE

VARIANT

B. NGS / Massively parallel sequencing (MPS)



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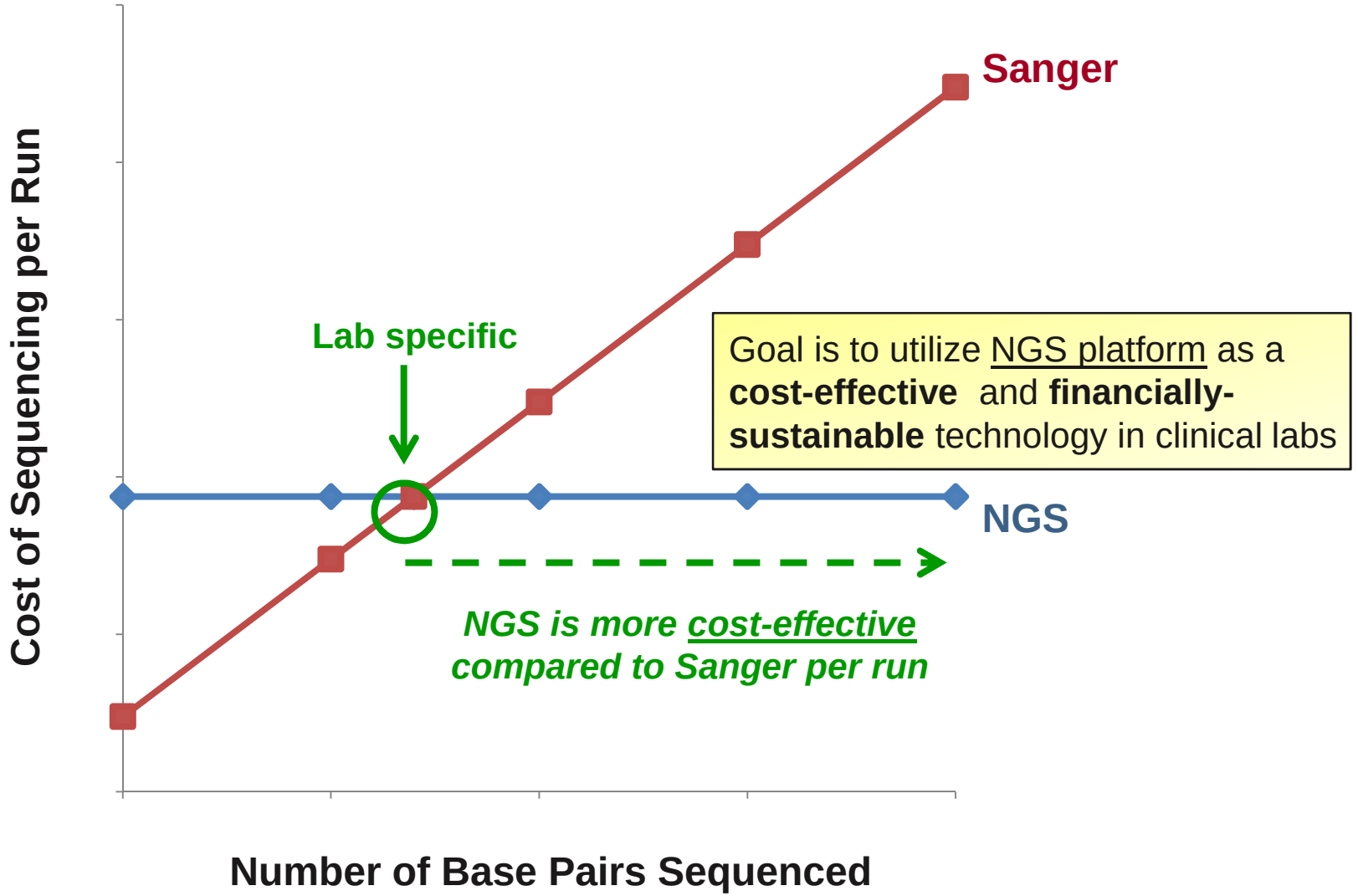
Clinical Laboratory Analysis

Sanger vs NGS cost of sequencing per run



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NGS vs. Sanger

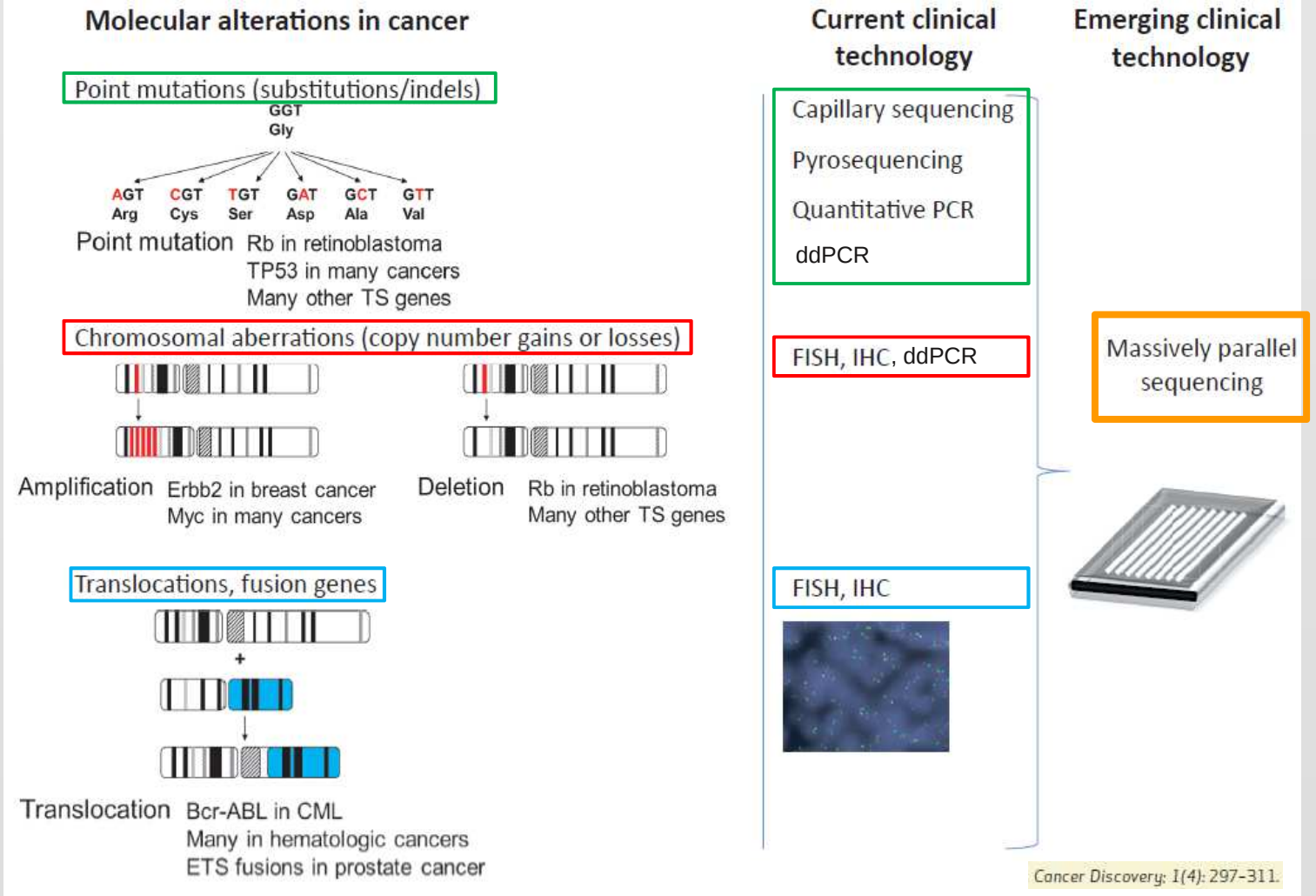
Summary table

Technology	Data Generated	Analysis	Output per Run	Limited of Detection (LOD)
Sanger	Electropherograms ("Sanger traces")	Manual Automated	550 bp – 86,400 bp	**20%**
NGS	Raw Data FASTQ Files * BAM Files ** VCF Files	Bioinformatics (Automated)	15 Gb – 600 Gb	**3 – 5%**

* **BAM** or **SAM** = **B**inary **A**lignment/**M**ap or **S**equence **A**lignment/**M**ap
** **VCF** = **V**ariant **C**all **F**ormat

Characterization of Cancer Genomes

Technologies



Adapted from: Clinical Implementation of Comprehensive Strategies to Characterize Cancer Genomes: Opportunities and Challenges
MacConaill, et al. *Cancer Discovery* 2011;1:297-311.

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Genomic Alterations in Cancer

Categories of Genomic Alteration and Exemplary Cancer Genes

Category of Genomic Alteration	Exemplary Cancer Gene	Type of Cancer	Targeted Therapeutic Agent
Translocation	*BCR-ABL*	Chronic myelogenous leukemia	Imatinib
	PML-RARα	Acute promyelocytic leukemia	All-*trans*-retinoic acid
	EML4-ALK	Breast, colorectal, lung	ALK inhibitor
	ETS gene fusions	Prostate	—
	Other	Leukemias, lymphomas, sarcomas	—
Amplification	*EGFR*	Lung, colorectal, glioblastoma, pancreatic	Cetuximab, gefitinib, erlotinib, panitumumab, lapatinib
	ERBB2	Breast, ovarian	Trastuzumab, lapatinib
	KIT, PDGFR	GISTs, glioma, HCC, RCC, CML	Imatinib, nilotinib, sunitinib, sorafenib
	MYC	Brain, colon, leukemia, lung	—
	SRC	Sarcoma, CML, ALL	Dasatinib
	PIK3CA	Breast, ovarian, colorectal, endometrial	PI3-kinase inhibitors
Point mutation	*EGFR*	Lung, glioblastoma	Cetuximab, gefitinib, erlotinib, panitumumab, lapatinib
	KIT, PDGFR	GISTs, glioma, HCC, RCC, CML	Imatinib, nilotinib, sunitinib, sorafenib
	PIK3CA	Breast, ovarian, colorectal, endometrial	PI3-kinase inhibitors
	BRAF	Melanoma, pediatric astrocytoma	RAF inhibitor
	KRAS	Colorectal, pancreatic, GI tract, lung	Resistance to erlotinib, cetuximab (colorectal)

Abbreviations: ALK, anaplastic lymphoma kinase; GIST, GI stromal tumor; HCC, hepatocellular carcinoma; RCC, renal cell carcinoma; CML, chronic myelogenous leukemia; ALL, acute lymphoblastic leukemia; PI3, phosphatidylinositol-3.

Clinical Implications of the Cancer Genome. J Clin Oncol 28:5219-5228.

Nucleic Acid Companion Diagnostics

FDA-approved CDx tests

	Drug Trade Name	Device Trade Name	Device Manufacturer
1	Erbitux; Vectibix	therascreen KRAS RGQ PCR Kit	Qiagen Manchester, Ltd.
2	Gilotrif	therascreen EGFR RGQ PCR Kit	Qiagen Manchester, Ltd.
3	Herceptin	INFORM HER-2/NEU	Ventana Medical Systems, Inc.
4	Herceptin	PATHVYSION HER-2 DNA Probe Kit	Abbott Molecular Inc.
5	Herceptin	SPOT-LIGHT HER2 CISH Kit	Life Technologies, Inc.
6	Herceptin	HER2 CISH PharmDx Kit	Dako Denmark A/S
7	Herceptin	INFORM HER2 DUAL ISH DNA Probe Cocktail	Ventana Medical Systems, Inc.
8	Herceptin; Perjeta	HER2 FISH PharmDx Kit	Dako Denmark A/S
9	Mekinist; Tafinlar	THxID™ BRAF Kit	bioMérieux Inc.
10	Tarceva	cobas EGFR Mutation Test	Roche Molecular Systems, Inc.
11	Xalkori	VYSIS ALK Break Apart FISH Probe Kit	Abbott Molecular Inc.
12	Zelboraf	COBAS 4800 BRAF V600 Mutation Test	Roche Molecular Systems, Inc.

TOTAL (12): FISH/CISH → HER2 (6); ALK (1) **qPCR →** KRAS (1) ; EGFR (2); BRAF (2)

US Food and Drug Administration [Last Updated: 07/31/2014]

Companion Diagnostics Scene 2012: Single Genes

Selected Genetic Markers and Their Application in Cancer Treatment

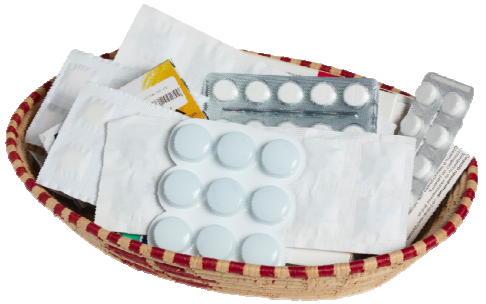
Genetic Marker	Application		Drug
BCR-ABL	Ph+ CML; Ph+ ALL	Small molecule inhibitors	Imatinib, dasatinib, nilotinib
BCR-ABL/T315I	Resistance to anti-BCR-ABL agents	Small molecule inhibitors	Imatinib, dasatinib, nilotinib
BRAF V600E	Metastatic melanoma	Small molecule inhibitors	Vemurafenib
BRCA1/2	Metastatic ovarian cancer and breast cancer with BRCA 1/2 mutations	Small molecule inhibitors	Olaparib, veliparib, iniparib
c-Kit	Kit (CD117)-positive malignant GIST	Small molecule inhibitors	Imatinib
EGFR	Locally advanced, unresectable, or metastatic NSCLC	Small molecule inhibitors	Erlotinib, gefitinib
EGFR T790M	Resistance to EGFR tyrosine kinase inhibitors in advanced NSCLC	Small molecule inhibitors	Erlotinib, gefitinib
EML4-ALK	ALK kinase inhibitor for metastatic NSCLC with this fusion gene	Small molecule inhibitors	Crizotinib
HER2 amplification	HER2-positive breast cancer or metastatic gastric or gastroesophageal junction adenocarcinoma	mAbs	Trastuzumab
KRAS	Resistance to EGFR antibodies in metastatic colorectal cancer	mAbs	Cetuximab, panitumumab
PML/RAR	Acute promyelocytic leukemia	Chemo	ATRA, arsenic trioxide
TPMT	Deficiency is associated with increased risk of myelotoxicity	Chemo	Mercaptopurine, azathioprine
UGT1A1	Homozygosity for UGT1A1*28 is associated with risk of toxicity	Chemo	Irinotecan
DPD	Deficiency is associated with risk of severe toxicity	Chemo	5-Fluorouracil

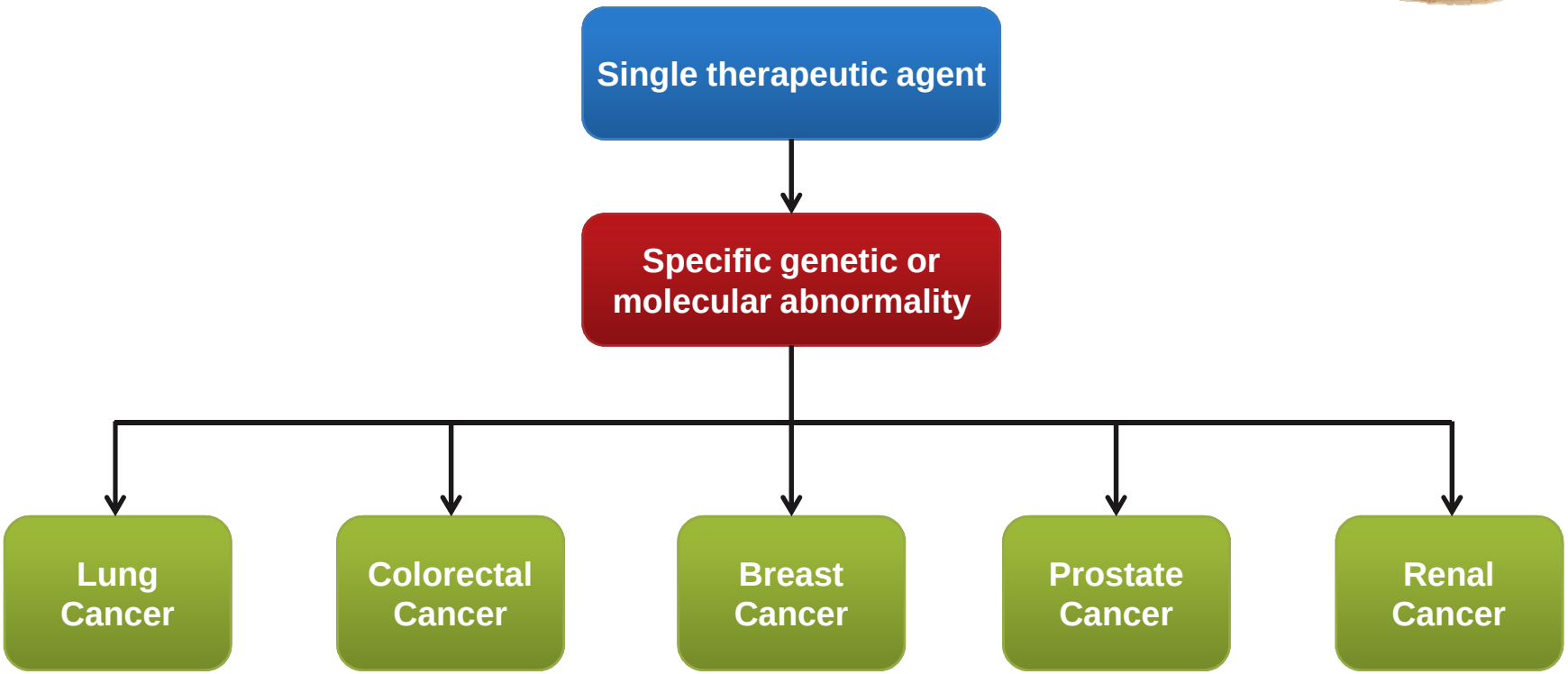
ATRA, all trans retinoic acid; Ph+, Philadelphia-positive chromosome; DPD, dihydropyrimine dehydrogenase; EGFR, epidermal growth factor receptor; EML4-ALK, echinoderm microtubule-associated protein-like 4 anaplastic lymphoma kinase; HER2, human epidermal growth receptor 2; GIST, gastrointestinal stromal tumors; ALL, acute lymphocytic leukemia; NSCLC, non-small cell lung cancer; TPMT, thiopurine S-methyltransferase.

The Genetic Basis for Cancer Treatment Decisions. Hudson et at. Cell 148, February 3, 2012

Molecularly Informed Clinical Trials

Basket study design





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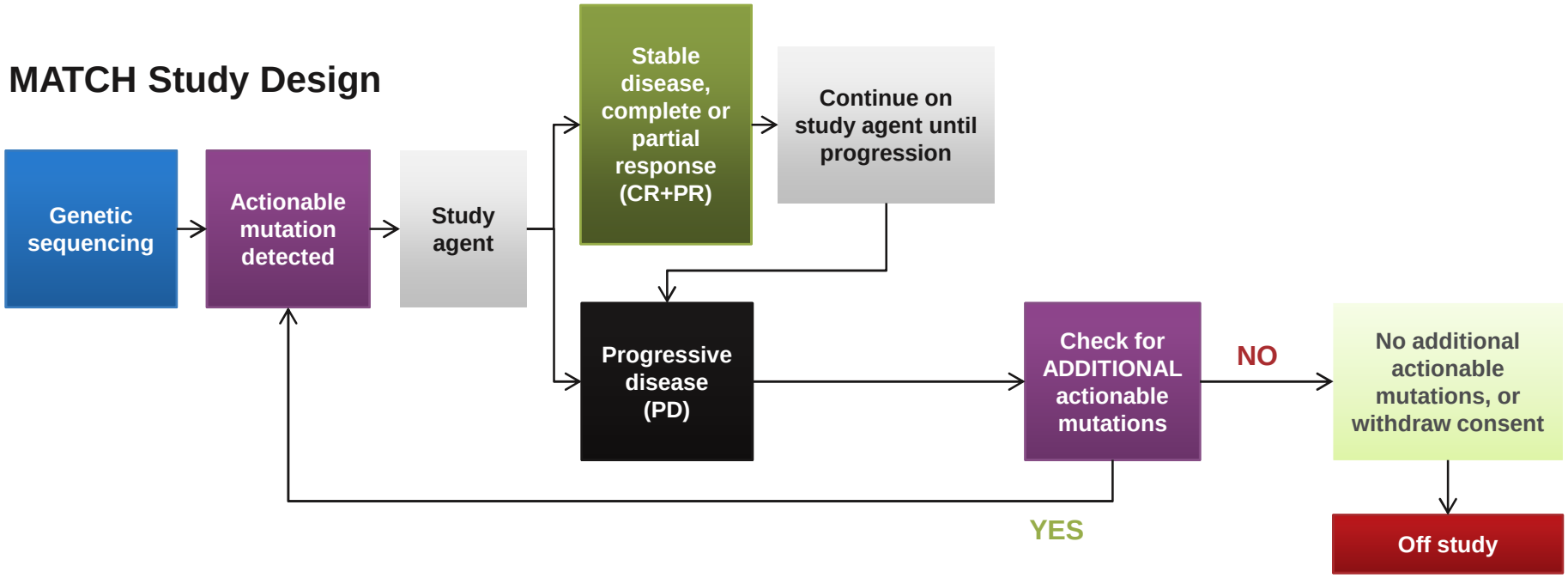
Molecularly Informed Clinical Trials

Basket study example

National Cancer Institute
at the National Institutes of Health

NCI's MATCH (Molecular Analysis for Therapy CHoice)

- Identify mutations/amplifications/translocations in patient tumor sample – eligibility determination
- Assign patient to relevant agent/regimen



Adapted from http://deainfo.nci.nih.gov/advisory/ncab/164_1213/Conley.pdf

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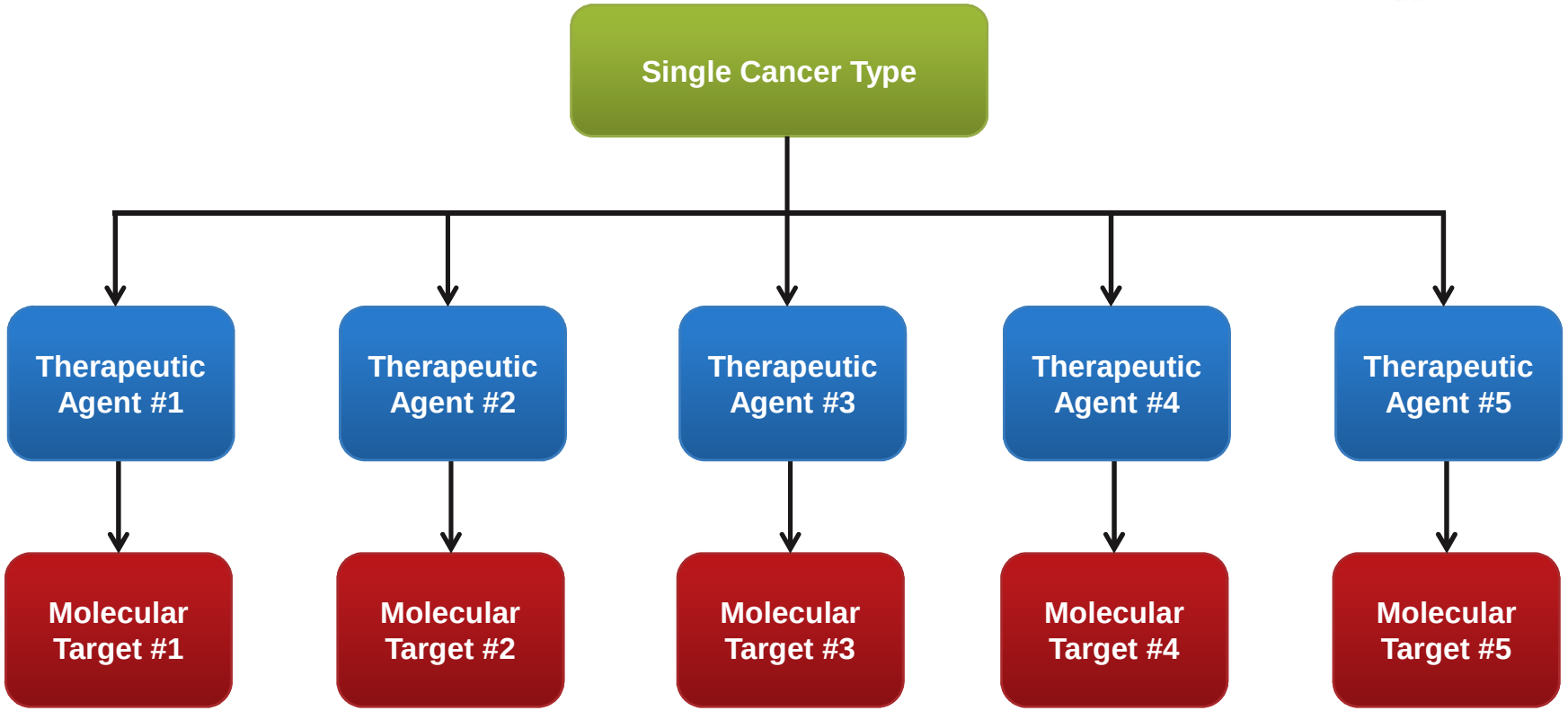
Molecularly Informed Clinical Trials

Umbrella study design



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Molecularly Informed Clinical Trials

Umbrella study example

I-SPY 2 TRIAL (**I**nvestigation of **S**erial Studies to **P**redict **Y**our **T**herapeutic **R**esponse with **I**maging **A**nd mo**L**ecular Analysis **2**)

- Clinical trial for women with newly diagnosed locally advanced breast cancer
- Test whether adding investigational drugs to standard chemotherapy is better than standard chemotherapy alone before having surgery
- Treatment phase of this trial will be testing multiple investigational drugs that are thought to target the biology of each participant's tumor
- Help the study researchers learn more quickly which investigational drugs will be most beneficial for women with certain tumor characteristic

http://www.ispy2.org/

Exceptional Responders

N-of-1 experiences

Case #1

- A 70-year-old woman with advanced melanoma
- **29-patient study** of a drug under development by Pfizer Inc.
- **Only 1 of 29 patients**, the 70-year-old woman came away with her cancer in remission
- Researchers are now studying how **her unique genomic alterations** may have interacted with the drug to spur her recovery

Case #2

- A woman with advanced bladder cancer
- **45-patient study** of a drug by Novartis
- "**Every other patient died**, but she's without evidence of disease for more than three years now," said Dr. Solit (MSKCC oncologist)
- Researchers discovered a **combination of two gene mutations** made her particularly receptive to the treatment

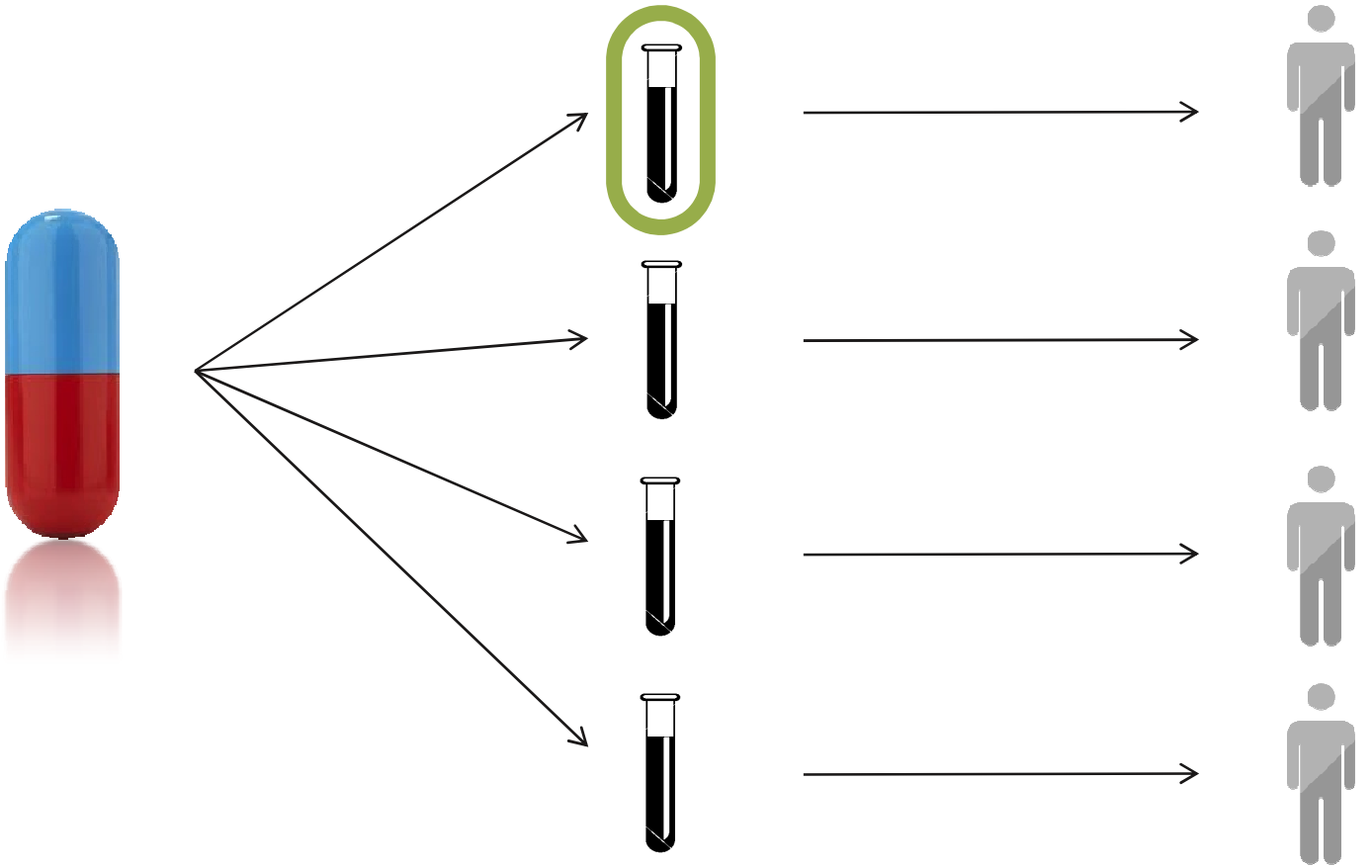
Case #1 - http://www.bloomberg.com/news/2014-04-11/cancer-miracle-patients-studied-anew-for-disease-clues.html
Case #2 - http://www.reuters.com/article/2013/09/15/us-cancer-superresponders-idUSBRE98E07420130915

Drug-Centered Oncology Rx: Traditional Approach

The (One) Drug

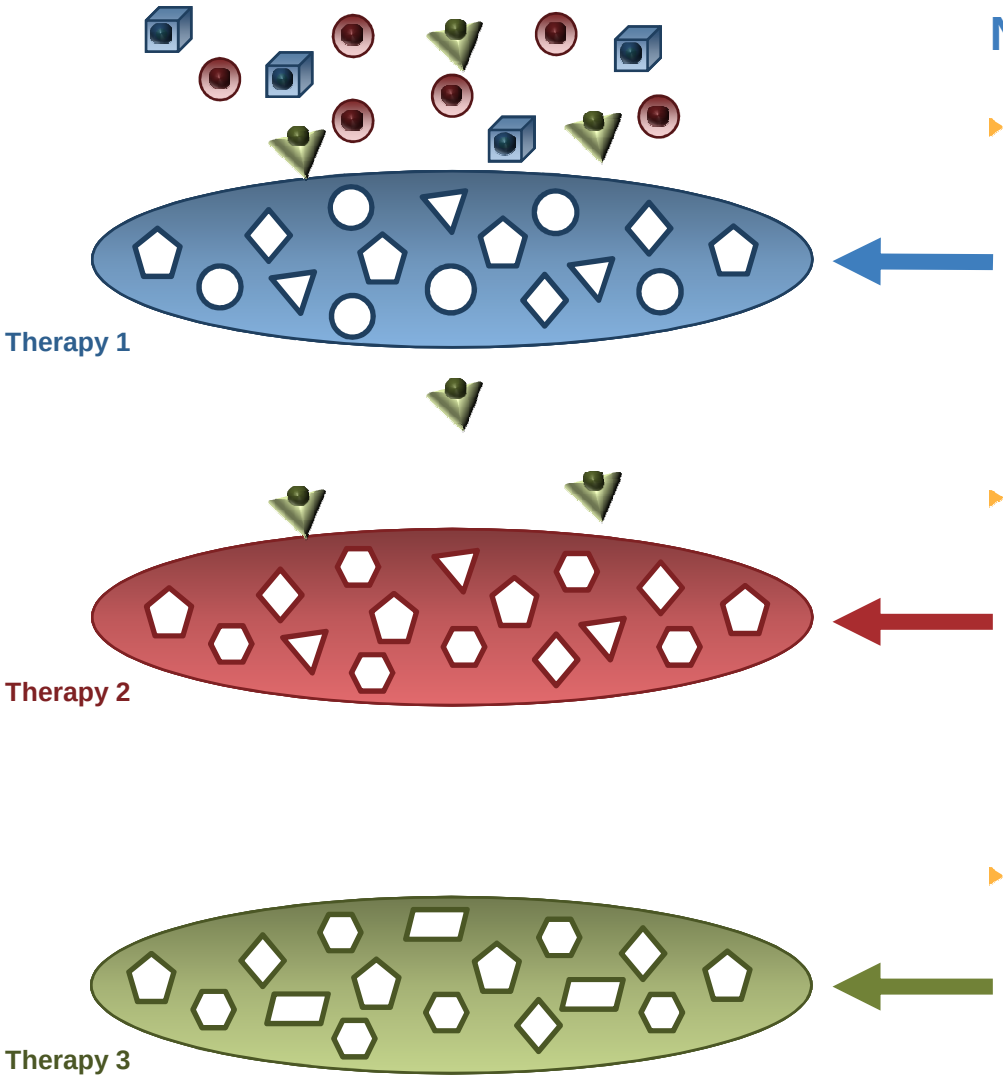
The "Companion" Test (single-target)

The Patients



- One drug … that is efficacious in a small fraction of patients…
- Requires a (single-target) CDx for each patient… to identify likely responders

Cancer Is A Heterogeneous Disease



Need For Combination Therapies

- **A tumor consists of…**
  - **genetically distinct subpopulations** of cancer cells, each with its own **characteristic sensitivity profile** to a given therapy
- **Each cancer therapy can be viewed as…**
  - a **filter** that removes a subpopulation of cancer cells that are sensitive to this treatment
- **Combination therapy…**
  - for management of cancer as a ***chronic disease***

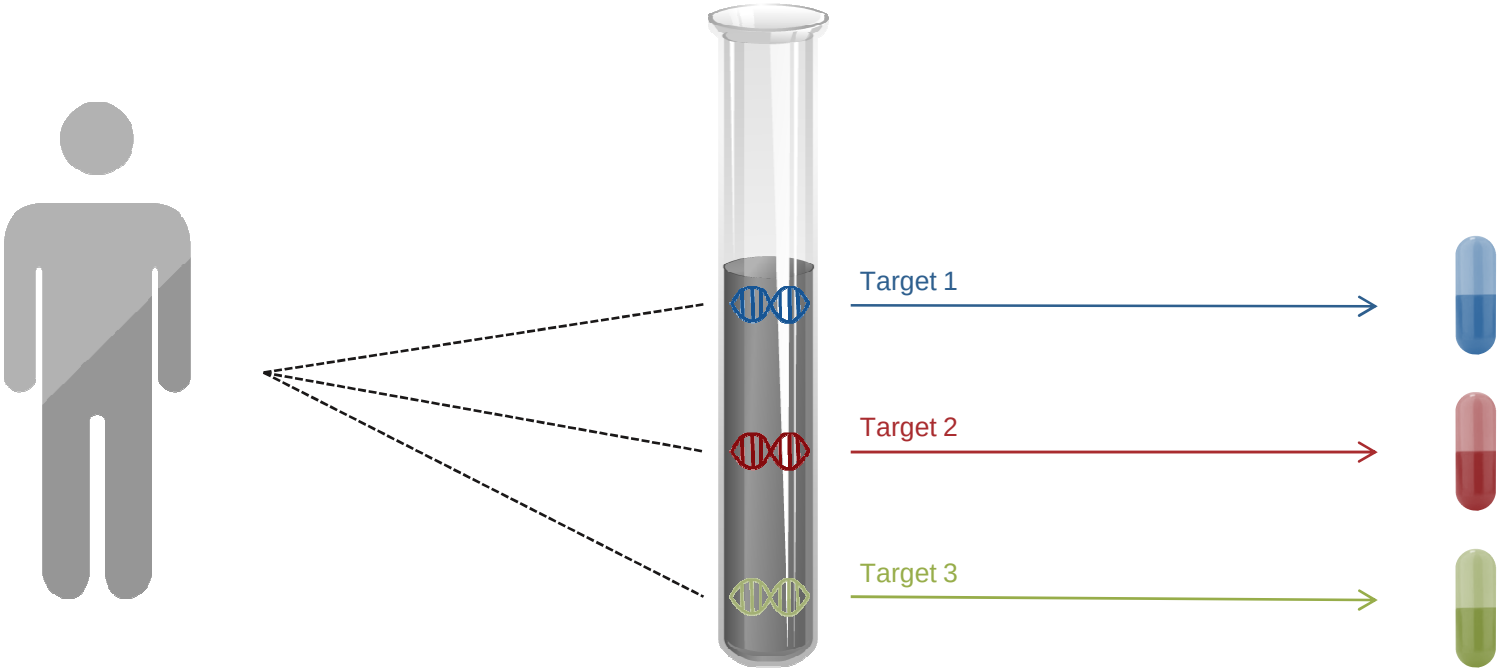
Adapated from Luo J, Solimini NL, Elledge SJ. Principles of cancer therapy: oncogene and non-oncogene addiction. *Cell*, 136(5), 823-837 (2009).

Patient-Centered Oncology Rx: Emerging Paradigm

The Patient

The (One) Test
(multi-target)

The Drug
CRx



- One patient… evaluated by one (multi-target) test…
- … to identify the best drug for each patient
- Rise of the “companion therapeutic”?

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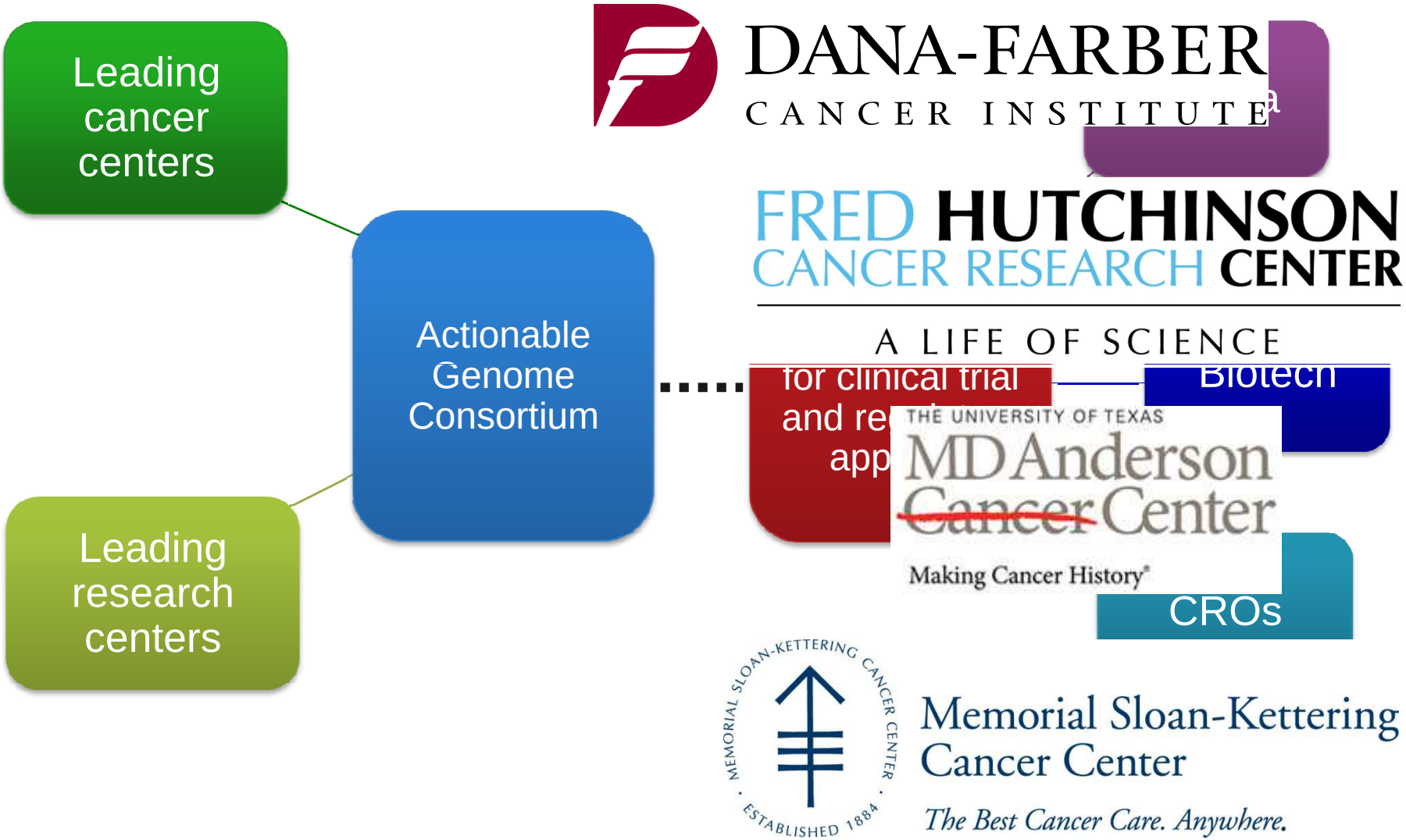
Partnering for New Paradigm of Precision Oncology



Partnering for New Paradigm of Precision Oncology

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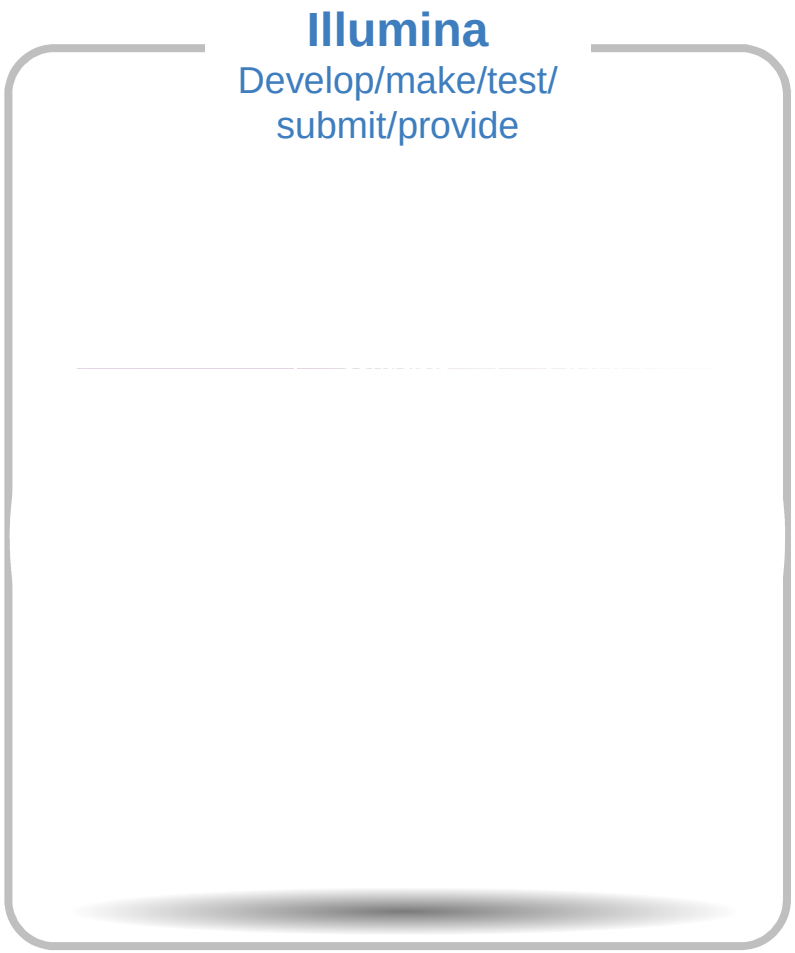
Partnering for Precision Oncology Enables

A Collaborative Ecosystem:

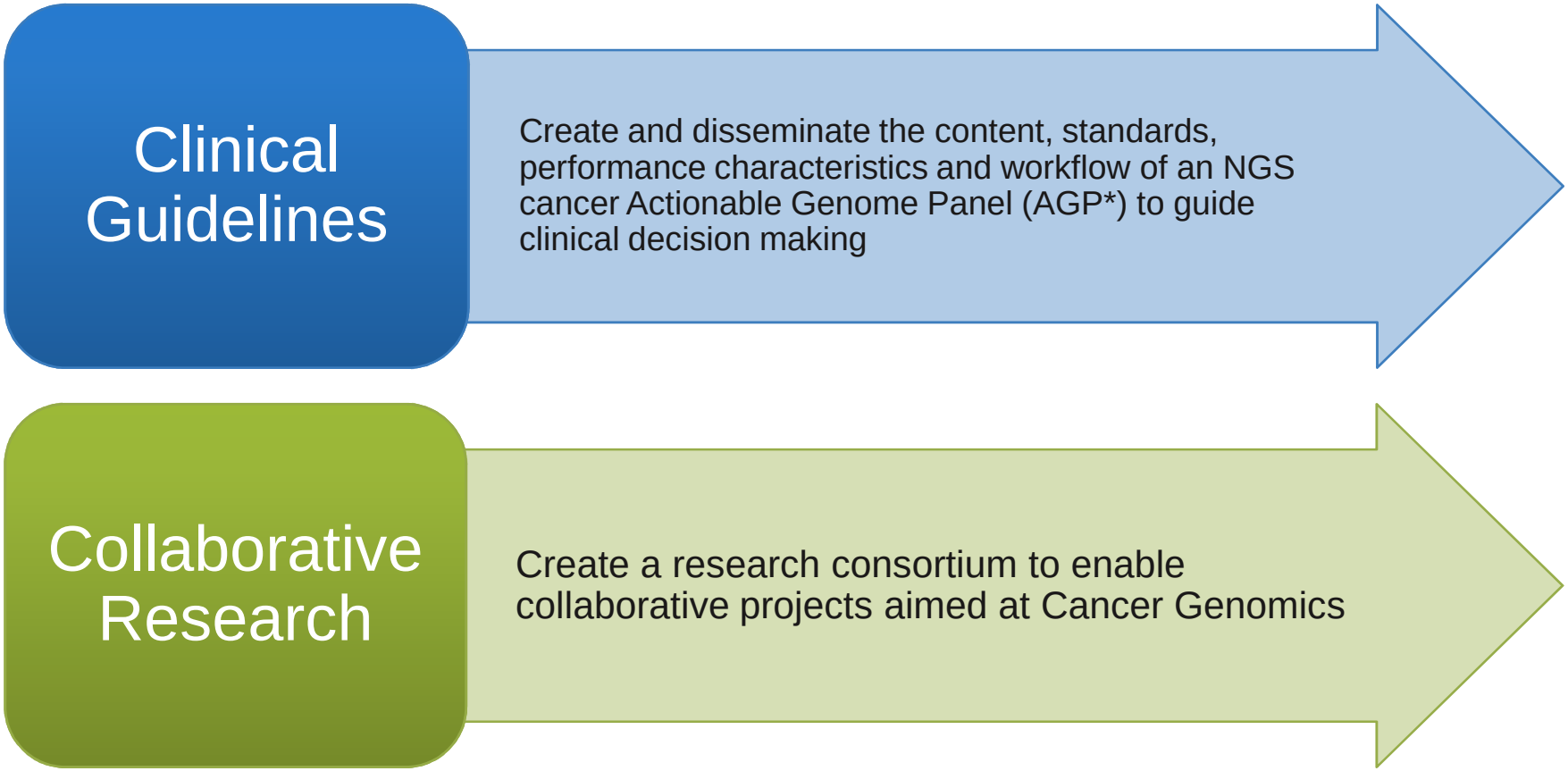


With the Ability To:

- Standardize
  - Enables standardization of multiplexed platform for relevant genes
- Streamline
  - Optimizes introduction of new biomarkers through standard system
- Decentralize
  - Deliver universal platform for routine testing enabling rapid commercial access
- Investigate
  - Brings trial enrollment to local clinics, increasing candidate pool for studies
- Collaborate
  - Facilitates combination trials within and across pharma companies

The Actionable Genome Consortium

Driving guidelines and answering questions



*AGP: The set of molecular assays that can be recommended to all practicing oncologists as necessary to guide clinical decision making.

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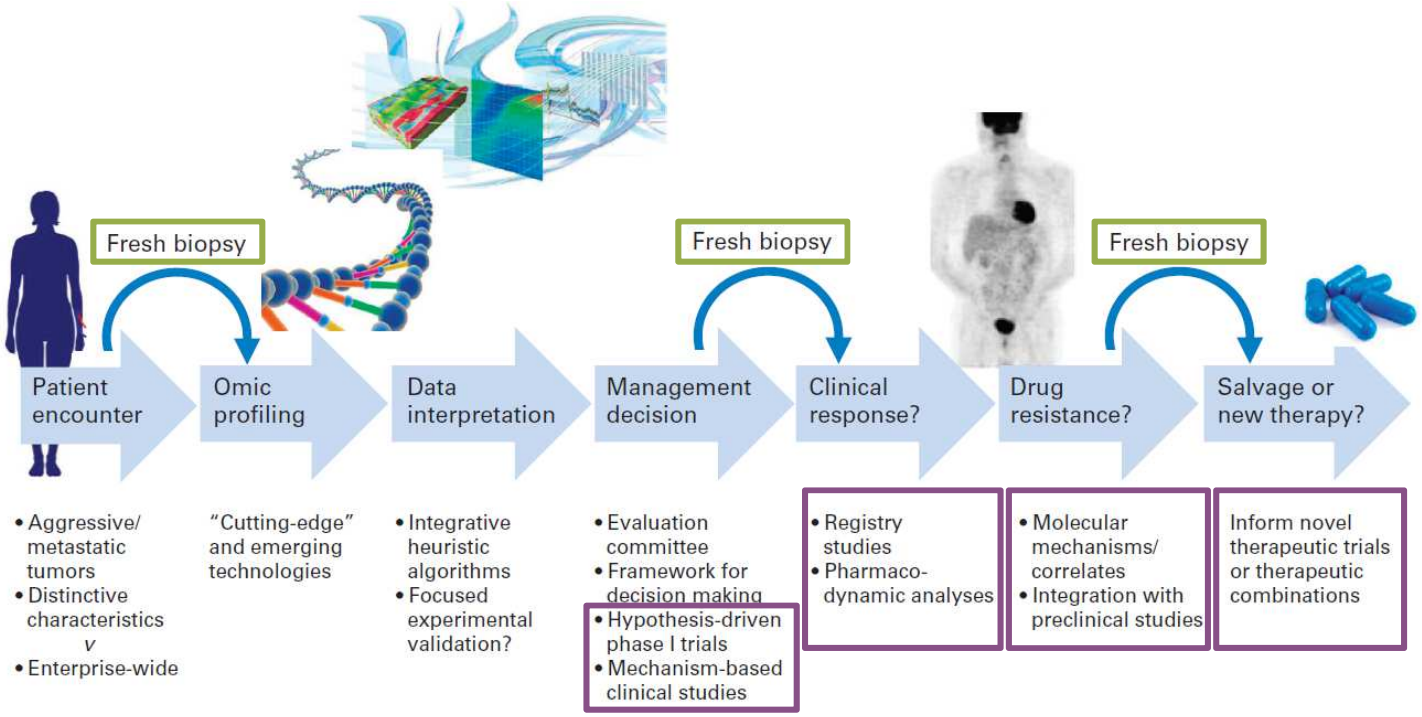
Transforming Oncology with Genomics

Conclusions

Comprehensive genomic interrogation of tumors will be commonplace

- At multiple-time points, from primary screening to advanced disease
- Resulting in earlier detection, precise diagnosis, and targeted treatment
- With great potential for non-invasive testing methods (CTCs and ctDNA)
- Leading to improved outcomes (chronic management and ultimately cure)



Garraway LA. Genomics-driven oncology: framework for an emerging paradigm. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*, 31(15), 1806-1814 (2013).

Thank You!