Το μεταβαλλόμενο πεδίο Κλινικής Έρευνας
&
Ανάπτυξη προηγμένων θεραπειών στην Ογκολογία

Δημήτρης Μαυρουδής

Καθηγητής Παθολογικής Ογκολογίας

Πανεπιστήμιο Κρήτης

Historical milestones

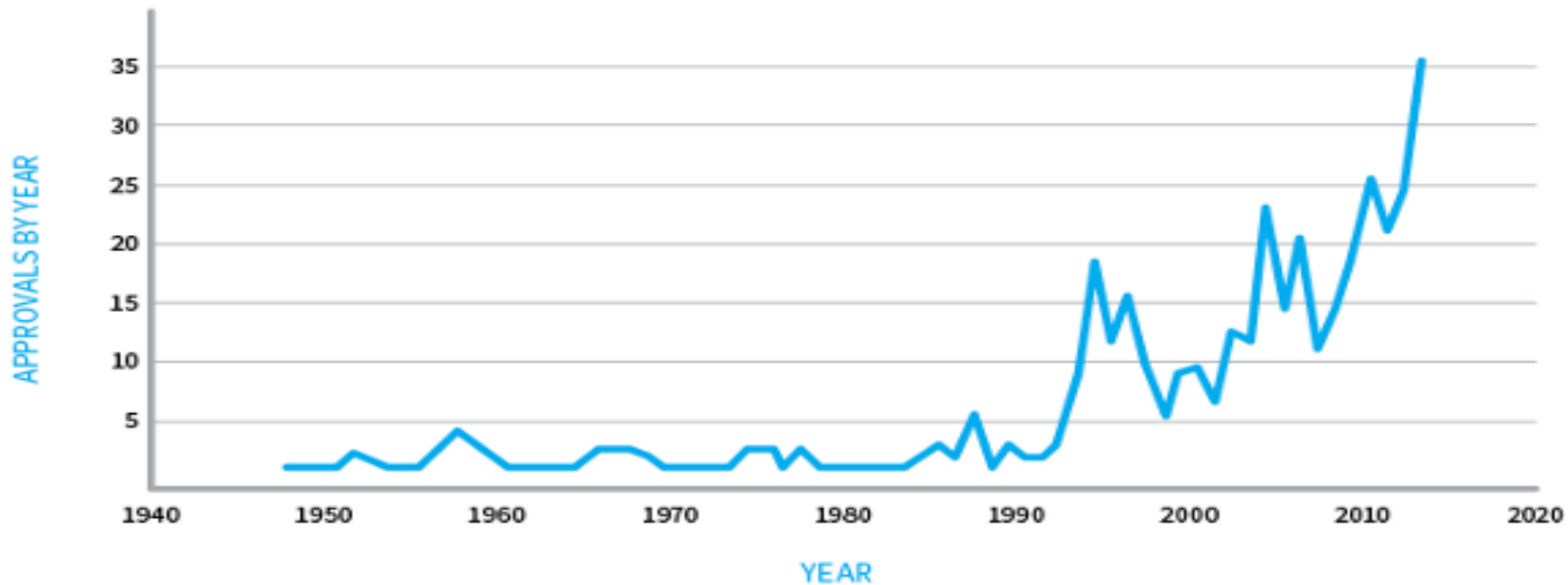
- 1971 National Cancer Act
  War on Cancer by President Richard Nixon

- 1970's
  - ER needed for response to tamoxifen

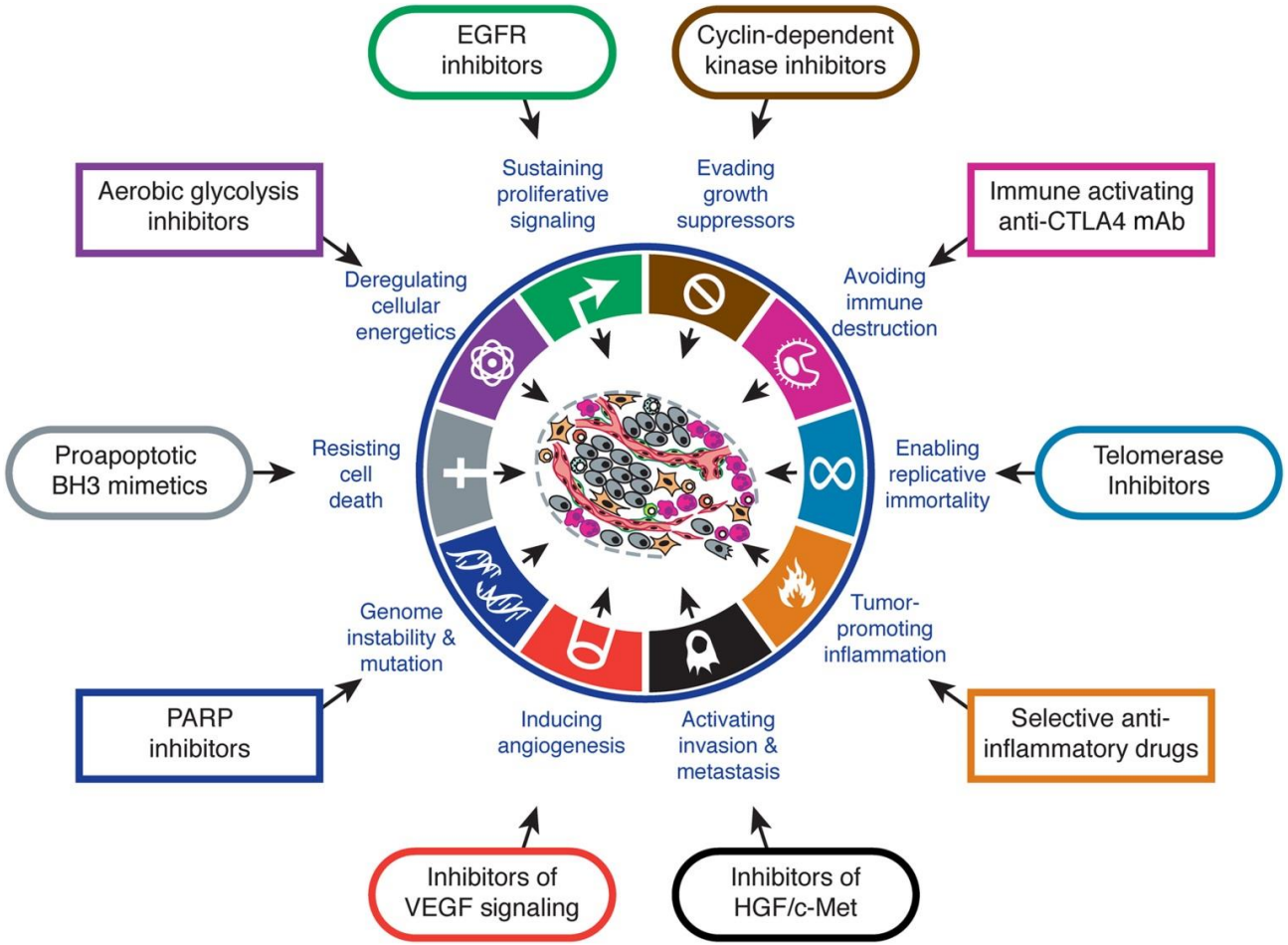
- 1990's
  - Retinoic acid – *PML_RAR*
  - Rituximab – (CD20) B-NHL
  - Trastuzumab – Her2*neu* Amplified Breast Cancer

- 2001
  - Imatinib – BCR-abl CML (c-kit – GIST)

FDA Cancer Drug Approvals by Year

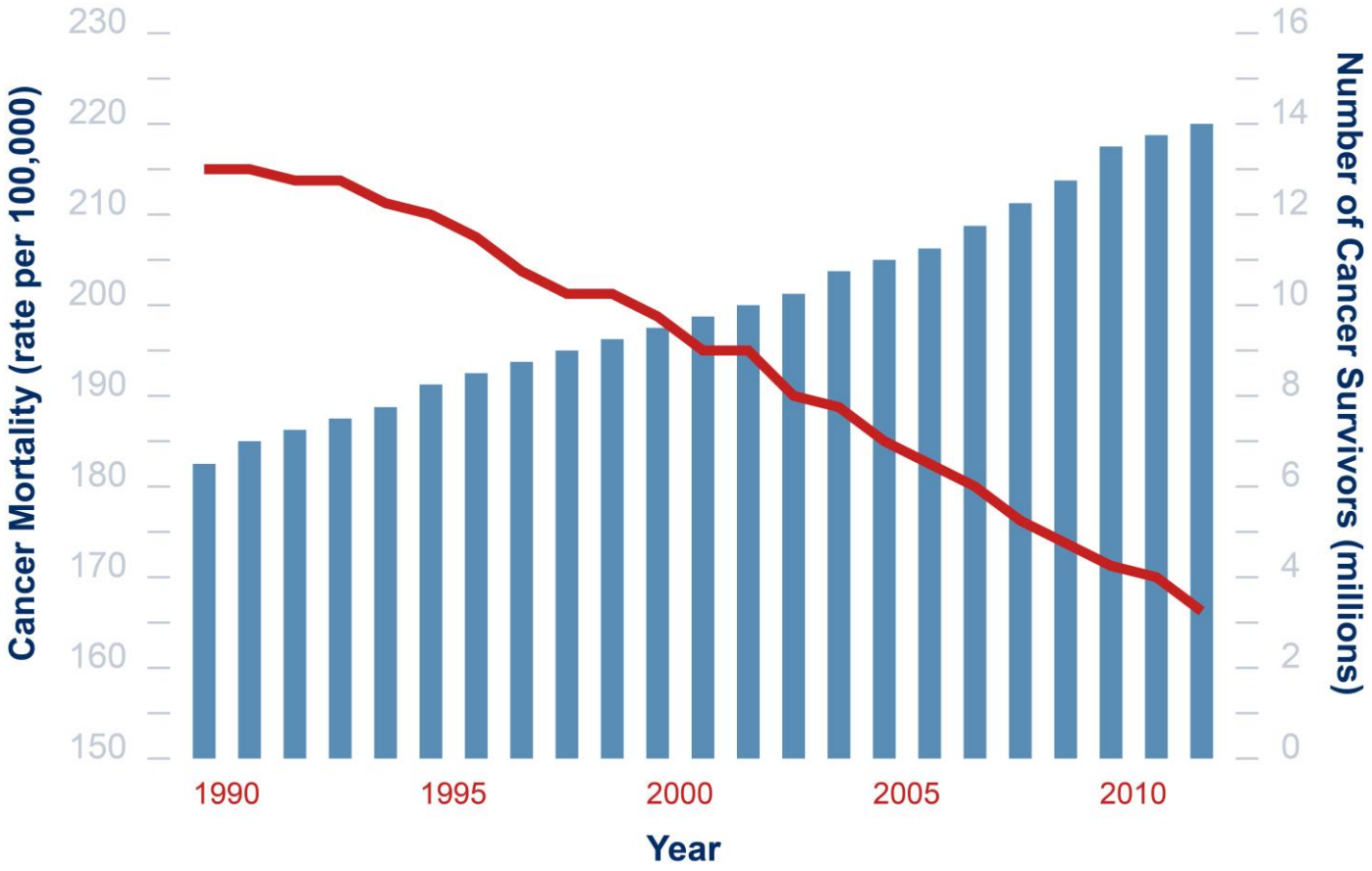


Hallmarks of Cancer

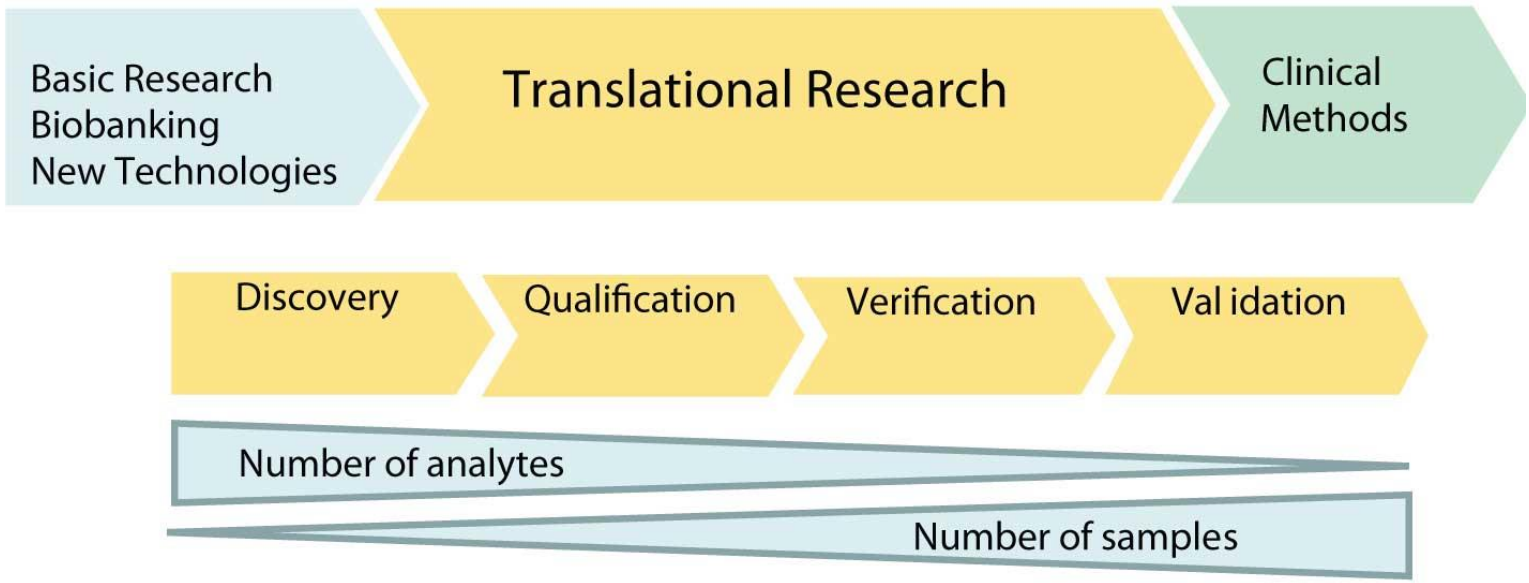


Cell 2011 144, 646-674

Decreased mortality, Improved survival of cancer patients

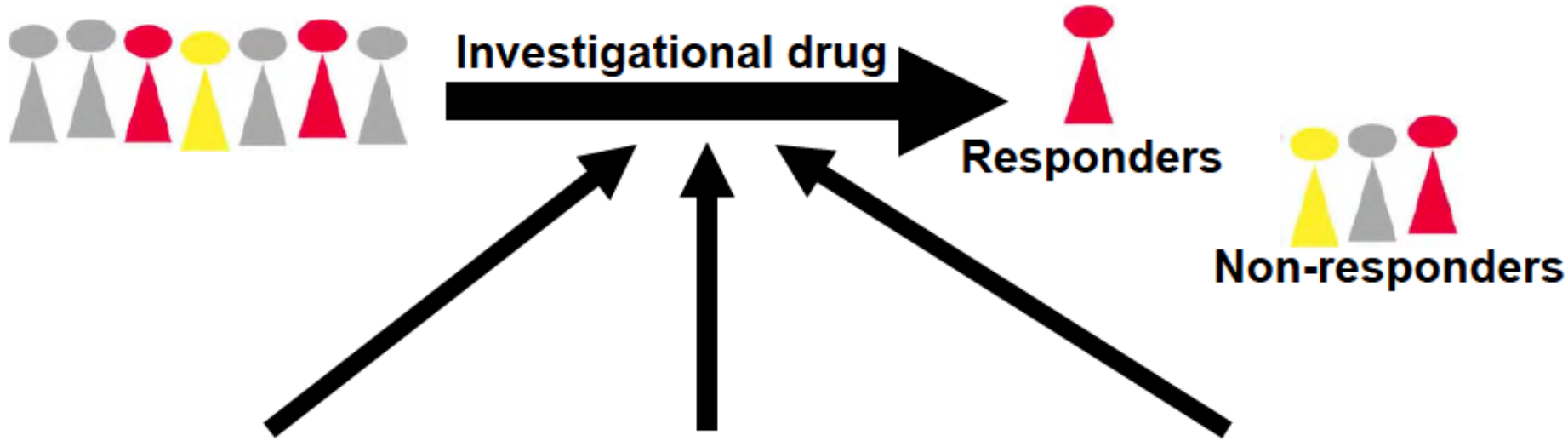


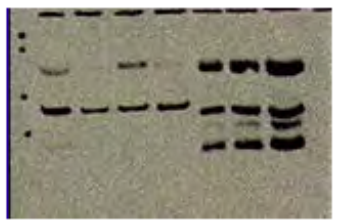
Roadmap to progress

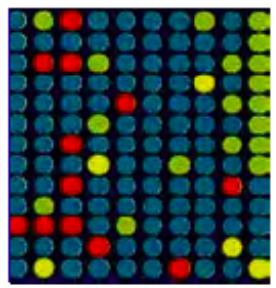


Toward Precision Medicine

Put more science into clinical trials

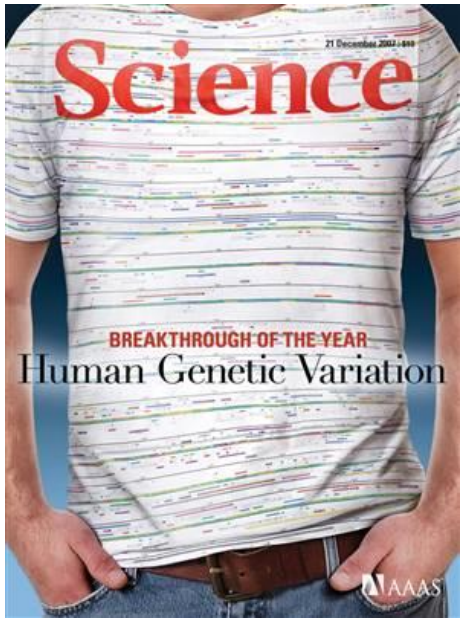




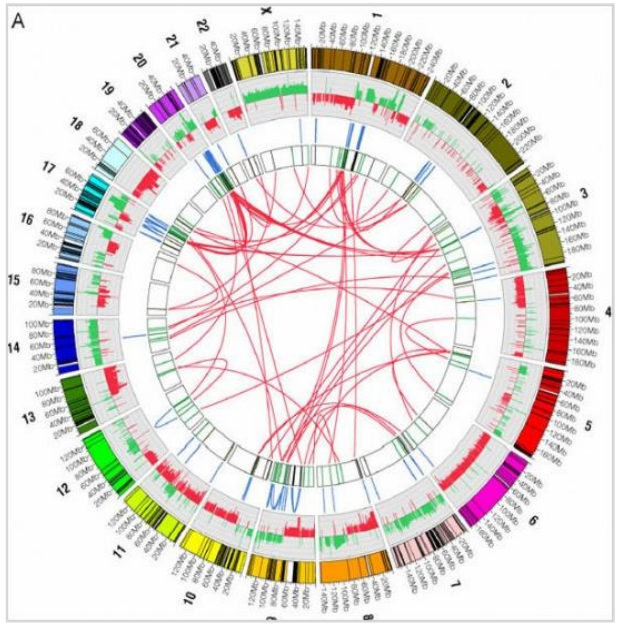


Modified from American Association for Cancer Research

Precision Medicine



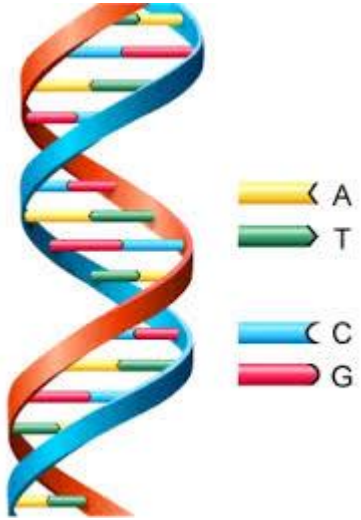
Germline Variation



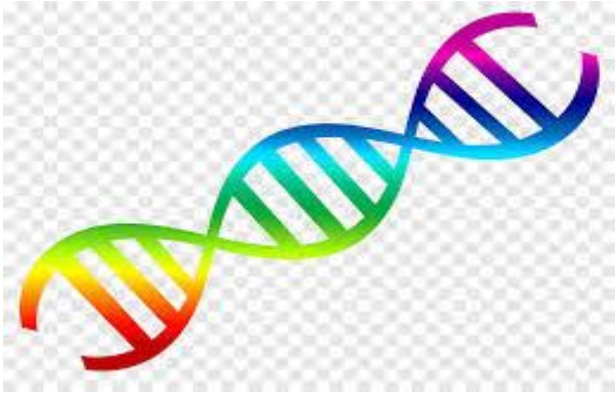
Somatic Mutation

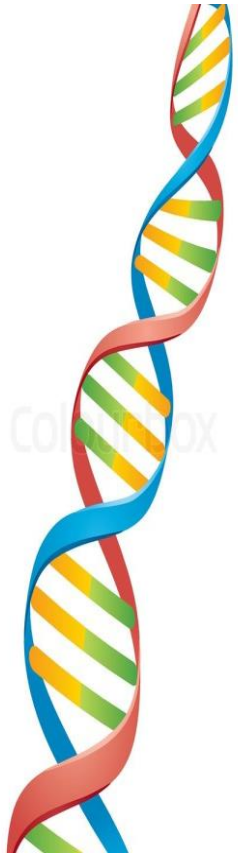
Personalized Care

“It’s far more important to know what person the disease has than what disease the person has”



Hippocrates (ca. 400 BC)





Precision & Personalized Medicine - Definitions

Precision Medicine

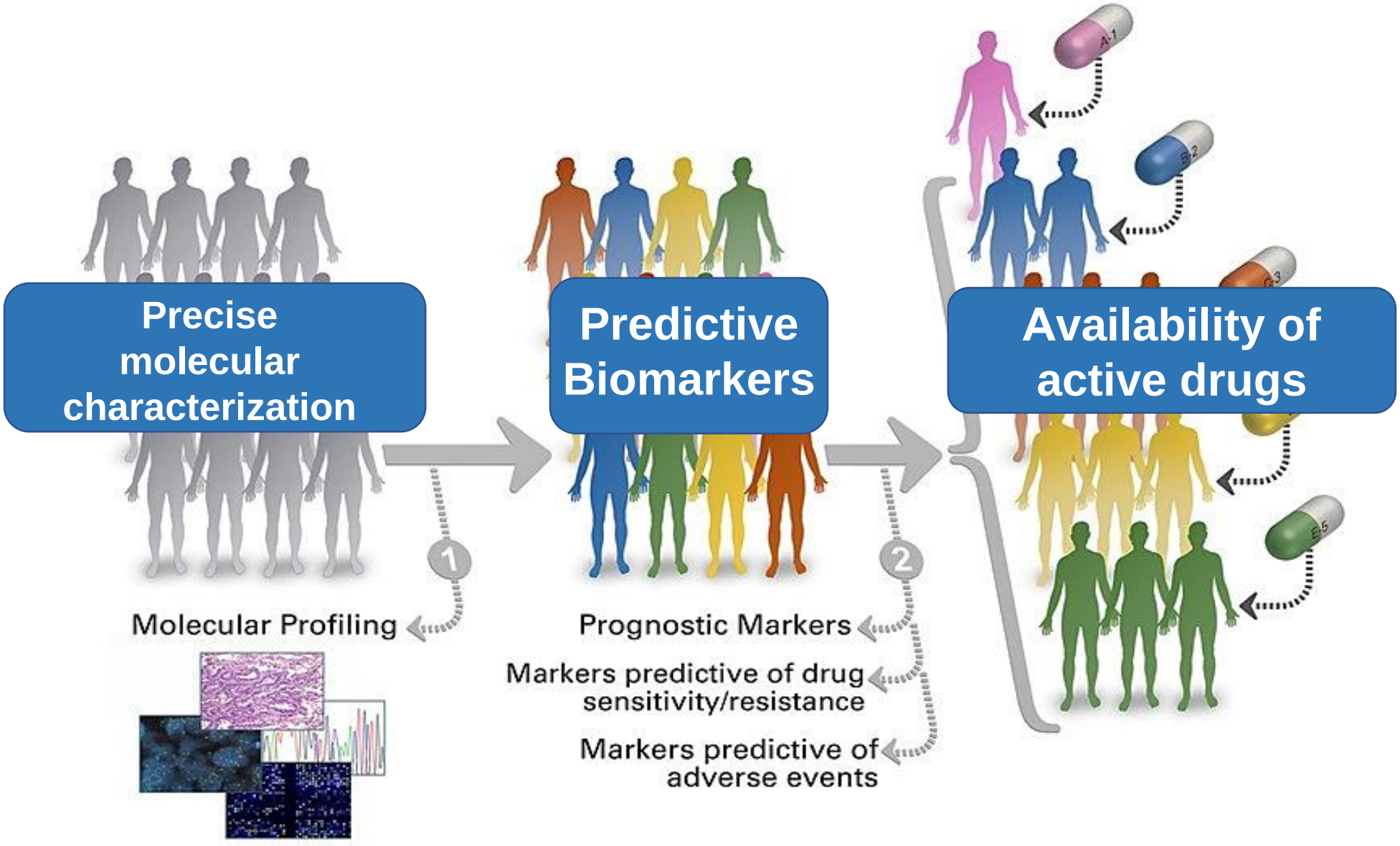
- The tailoring of therapeutic interventions to the individual molecular features of patients and/or their disease

Personalized Medicine

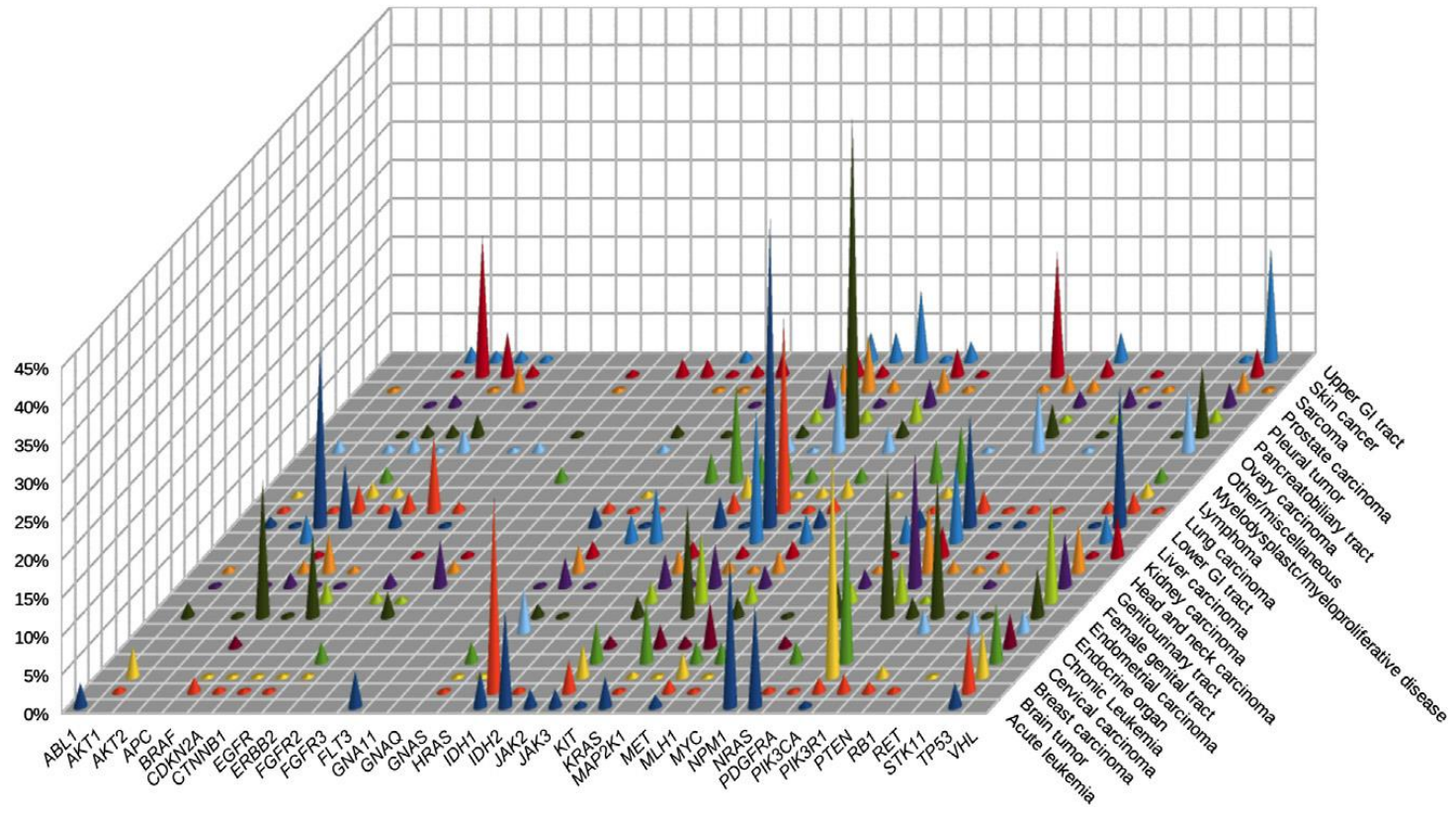
- The tailoring of medical treatment to the individual characteristics of each patient

- Preventative or therapeutic interventions can then be concentrated on those who will benefit, sparing expense and side-effects for those who will not

Basic elements of Precision Medicine

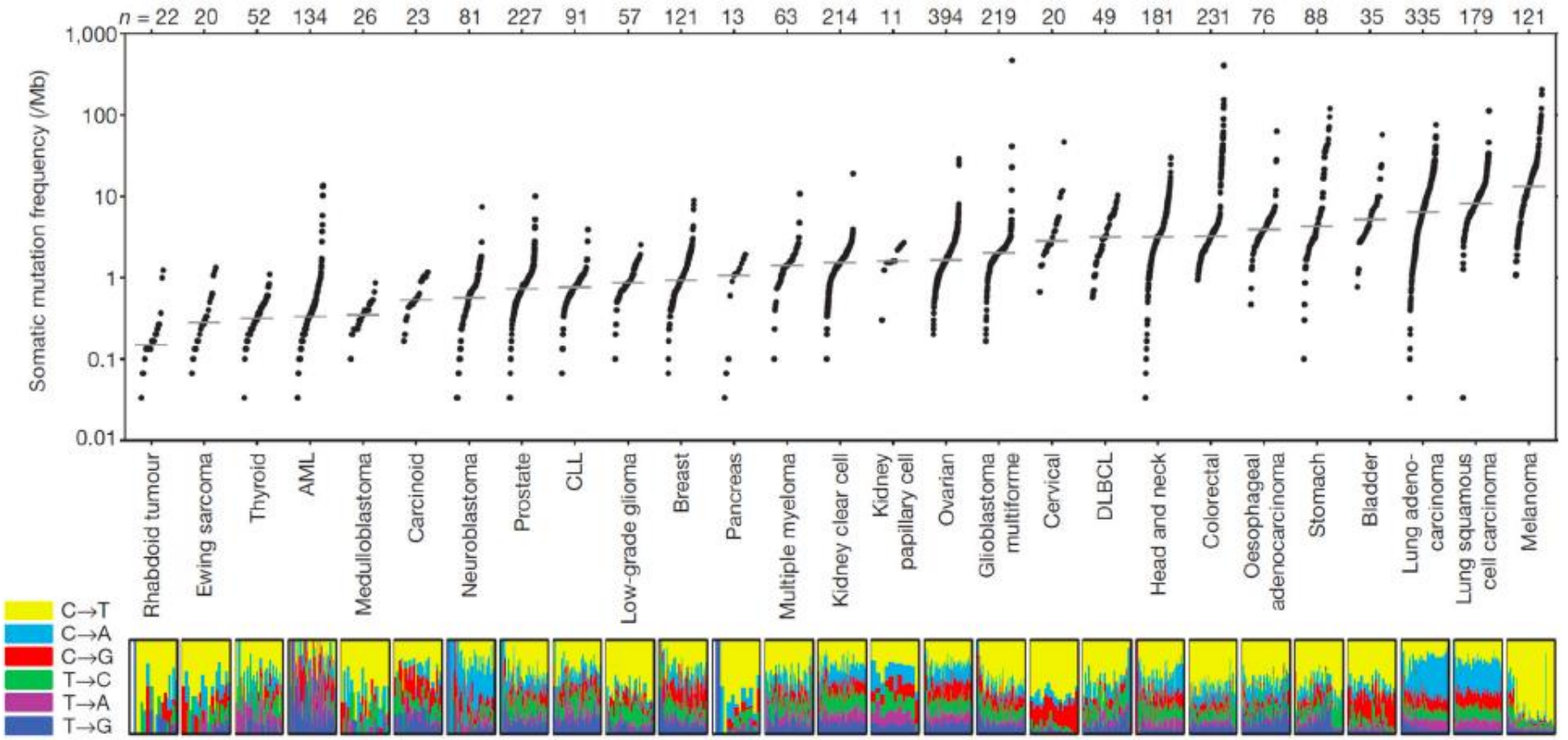


Genomic Landscape of 5,000 Human Cancers



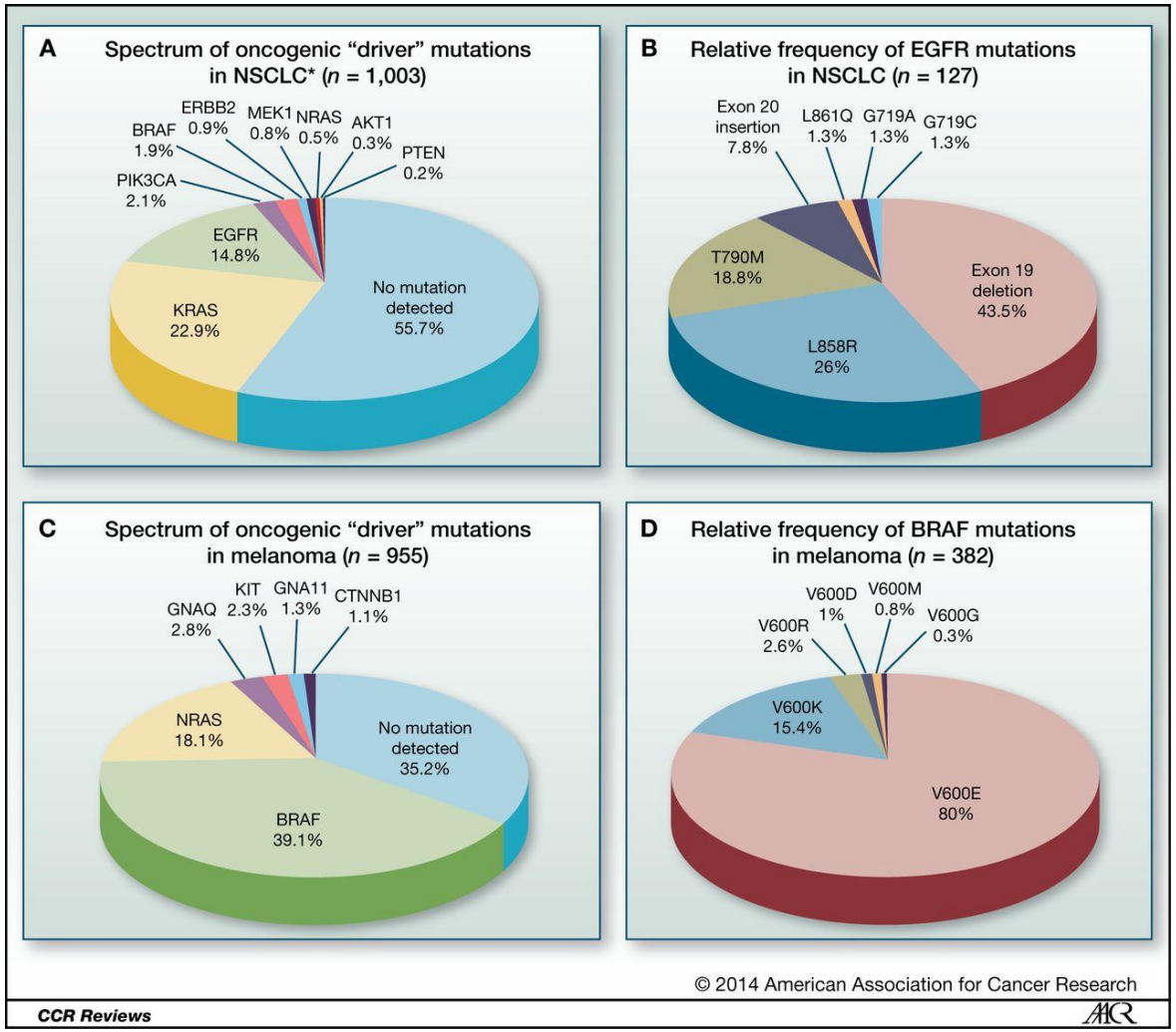
MacConaill, L, et. al., J Mol Diagn 2014, 16: 660-672

Mutation load varies among different cancer types



Adapted from Roychowdhury, Science Translational Medicine 2011,

Common cancers are collections of rare cancers



Catherine B. Meador et al. Clin Cancer Res 2014;20:2264-2275

NSCLC – Targeted therapy for advanced or metastatic disease

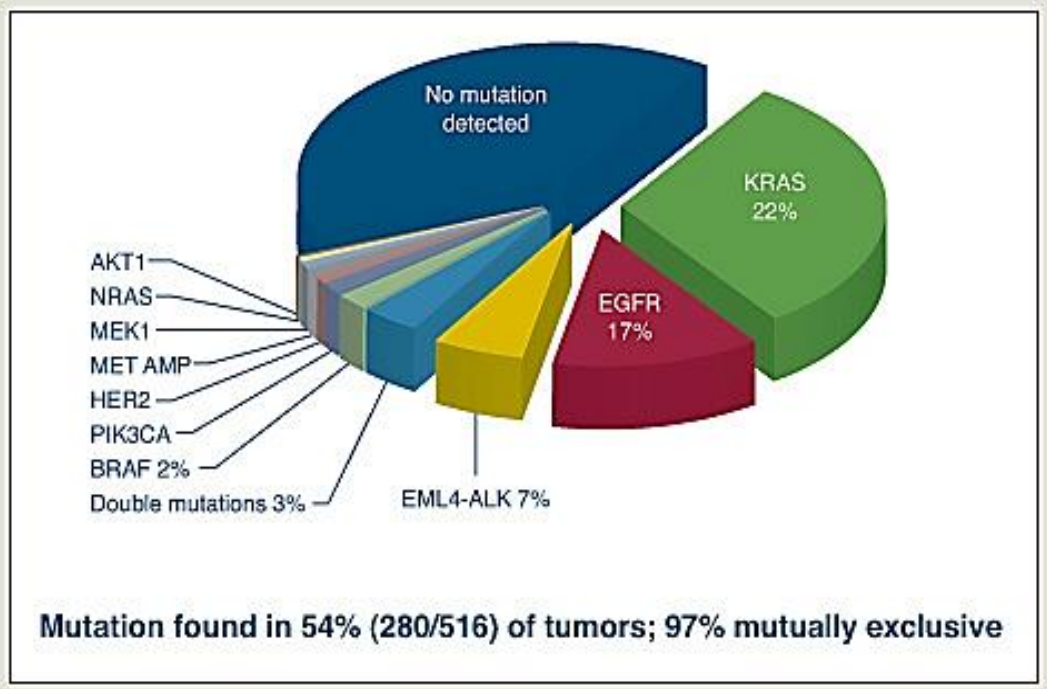
Genetic alteration	Approved targeted therapies
EGFR	Afatinib Erlotinib Gefitinib Osimertinib
ALK	Alectinib Brigatinib Ceritinib Crizotinib
ROS1	Crizotinib
BRAF	Dabrafenib/Trametinib

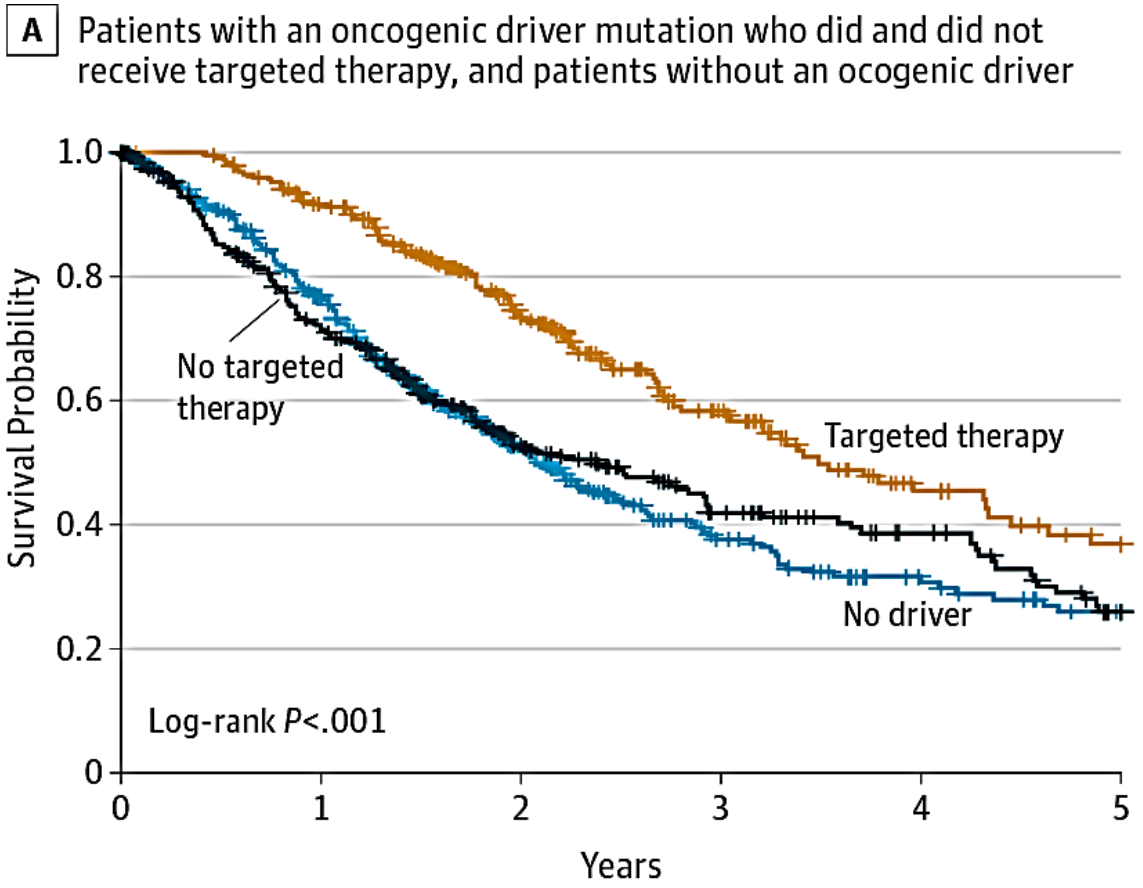
Emerging targets	Available active targeted agents
High level *MET* amplification or *MET* exon 14 skipping mutation	Crizotinib
***RET* rearrangements**	Cabozantinib Vandetanib
***HER2* mutations**	Ado-trastuzumab emtansine

Approved targeted therapies for other solid tumors

Genetic alteration	Approved targeted therapies
Breast Cancer	
ERBB2/HER2	Trastuzumab Ado-trastuzumab emtansine Trastuzumab/pertuzumab Lapatinib
BRCA	Olaparib
Melanoma	
BRAF V600	Dabrafenib/Trametinib Vemurafenib/Trametinib
Colorectal Cancer	
KRAS/BRAF/NRAS WT	Cetuximab Panitumumab
Ovarian Cancer	
BRCA	Olaparib Rucaparib

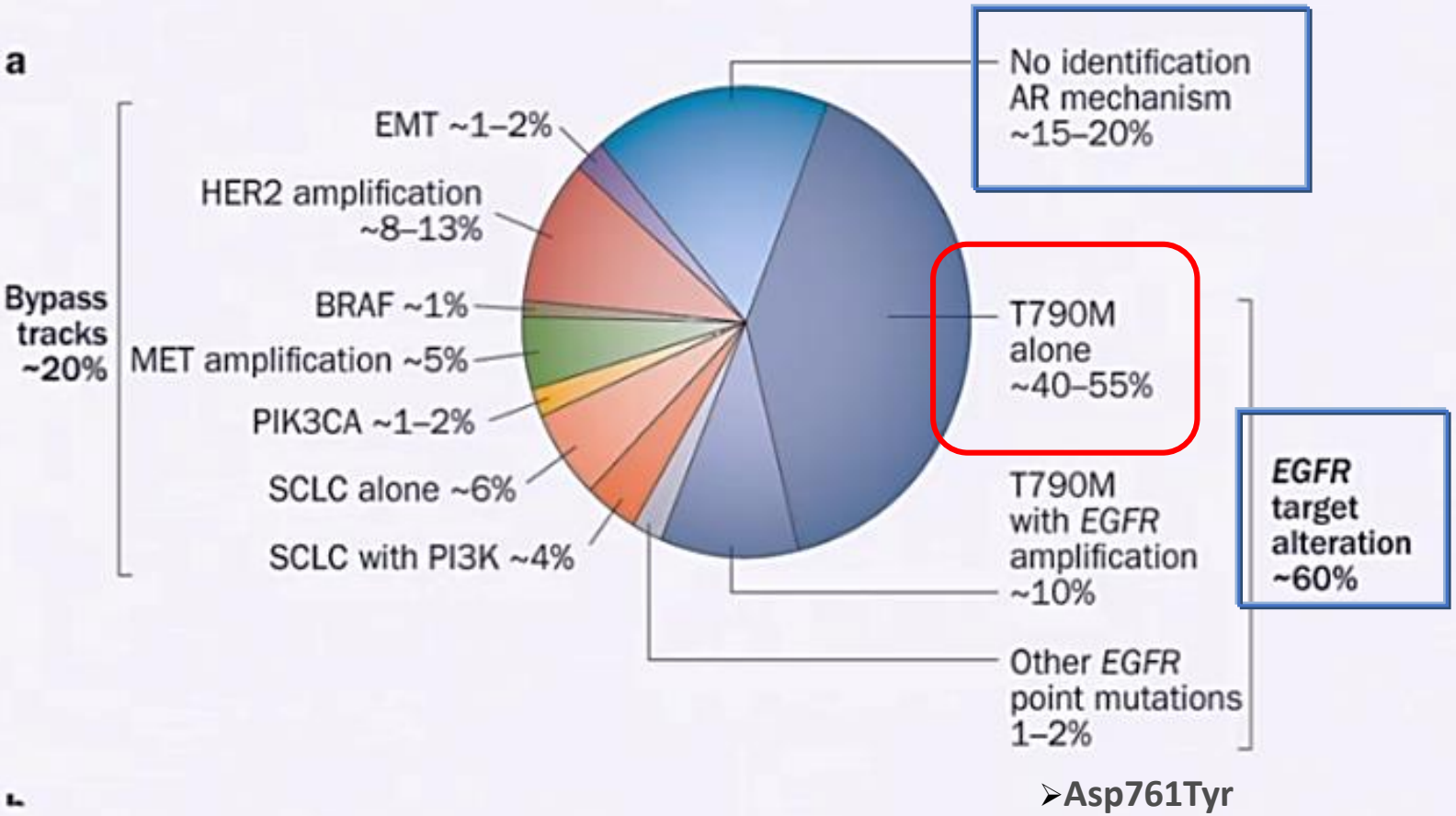
NSCLC patients with drivers receiving a matched therapy live longer





Kris MG et al. JAMA. 2014;311(19):1998-2006

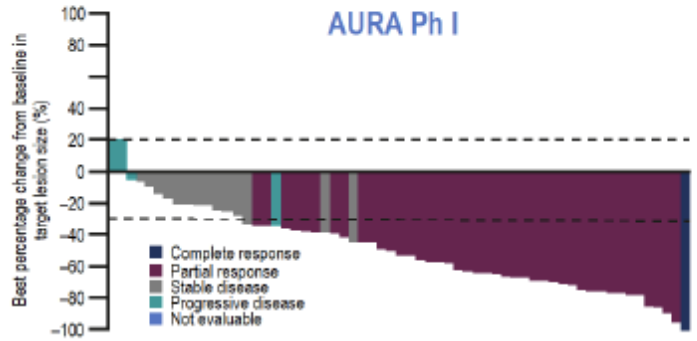
Mechanisms of acquired resistance in EGFR-mut

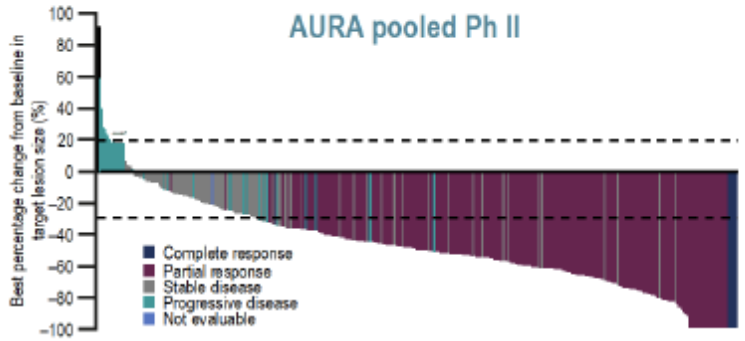


- Asp761Tyr
- Thr854Ala
- Leu747Ser

Camidge Nat Rev Clin Oncol 14

Targeting T790M- Osimertinib





	AURA Ph I (80 mg) N=61	AURA pooled Ph II (80 mg) N=397
Confirmed ORR	71% (95% CI 57, 82)	66% (95% CI 61, 71)
Disease control rate†	93% (95% CI 84, 98)	91% (95% CI 88, 94)
Best objective response		
Complete response	1	6
Partial response	42	256
Stable disease ≥6 weeks	14	99
Progressive disease	2	25

AURA Ph I data cut-off 4 January 2016; population: evaluable for response set; assessment: investigator assessed;
AURA pooled Ph II data cut-off 1 November 2015; population: evaluable for response set; assessment: BICR
*Represents imputed values: if it is known that the patient has died, has new lesions or progression of non-target lesions, has withdrawn due to disease progression, and has no evaluable target lesion (before or at progression) assessments, best change will be imputed as 20%;
†Complete response, partial response, stable disease ≥6 weeks
ORR, objective response rate; CI, confidence interval

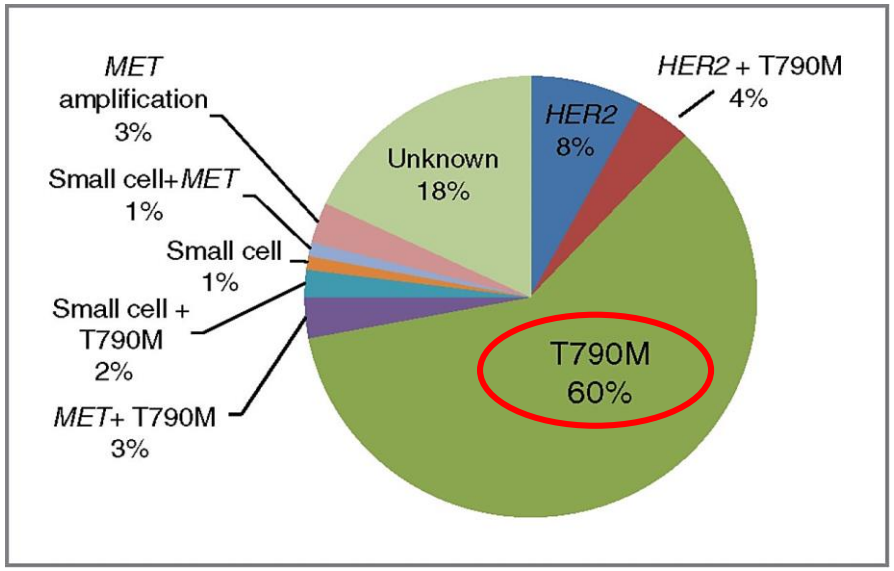
elcc

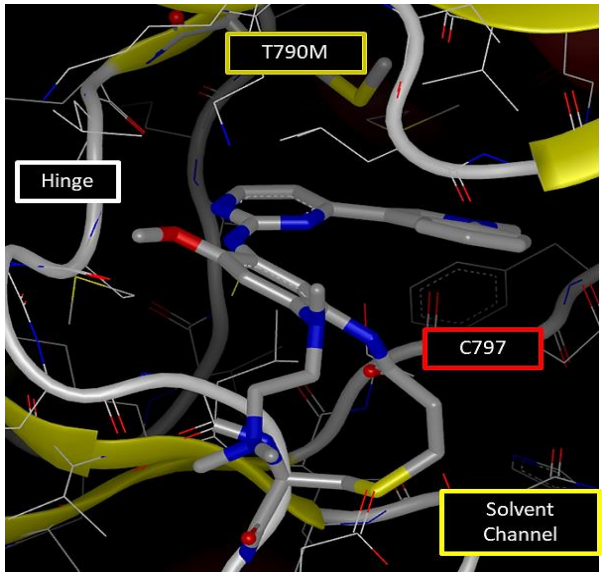
EUROPEAN LUNG CANCER CONFERENCE 2016

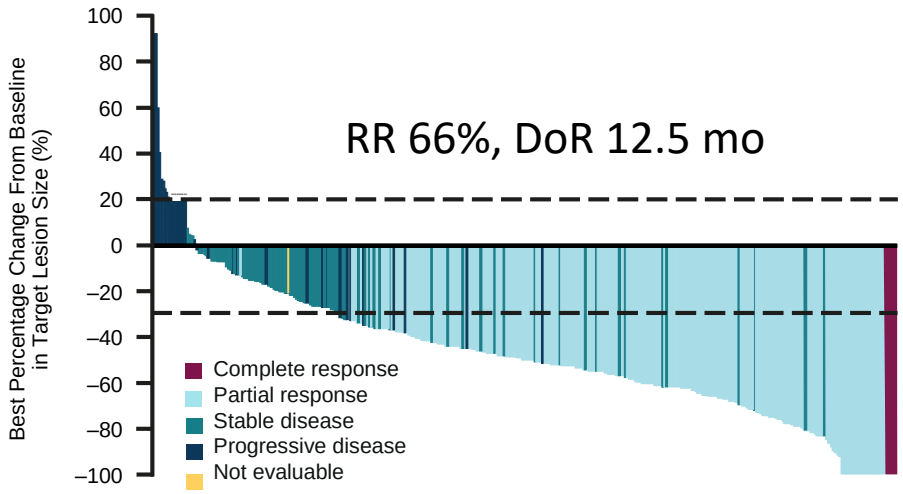
Presented by James C-H Yang at the 6th IASLC/ESMO European Lung Cancer Conference, 13–16 April 2016, Geneva, Switzerland; Abstract LBA2_PR; J Thorac Oncol 2016; 11(Issue 4): S152–S153

Addressing resistance to therapy

EGFR+

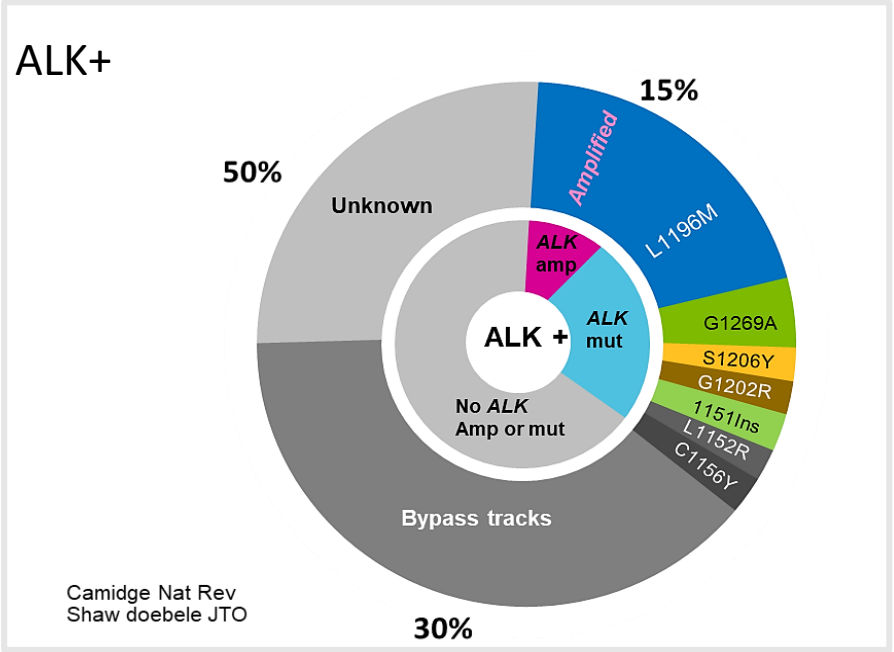


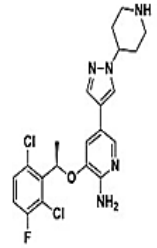




Helena A. Yu et al. Clin Cancer Res 2013;19:2240-2247

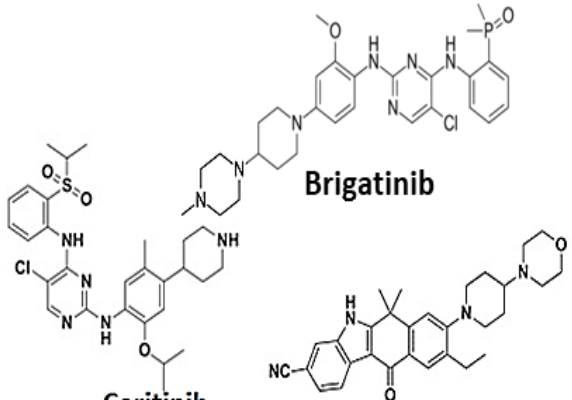
ALK+





Crizotinib

1st gen ALKi/ROS1i

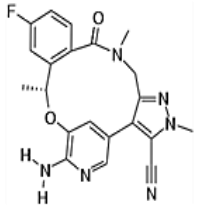


Brigatinib

Ceritinib

Alectinib

2nd gen ALKi

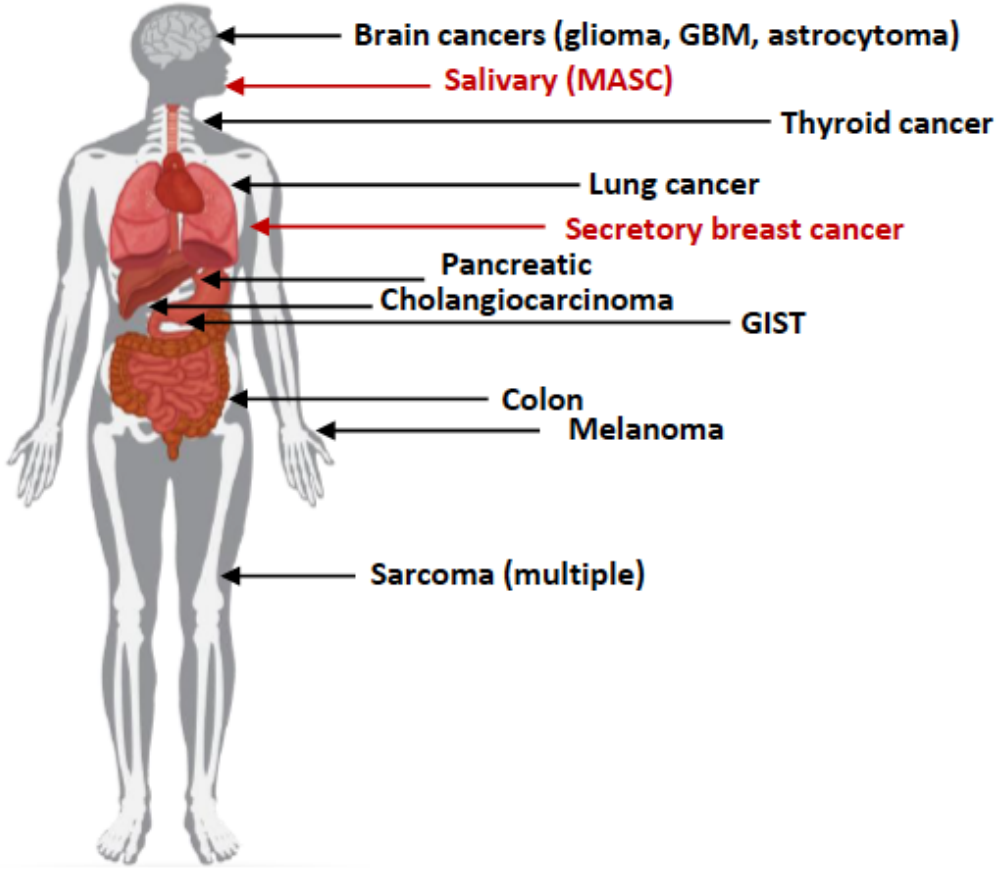


Lorlatinib

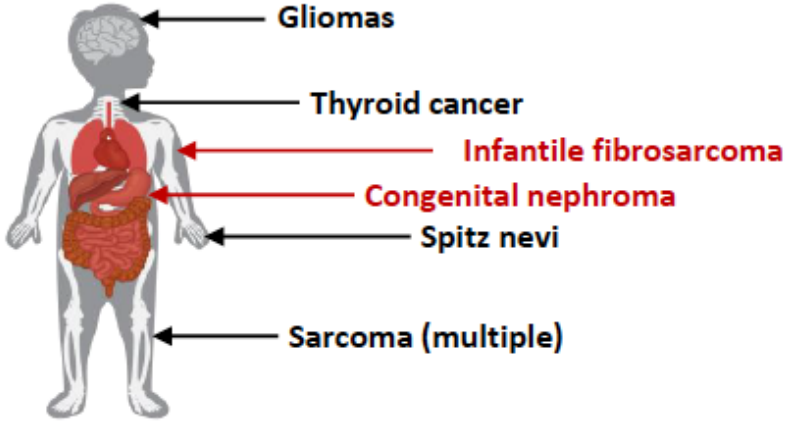
3rd gen ALKi

Targeted therapy beyond histology

TRK fusions found in diverse cancer histologies

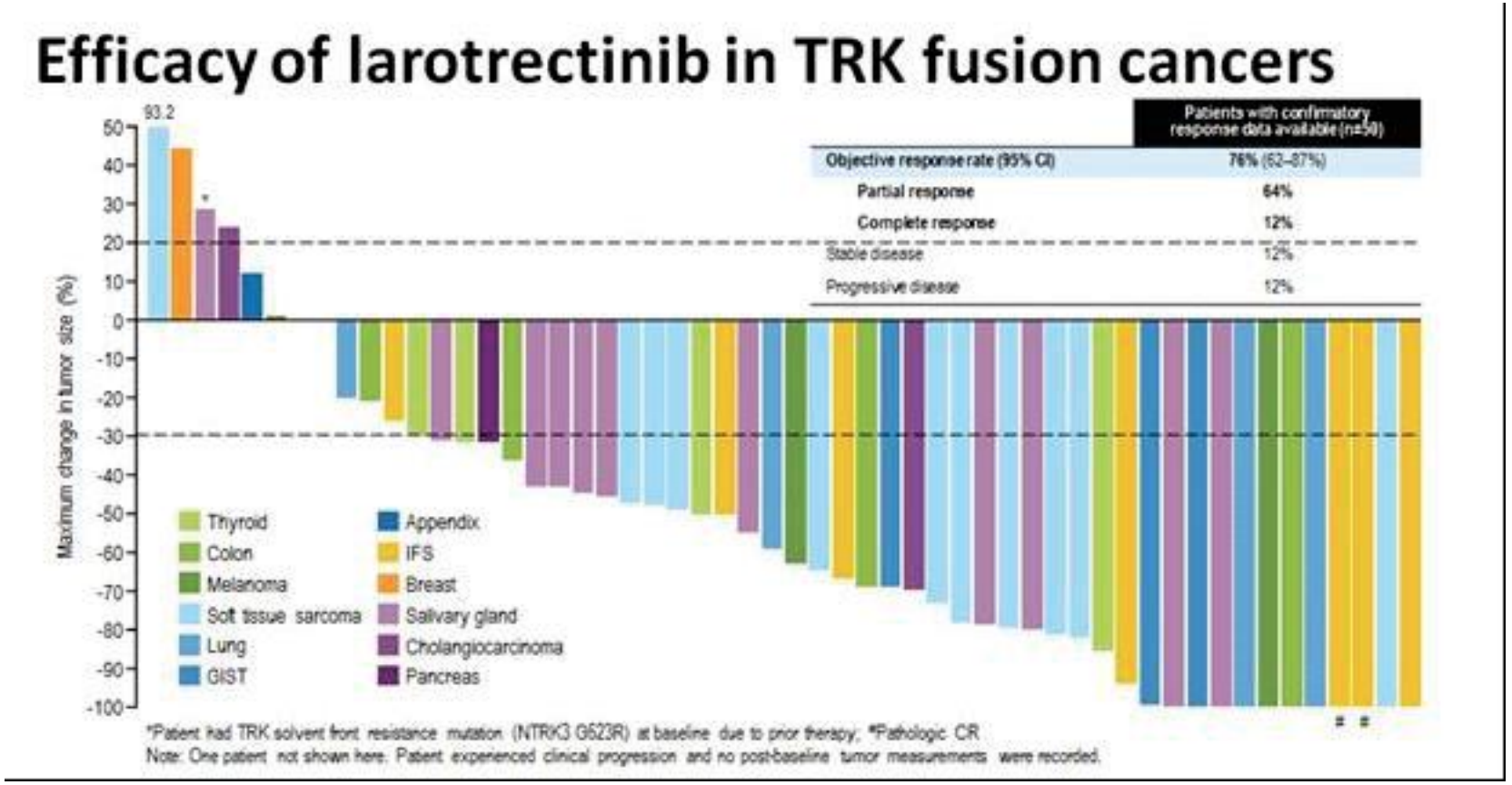


- Common cancer with low TRK fusion frequency
- Rare cancer with high TRK fusion frequency



Estimated 1,500–5,000 patients harbor TRK fusion-positive cancers in the United States annually

Success across histologies: NTRK as an example



ORR = 76%

Responses seen across all tumor types

ASCO 2017, LBA 2501

Cancer Immunotherapy

2011

Ipilimumab introduced for melanoma

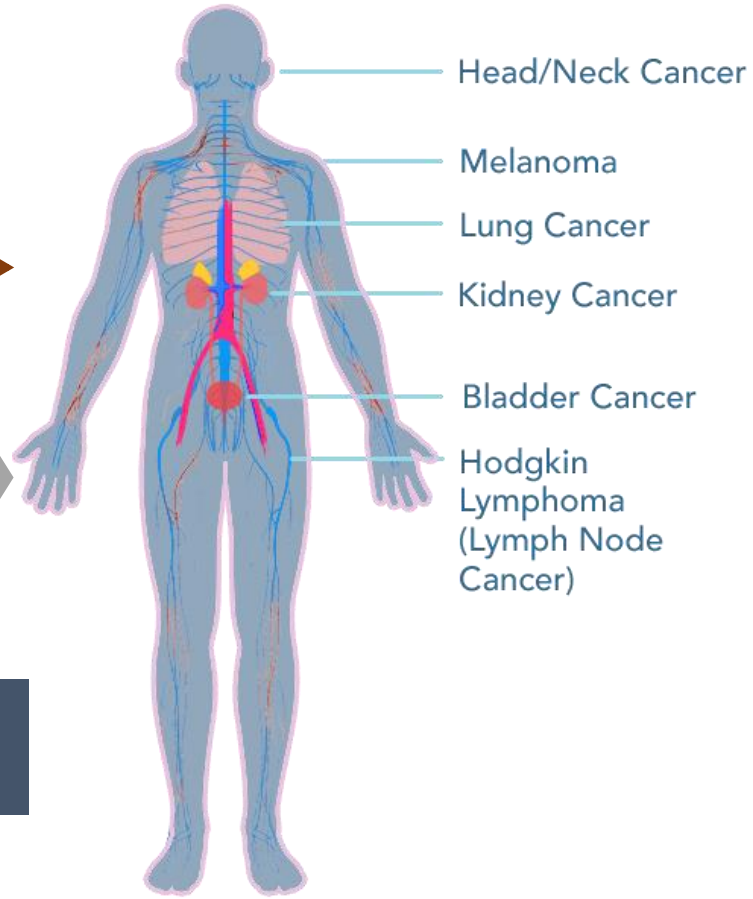
2014

Pembrolizumab, nivolumab approved for melanoma

2015-2016

PD-1/L-1 drugs benefit even more of cancers

2016 ASCO
Advance of the Year

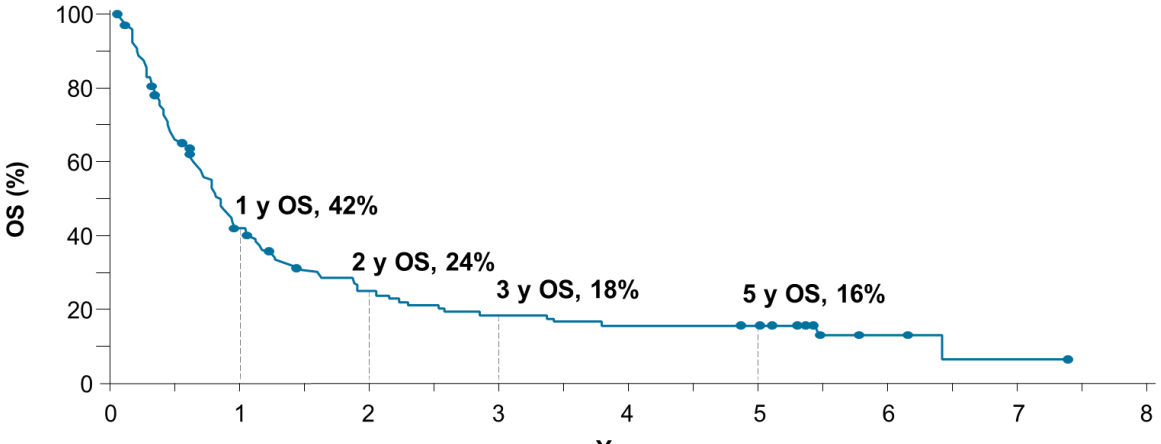


Beyond targeted therapy - Immune checkpoint blockade

Responses to immunotherapy across multiple tumor types

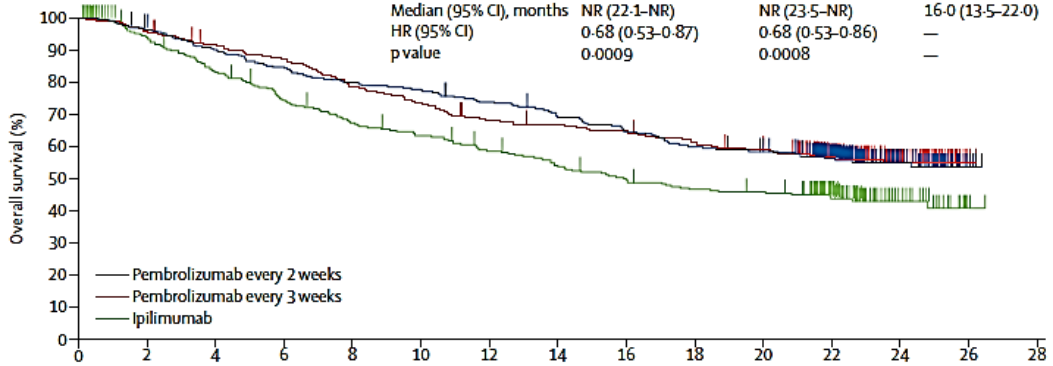
- NSCLC
- SCLC
- Melanoma
- Renal cell Ca
- Bladder Ca
- Head Neck Ca
- Hepatocellular Ca

Long – term survival



No. at Risk
A

	Pembrolizumab every 2 weeks, n=279	Pembrolizumab every 3 weeks, n=277	Ipilimumab n=278
Events, n	122	119	142
Median (95% CI), months	NR (22·1–NR)	NR (23·5–NR)	16·0 (13·5–22·0)
HR (95% CI)	0·68 (0·53–0·87)	0·68 (0·53–0·86)	—
p value	0·0009	0·0008	—



Number at risk

Pembrolizumab every 2 weeks	279	266	249	234	221	215	202	188	176	163	156	96	44	4	0
Pembrolizumab every 3 weeks	277	266	251	238	215	201	184	179	174	164	156	93	43	1	0
Ipilimumab	278	242	213	189	170	159	145	132	122	113	110	69	28	1	0

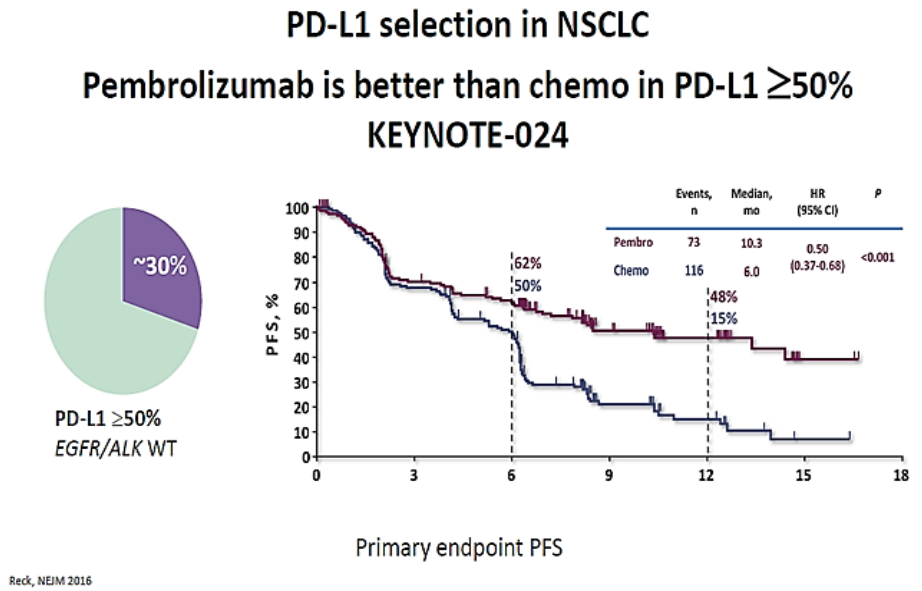
Biomarkers of response to immune checkpoint blockade

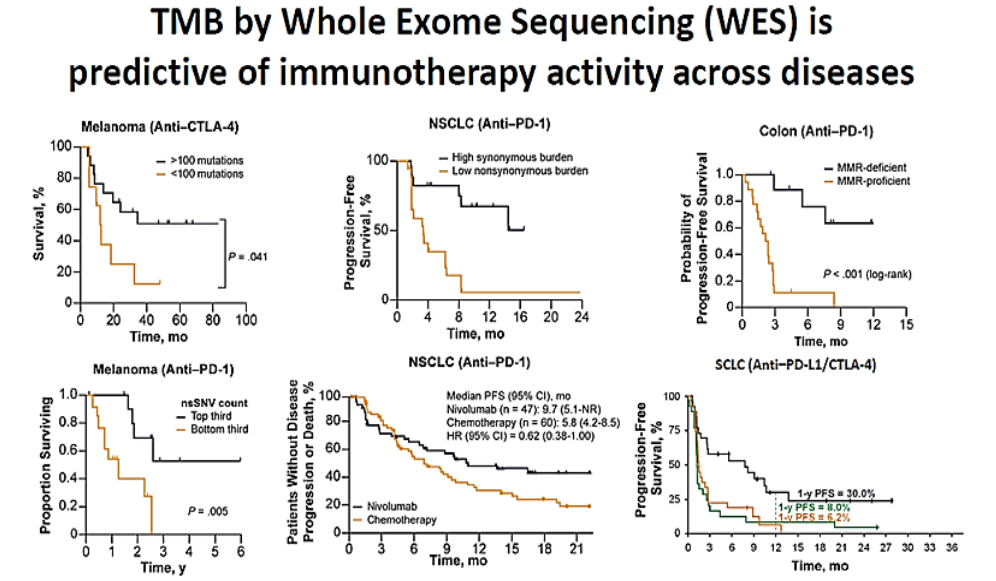
Established biomarkers

- PDL1
- Tumor mutational burden
- MMR deficiency (or MSI)

Research in the field is ongoing

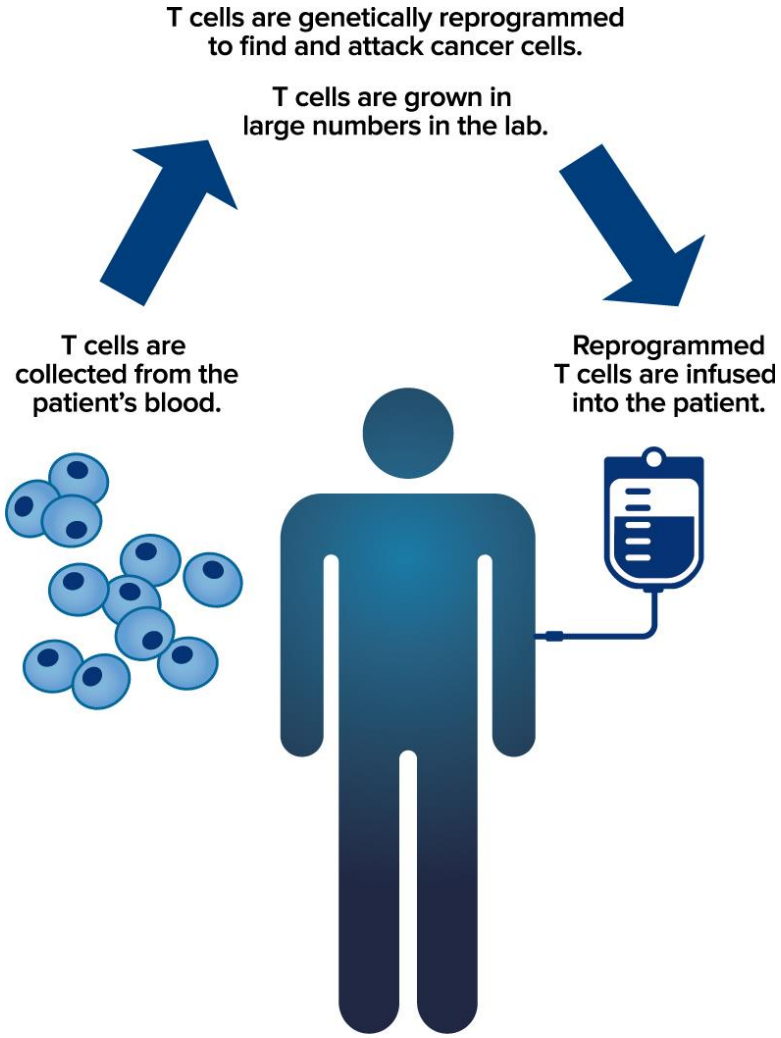
- Frameshift indel count
- Immune gene signatures
- Gut microbiome





1. Snyder, *N Engl J Med*. 2014; 2. Rizvi, *Science*. 2015; 3. Le DT, *N Engl J Med*. 2015; 4. Van Allen EM, *Science*. 2015 ; 5. Hugo, *Cell*. 2016 ; 6. Carbone, *N Engl J Med*. 2017; 7. Rizvi, WCLC 2017

Immunotherapy: more to come…….



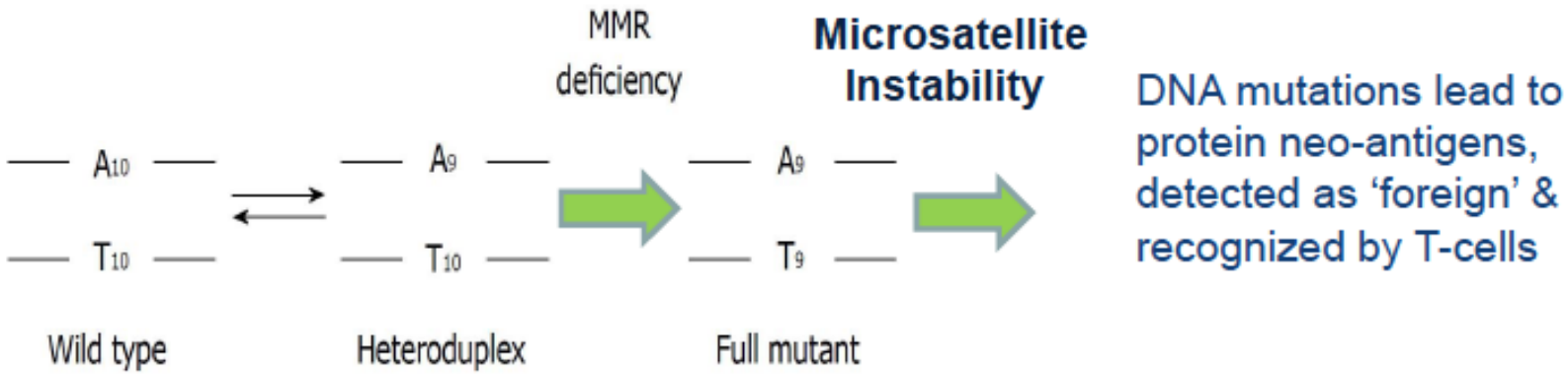
On the Horizon:

- CART-cell therapy
- Customized vaccines

Immunotherapy beyond histology

MSI-H Cancer Has a High Mutational Burden

- Mismatch repair (MMR) deficiency refers to deficiency in proteins responsible for DNA MMR: MSH2, MSH6, MLH1, PMS2.
- MMR deficiency leads to the MSI-H phenotype.
- MMR deficient/MSI-H cancers harbor thousands of mutations (i.e., high mutational burden; hypermutated phenotype).



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ORIGINAL ARTICLE

PD-1 Blockade in Tumors with Mismatch-Repair Deficiency

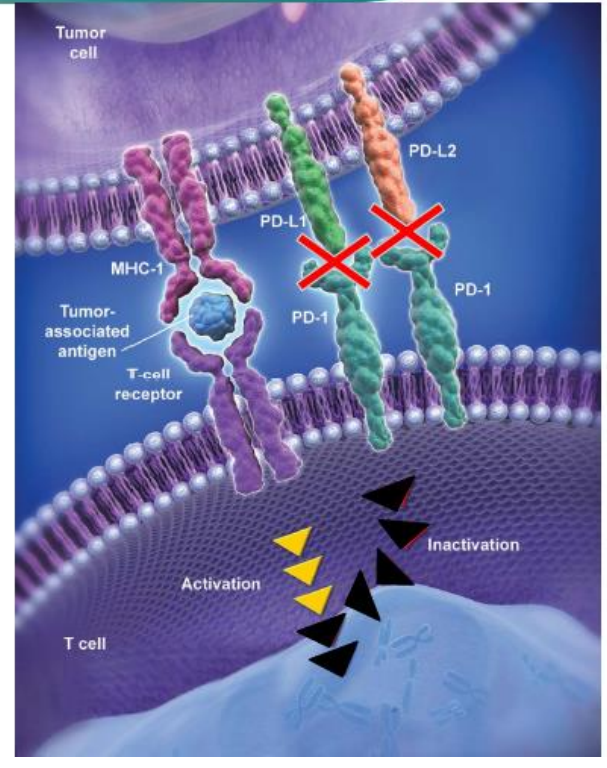
Biological Rationale for Tumor-Agnostic Approa

Table 24: Efficacy Results for Patients with MSI-H/dMMR Cancer

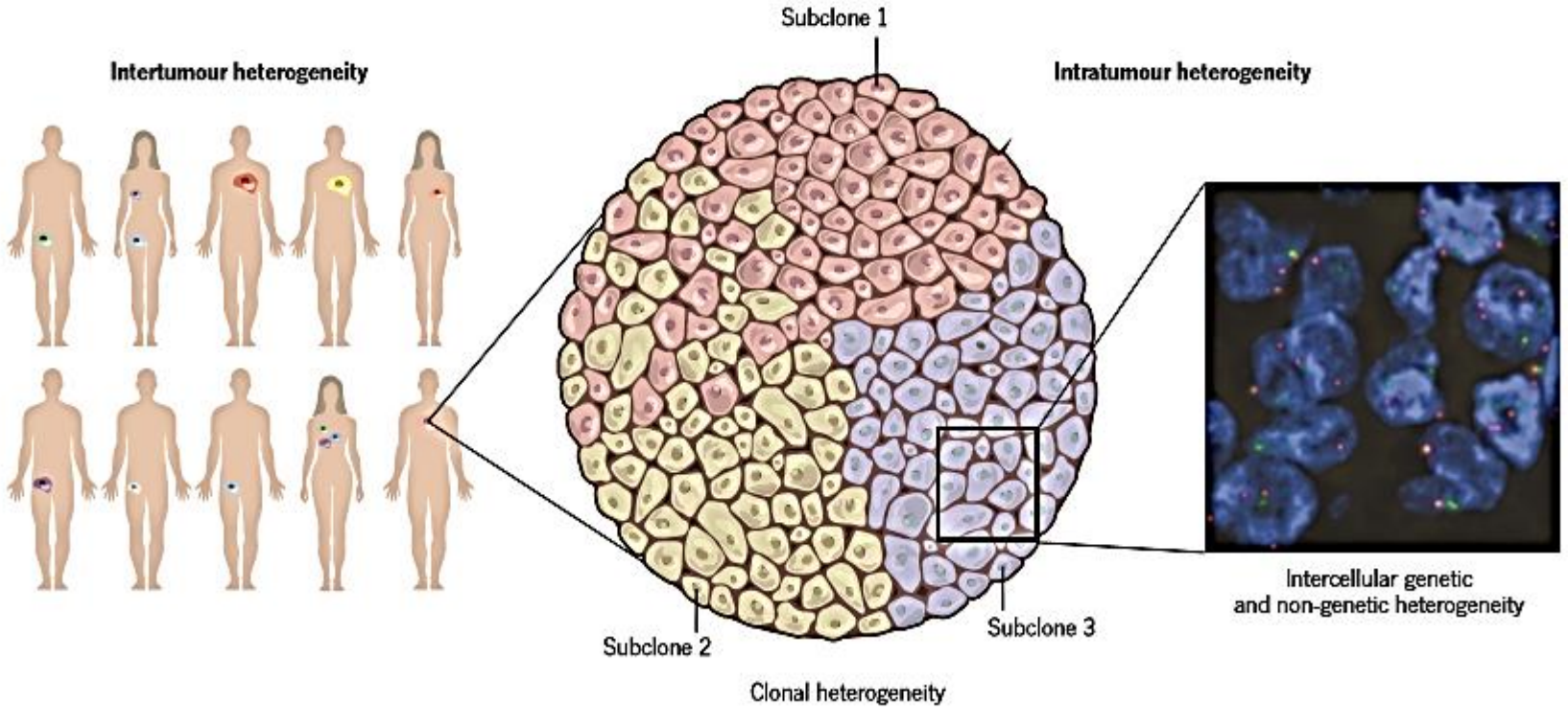
Endpoint	n=149
Objective response rate	
ORR (95% CI)	39.6% (31.7, 47.9)
Complete response rate	7.4
Partial response rate	32.2
Response duration	
Median in months (range)	NR (1.6+, 22.7+)
% with duration ≥6 months	78%

NR = not reached

- PD-1 blockade with pembrolizumab can restore effective anti-tumor immunity in MSI-H cancer, regardless of cancer type



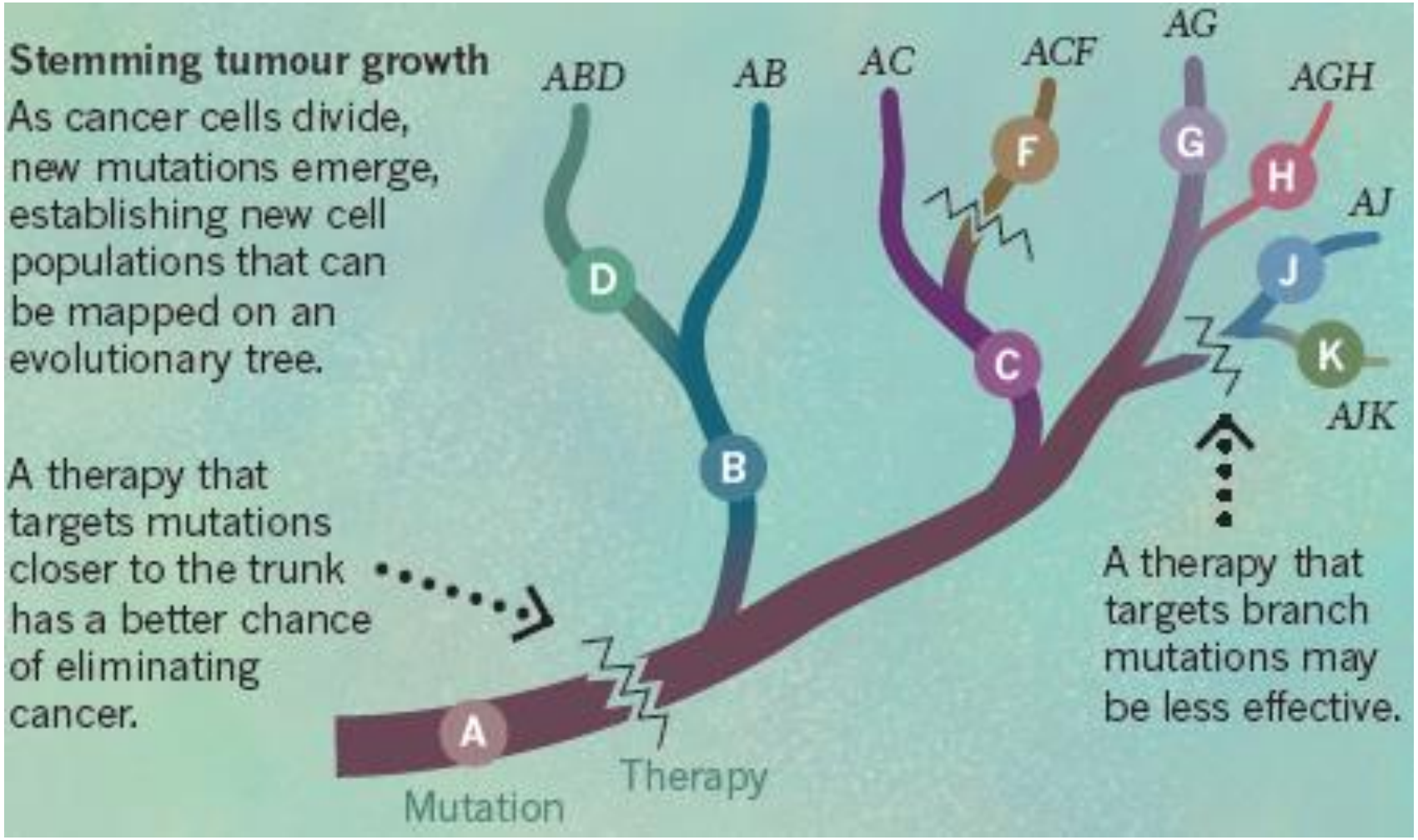
The genomic landscape of tumours is heterogeneous



- **Achieving cures in metastatic disease**
- **Cancer biomarker validation**

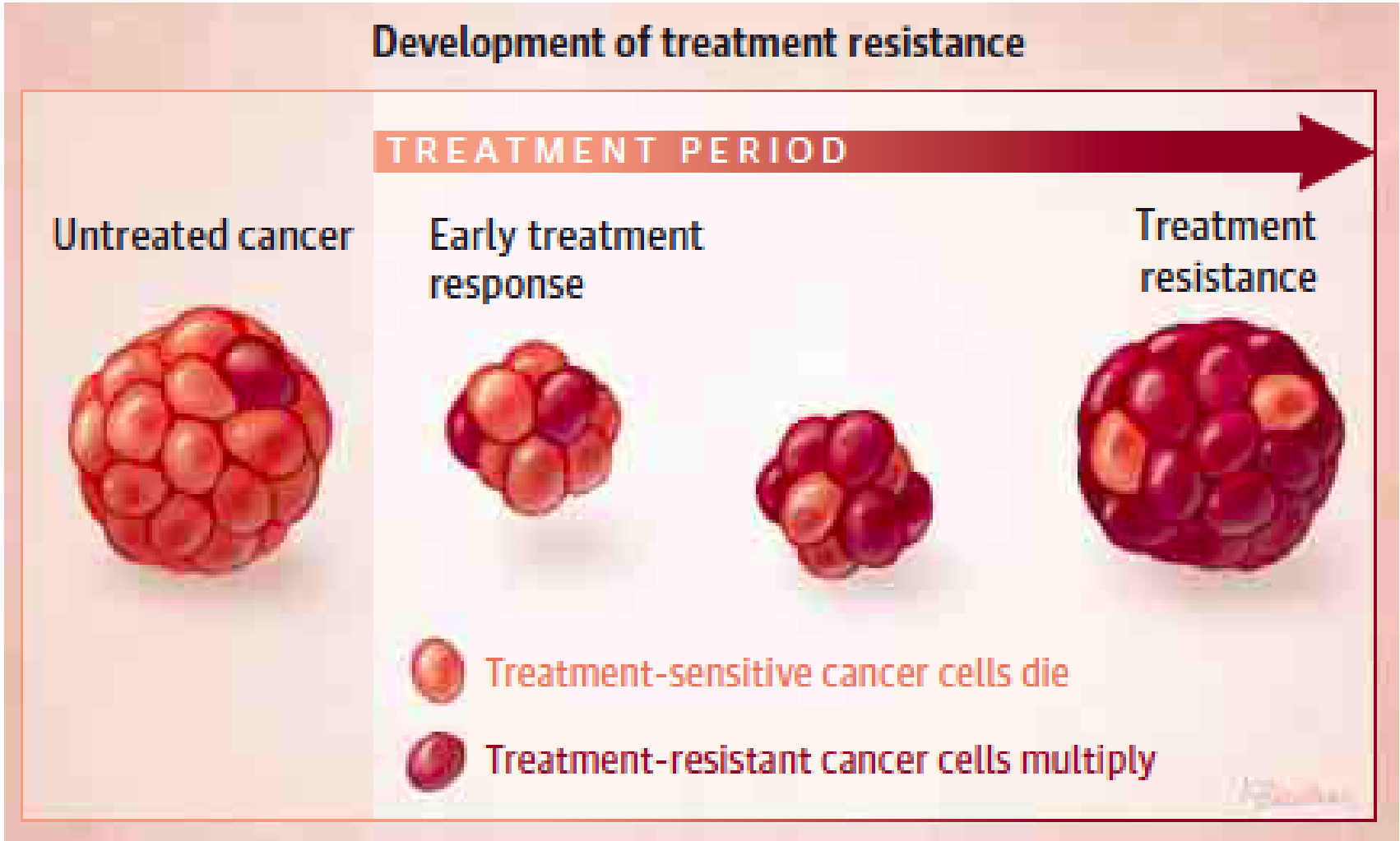
Burrell, McGranahan, Bartek & Swanton. Nature 2013

EVOLVING STRATEGIES



Cancer: an evolving threat. Nature 2016

The evolution of a cancer

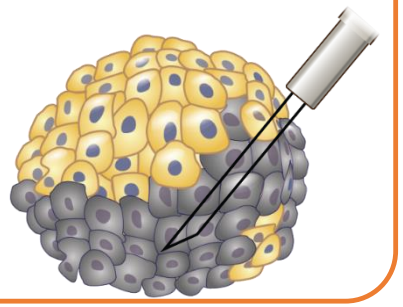


JAMA Oncology 2015

Various samples types may be used as a DNA source for mutation testing at disease progression

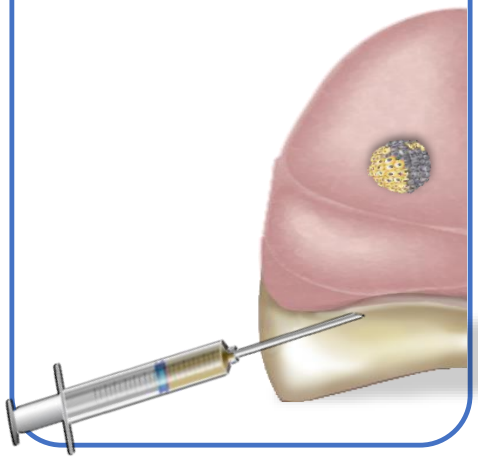
Tumor biopsy samples

Gold standard sample type for EGFR mutation testing in metastatic NSCLC[1,2]



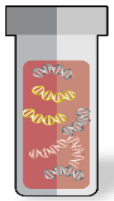
Cytology samples

Suitable alternative* if a tumor biopsy sample is not available[2-5]



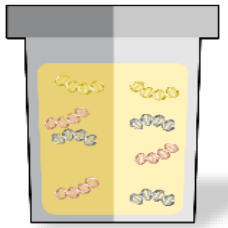
Plasma

Likely to be the preferred sample option since it is feasible, reliable, and minimally invasive[1,6]



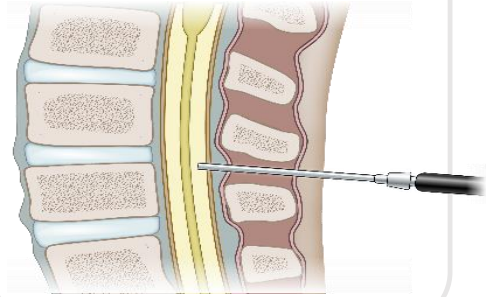
Urine samples

Should be considered a viable approach[7]



Cerebrospinal fluid

May be used to identify mutations in leptomeningeal disease[8]

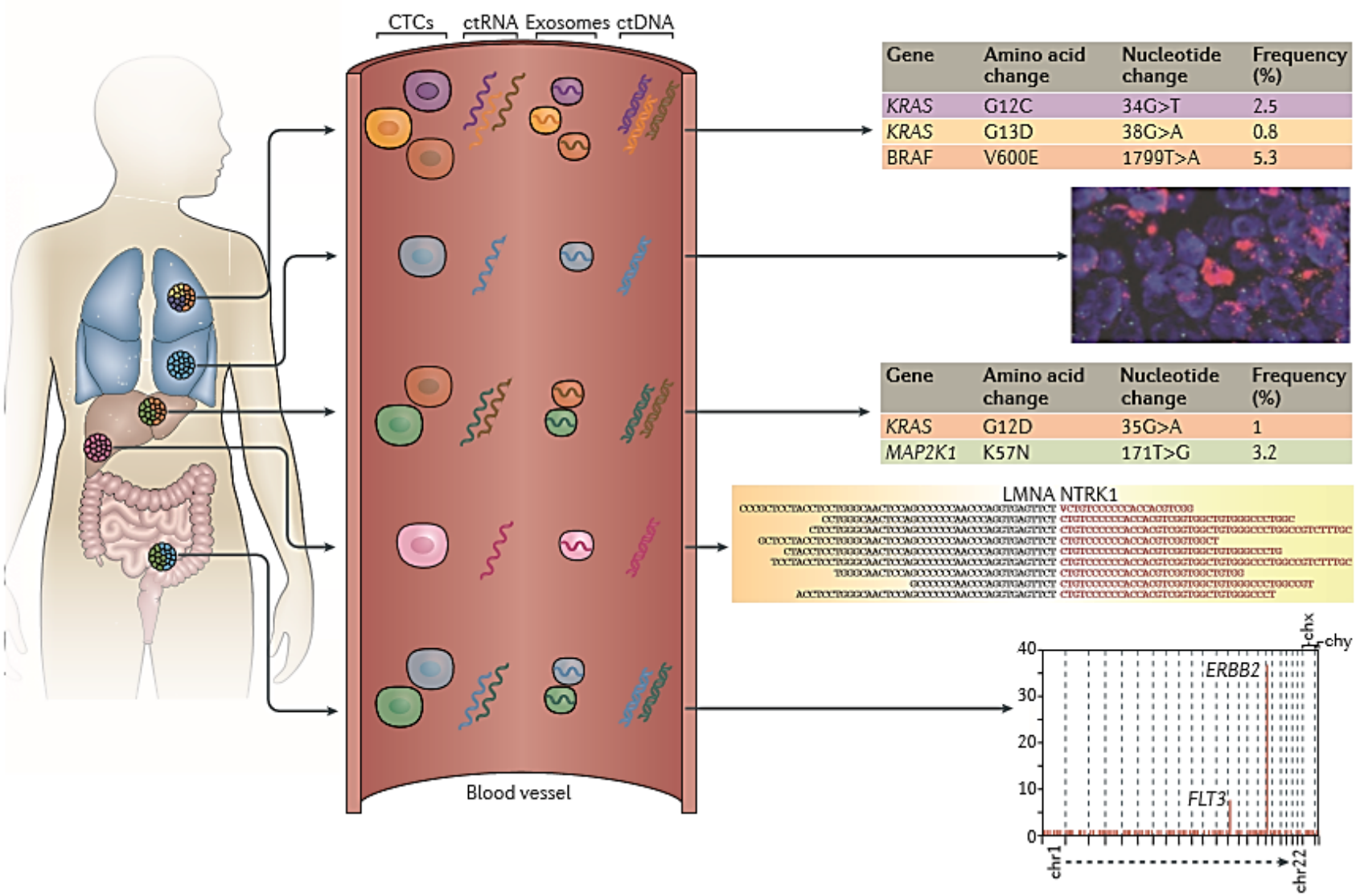


*Provided a proper validation has been conducted.

DNA, deoxyribonucleic acid; EGFR, epidermal growth factor receptor; NSCLC, non-small cell lung cancer.

1. Diaz LA, et al. *J Clin Oncol*. 2014;32(6):579-586. 2. Pirker R, et al. *J Thorac Oncol.* 2010;5(10):1706-1713. 3. Oshita F, et al. *Br J Cancer.* 2006;95(8):1070-1075. 4. Van Eijk R, et al. *PLoS One.* 2011;6(3):e17791. 5. Kimura H, et al. *Br J Cancer.* 2006;95(10):1390-1395. 6. Huang WL, et al. *Biomed Res Int*. 2015;2015:1-11. 7. Wakelee H, et al. *J Clin Oncol.* 2016;34(15_suppl):9001.
8. Yang JC-H, et al Presented at: American Society of Clinical Oncology Annual Meeting; 3-7 June 2016; Chicago, IL. *J Clin Oncol*. 2016;34(15 suppl). Abs 9002.

Liquid biopsies capture the molecular heterogeneity of metastatic cancers

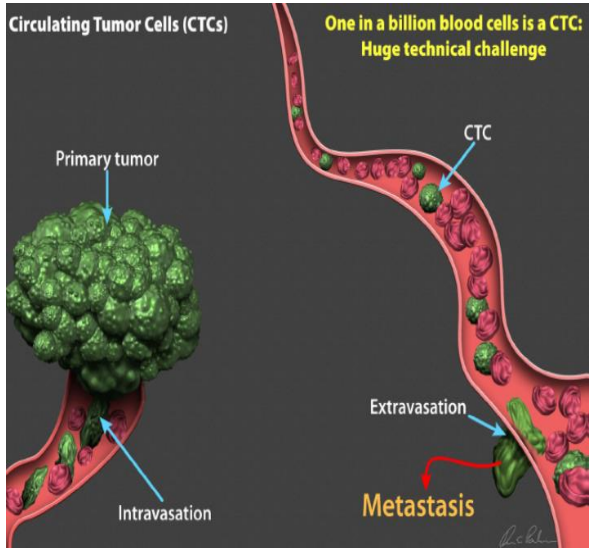


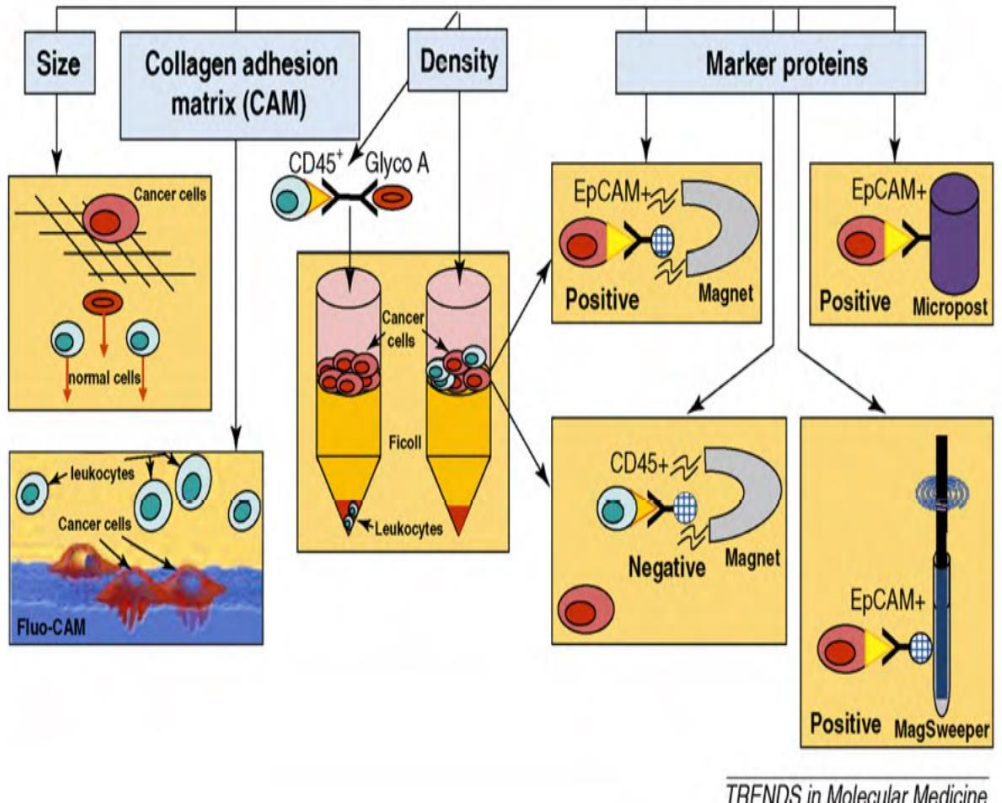
Gene	Amino acid change	Nucleotide change	Frequency (%)
KRAS	G12C	34G>T	2.5
KRAS	G13D	38G>A	0.8
BRAF	V600E	1799T>A	5.3

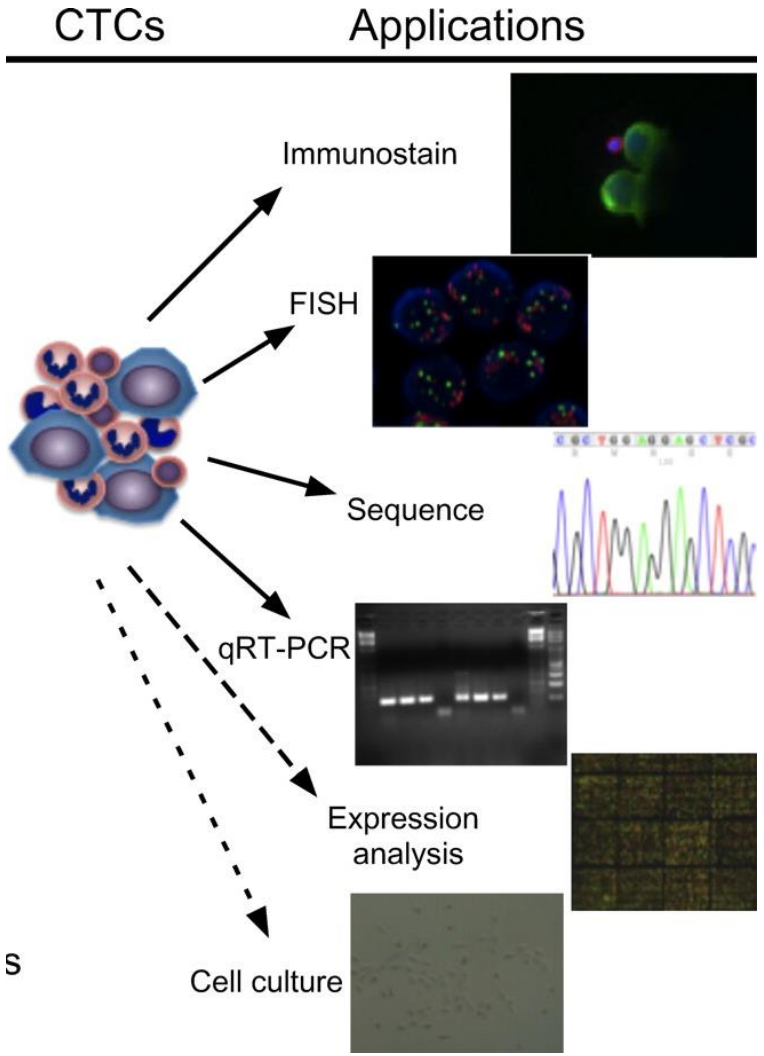
Gene	Amino acid change	Nucleotide change	Frequency (%)
KRAS	G12D	35G>A	1
MAP2K1	K57N	171T>G	3.2

Siravegna, Marsoni, Siena and Alberto Bardelli, Nat Rev Clin Oncol 2017

Analysis of CTCs

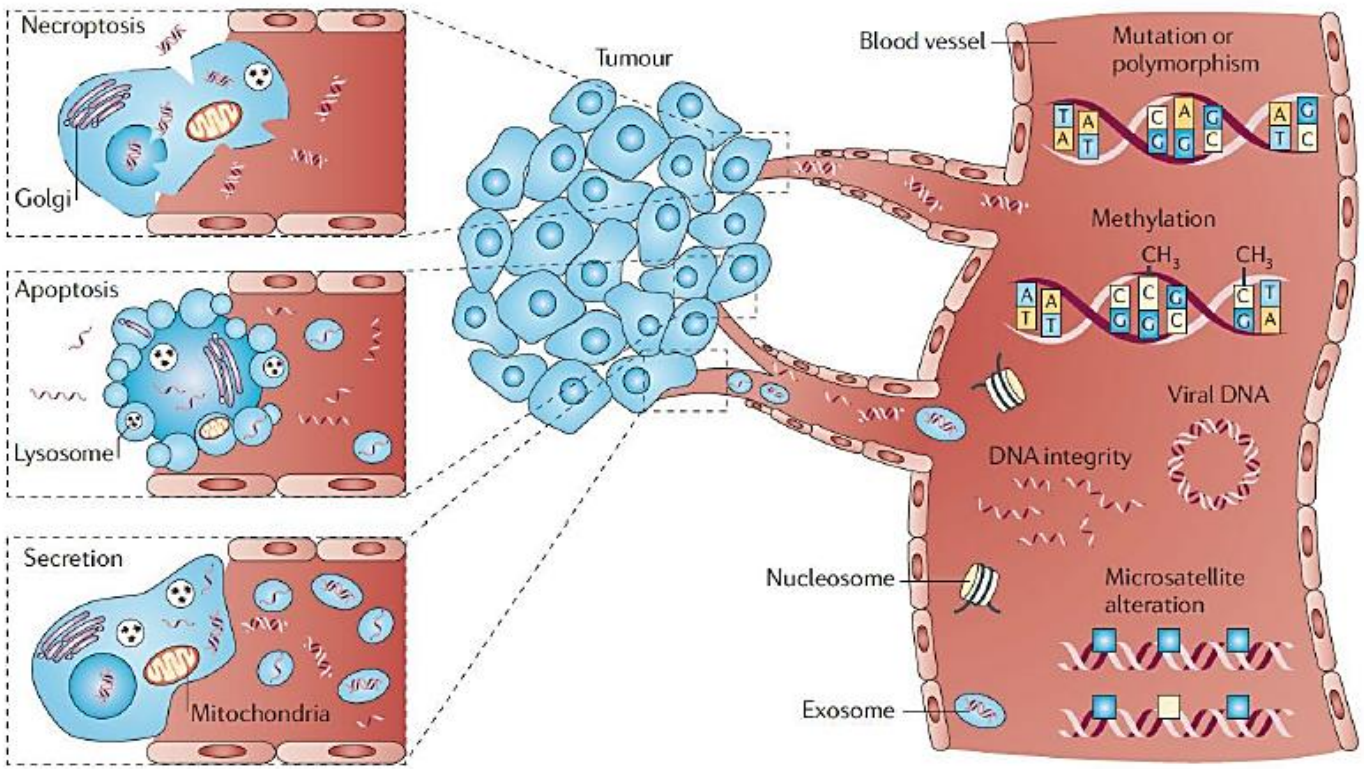






Yu et al. (2011) J Cell Biol

cell free DNA (cfDNA)



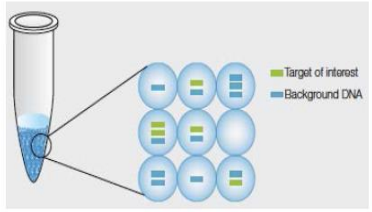
Schwarzenbach H, Hoon DS, Pantel K Nat Rev Cancer. 2011, Jun;11(6):

Testing ctDNA EGFR mutations: activating & T790M

Cobas EGFR test

Commercial Kits /Companion Diagnostics	
Advantages	**Disadvantages**
• Rapid • Quality control • Well tested (in clinical trials) • Stable results • FDA approved	• Cost (may be more expensive to develop and obtain FDA approval vs lab developed tests)[2]

Digital PCR



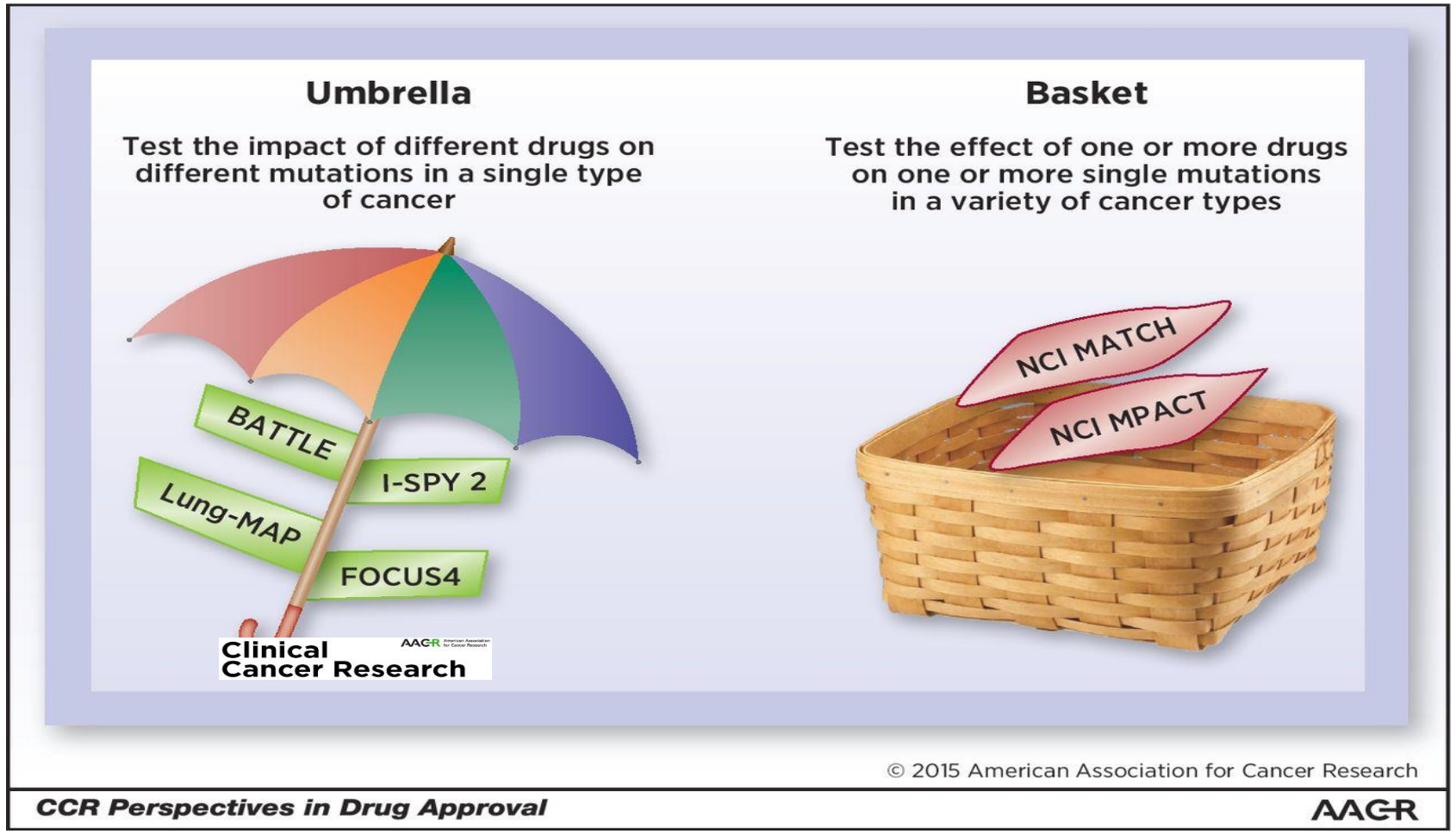
NGS

illumina

ion torrent

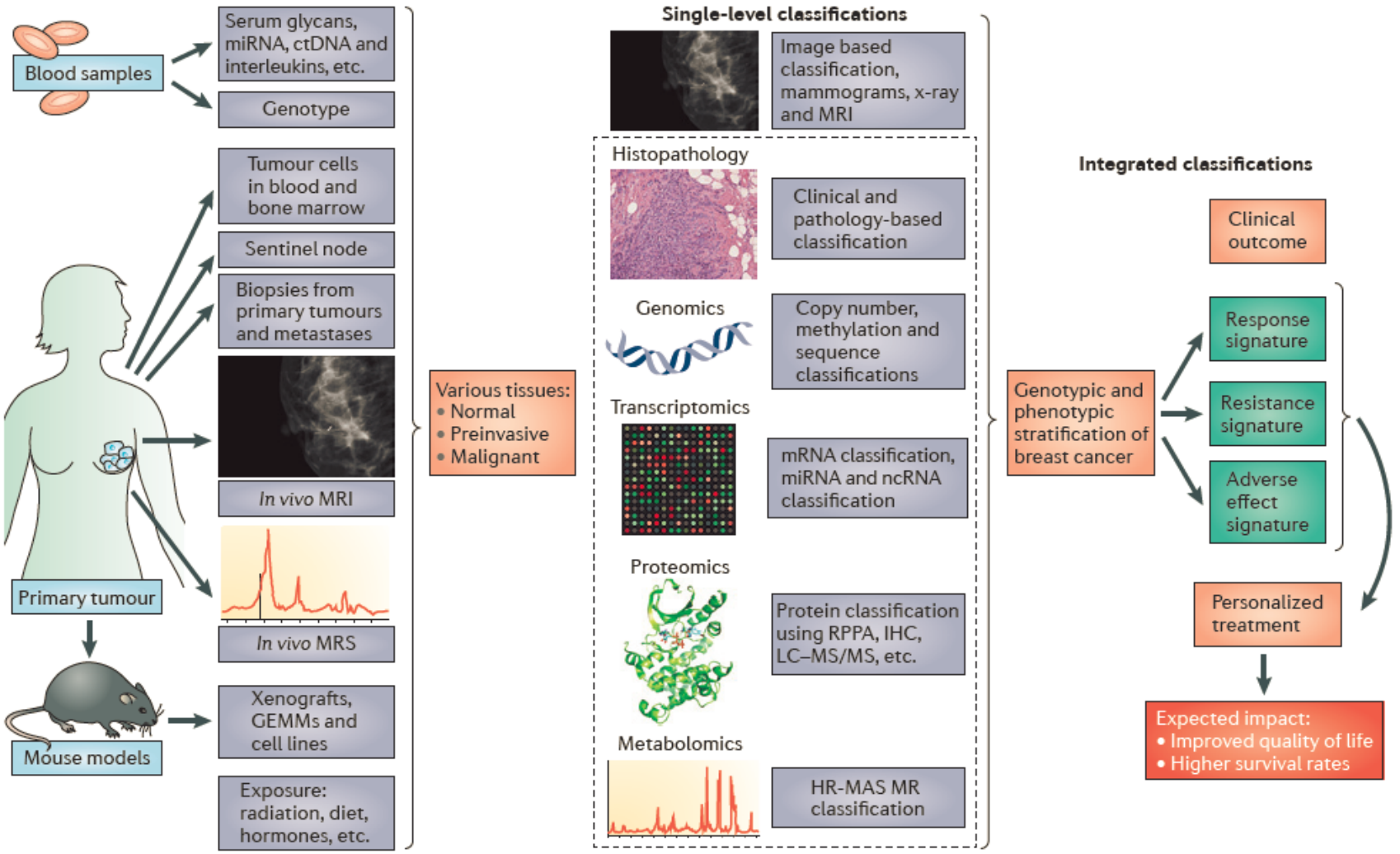
Laboratory Developed Tests (LTDs) based on emerging technologies	
Advantages	**Disadvantages**
• Can be less expensive using equipment that is commonly available • May offer high sensitivity	• Quality can be more difficult to control and maintain • Validation required • Sensitivity requires confirmation

New Clinical Trial Designs

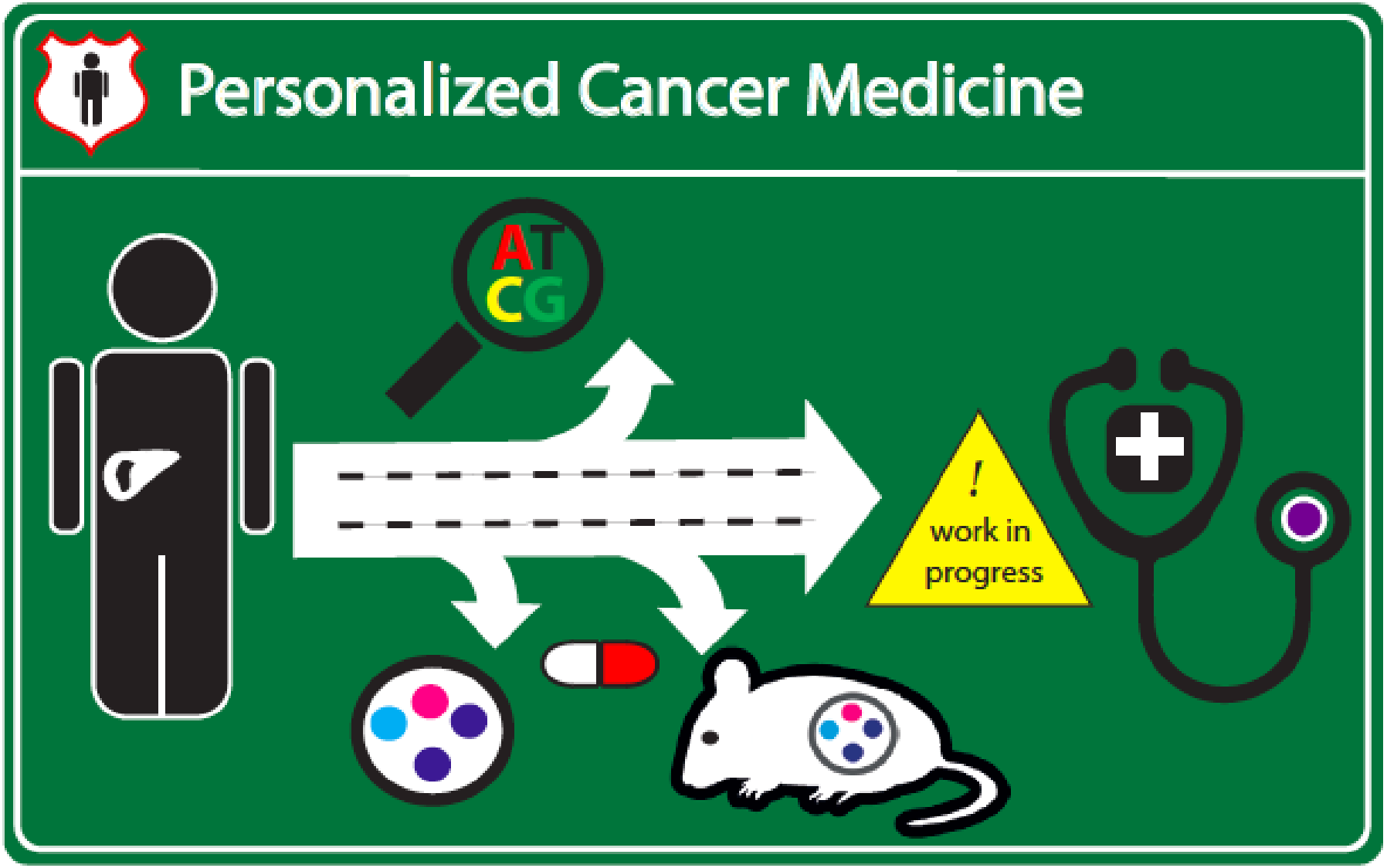


Herbst et al. Clin Cancer Res 2015;21:1514-1524

Systems Biology of Cancer



Kristensen, Nature Rev. Cancer, 14:299, 2014.



whole exome sequencing for actionable mutations
patient-derived tumor organoids for in vitro testing
organoid-derived PDX models for validation and safety testing

Cancer Discovery May 2017

Emerging Treatment Options vs Challenges…