

New Developments in the Treatment of Colorectal Cancer

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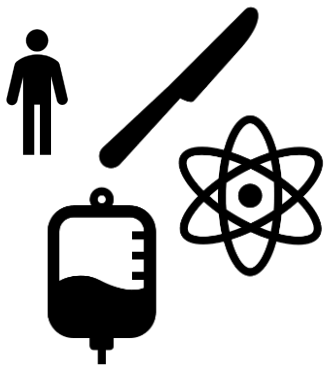
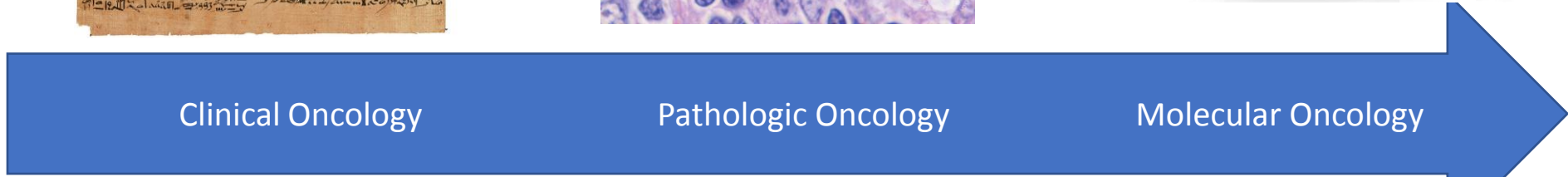
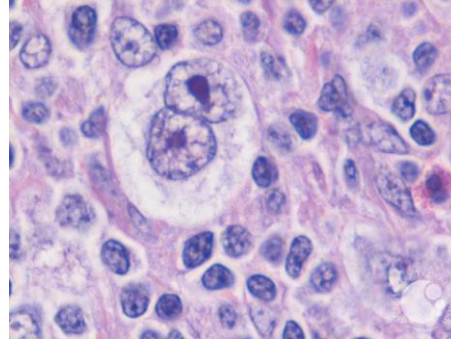
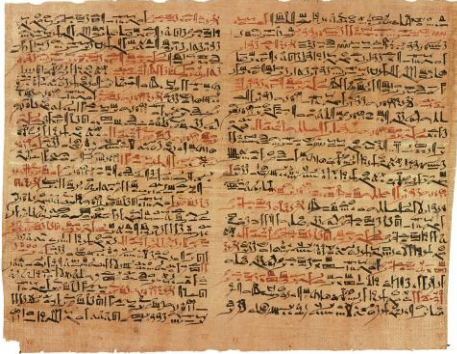
Personalized Medicine

- Currently already part of oncology:
 - What are the risks and benefits for taking chemotherapy based on pathology and the patient's health
 - Modify doses based on side effects
 - Modify treatment based on the response

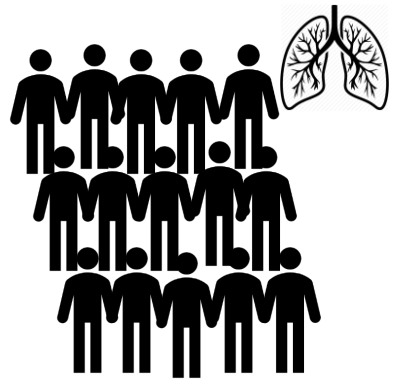
Precision Medicine

- Predictive markers – who will or will NOT respond to treatment
- Spare patients side effects/cost
- Examples: KRAS for EGFR therapy
 - A mutation in KRAS determines that the cancer would not respond to treatment

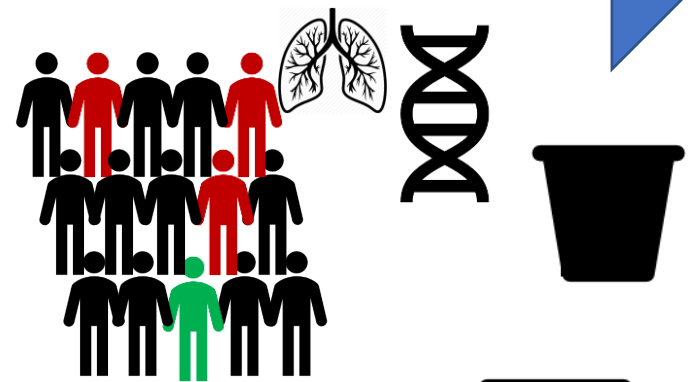
The Changing Face of Oncology



-clinical/disease specific treatment

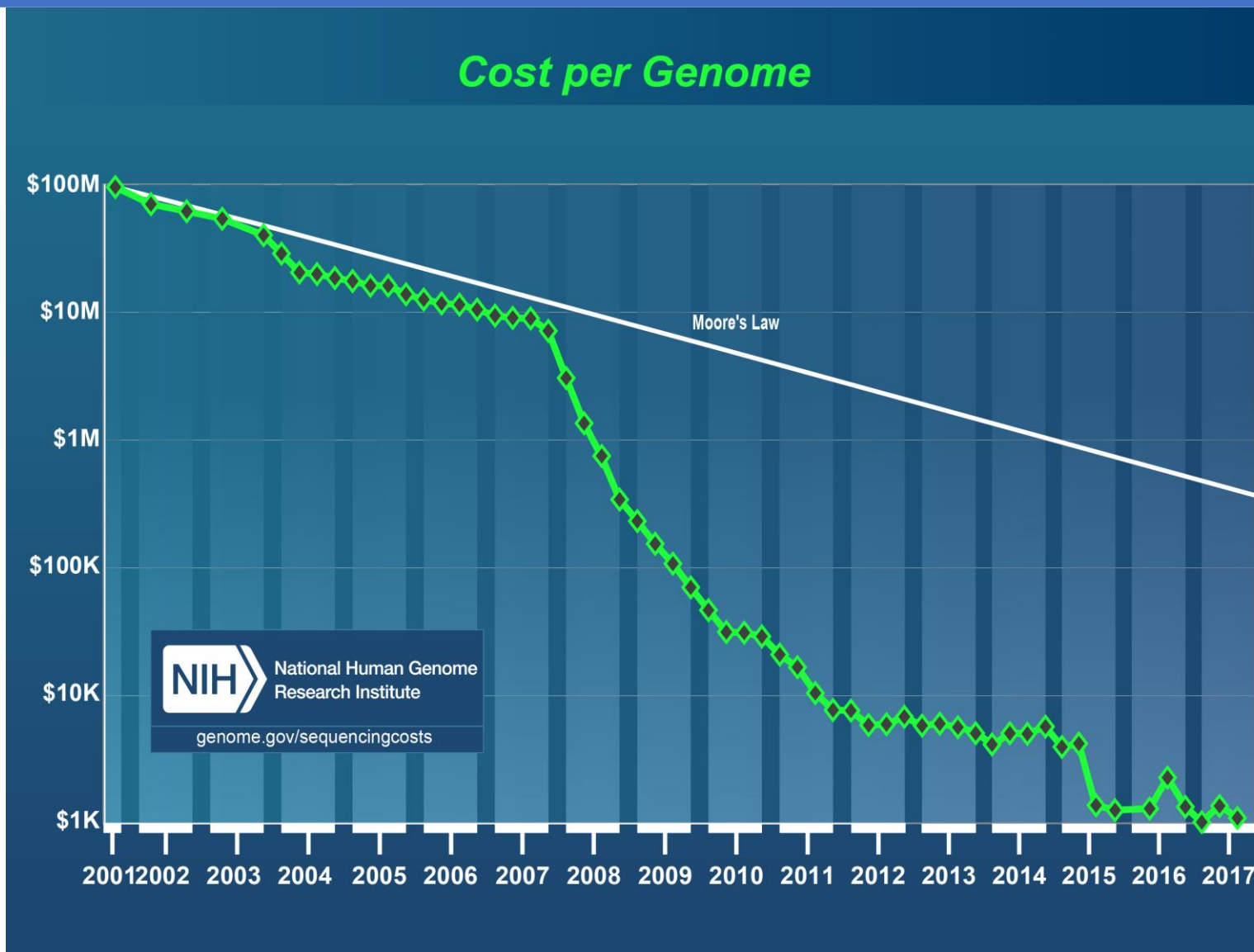


-specific therapies for different tumor types

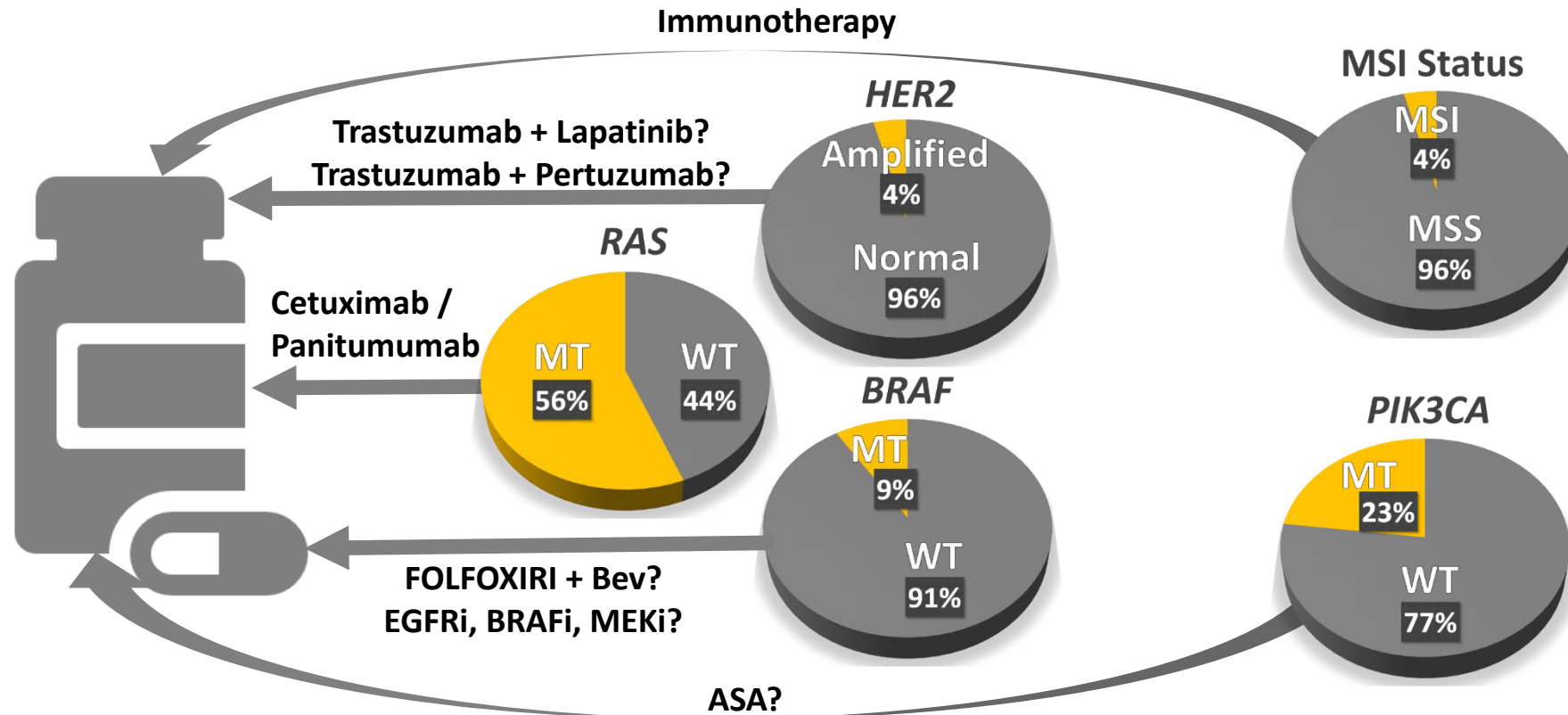


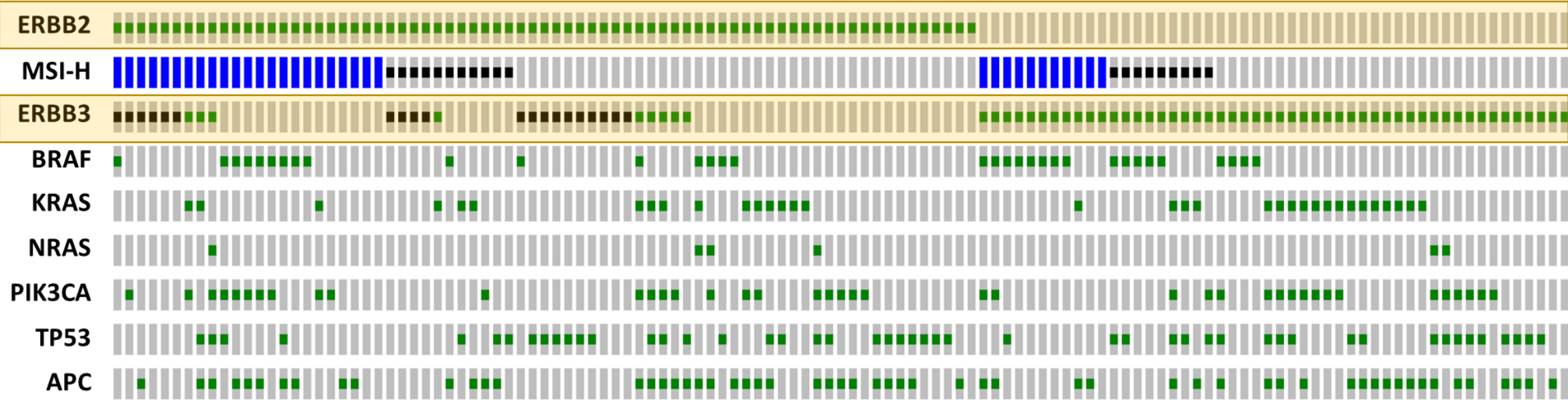
-molecular analysis and targeted agents

Sequencing Costs are Dropping Dramatically!



Current Biomarkers in Colorectal Cancer





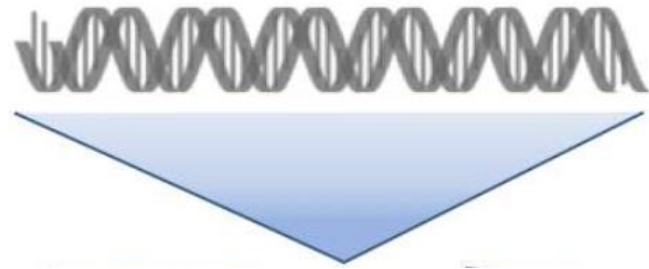
Personalized OncoGenomics (POG) Program



Personalized oncogenomics: “POG”

- Patients with metastatic (incurable) cancers
- Look at the genome of each person's cancer
- Identify aberrant pathways that drive that cancer
- Identify drugs that might block those pathways

Genomic Alterations in Cancer



Structural variants

- Translocations
- Fusions
- Inversion



Copy number alterations

- Amplifications
- Deletions
- LOH



Point mutations & indels

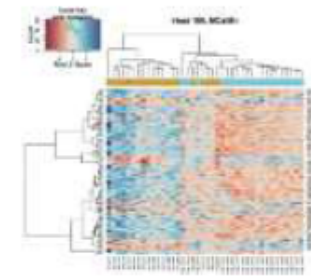
- Missense
- Nonsense
- Splice site
- Frameshift

Wild type AGTGA

Mutant AGA GA

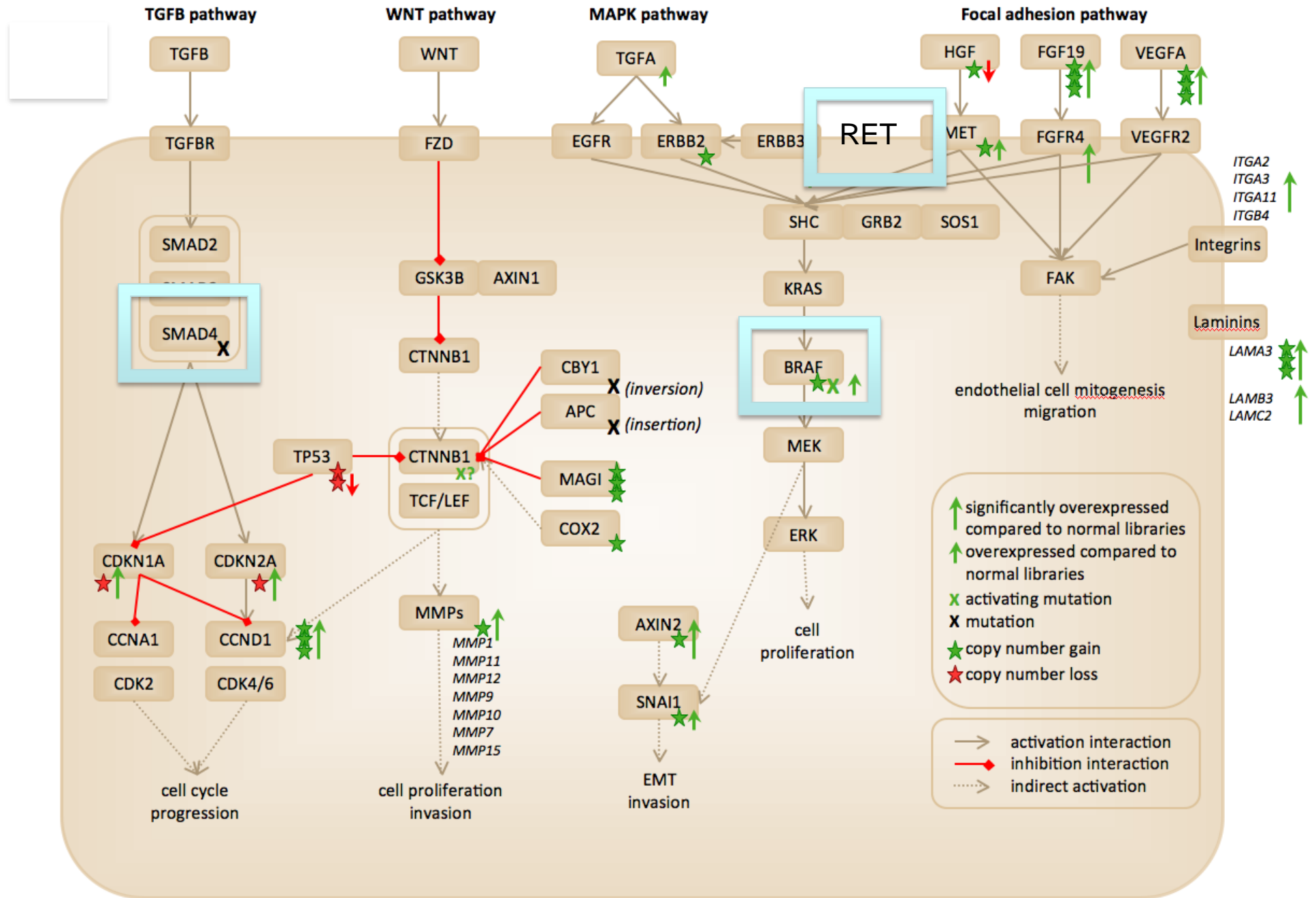
Gene expression

- Outlier expression
- Isoform usage
- Pathways & signatures



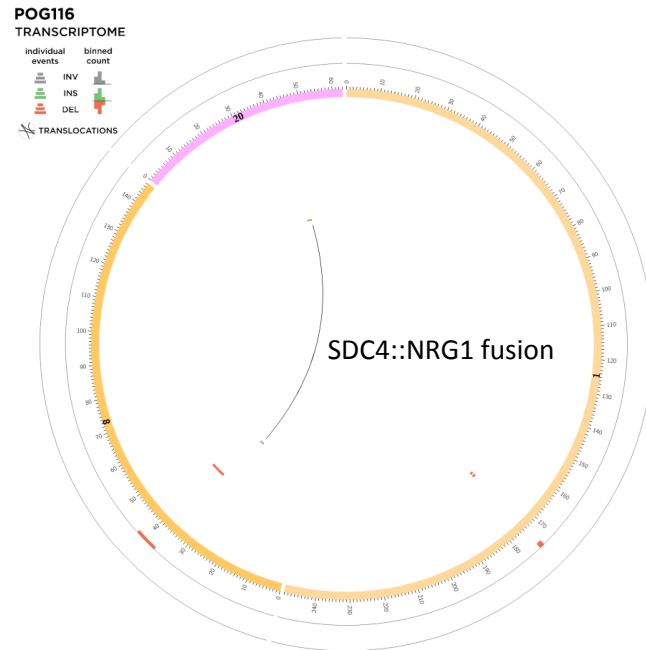
What does this entail?

- Whole genome sequencing = 6 billion bits of information
- Compare cancer to normal cells
- Patterns of RNA expression
- Analyze abnormalities and search for their function in databases
- Sift through scientific literature for evidence to link pathways to specific drugs

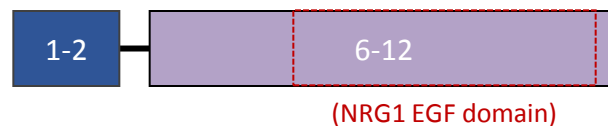


52 yo M with lung cancer

1. SDC4::NRG1 fusion uncovered from whole genome and transcriptome data

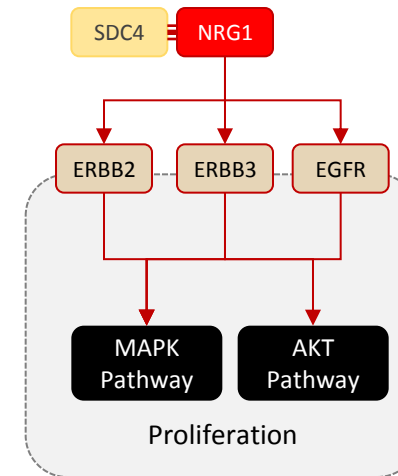


Canonical SDC4::NRG1 structure found



Exon 1 and 2 of SDC4 fused to exon 6-12 of NRG1 (Transcript NRG1-004 ENST00000287842)

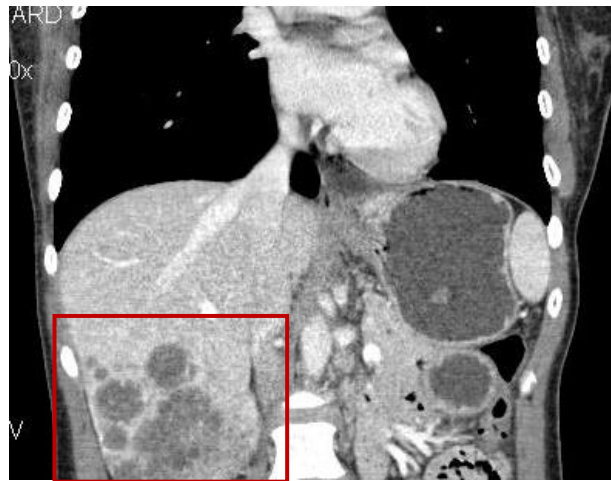
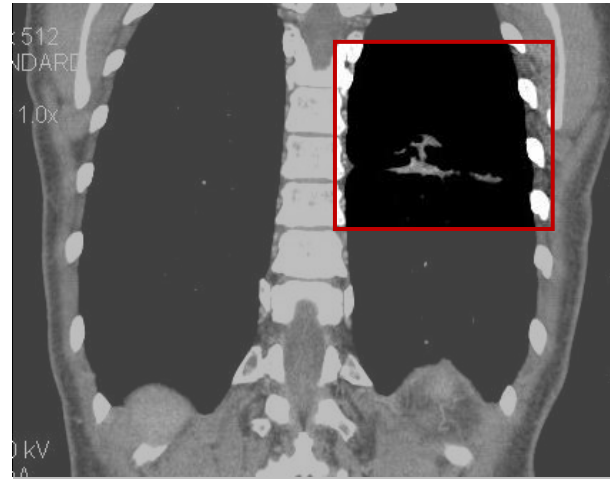
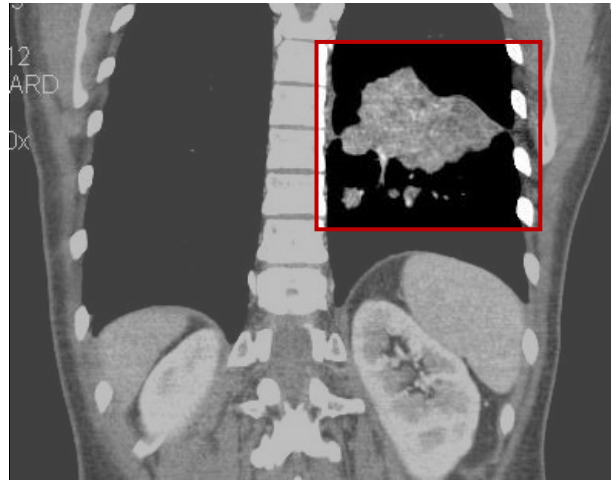
2. Fusion highly expressed in the tumour based on mRNA expression



3. Activation of ERBB pathways expected from literature evidence, and supported by pathway analysis based on expression data

4. Afatinib was suggested for ERBB-family targeted inhibition based on integrative analysis and literature evidence

5. Patient responded to recommended therapy

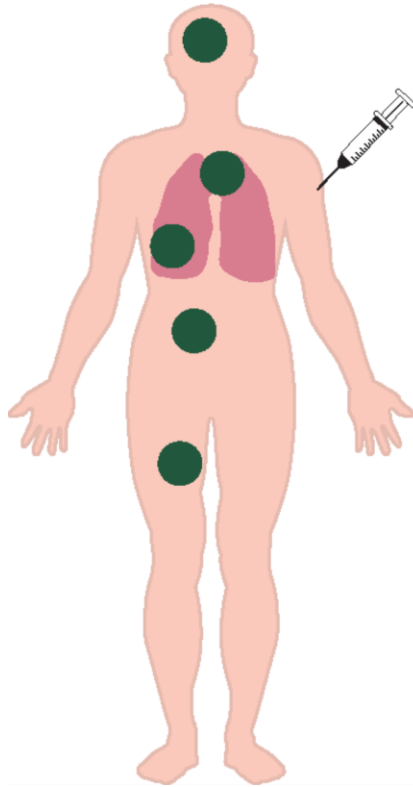


Baseline prior to therapy

+8 weeks with Afatinib

“Liquid Biopsies”

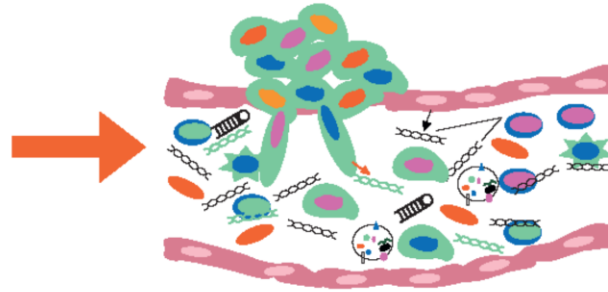
Metastasis/relapse
in different organs



Tumor microenvironment



Shedding of CTCs, ctDNAs,
cmiRNAs and exosomes from
primary tumor site



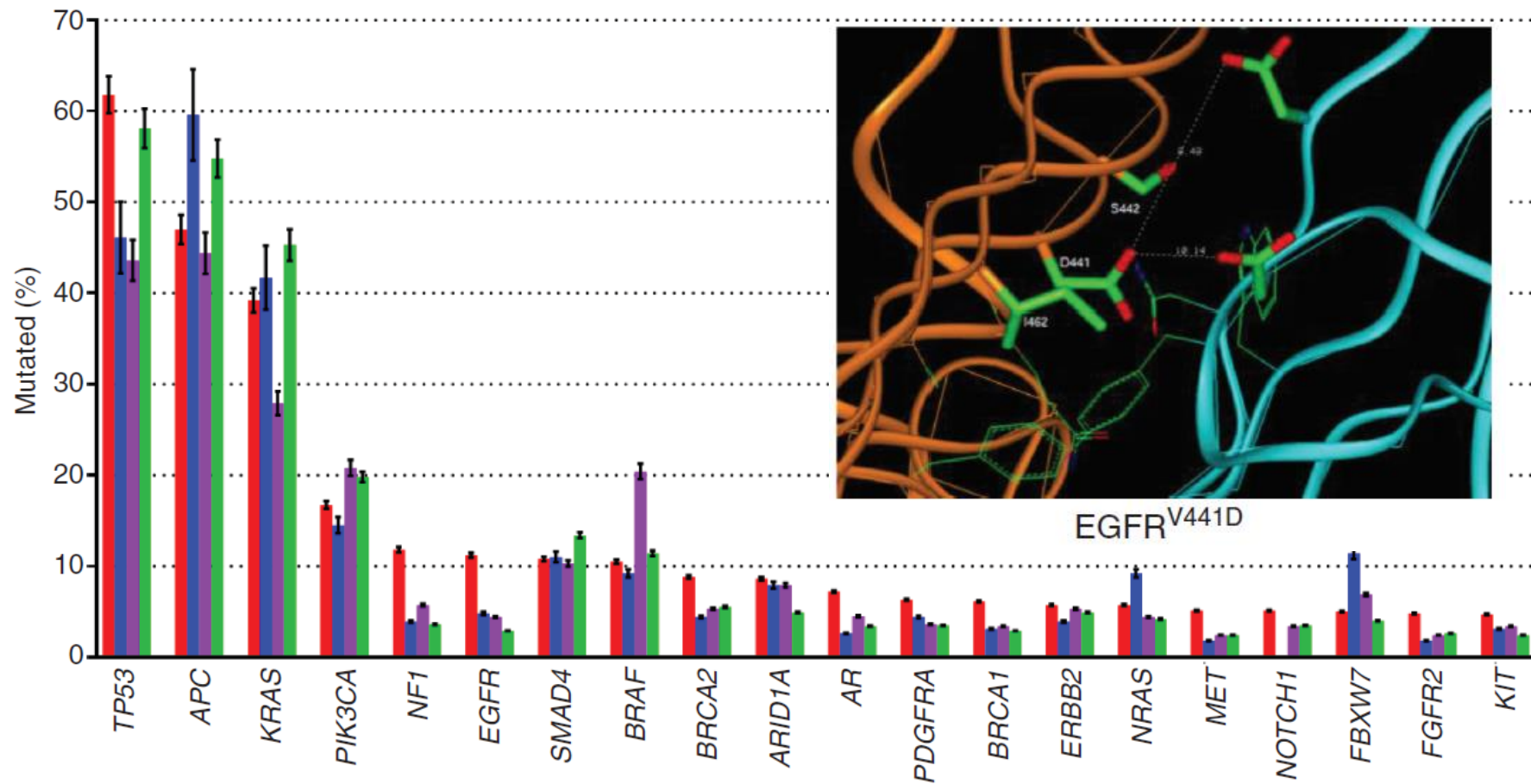
Cancer patient
blood sample to
analyze biomarkers



Genomic Landscape of Cell-Free DNA in Patients with Colorectal Cancer



John H. Strickler¹, Jonathan M. Loree², Leanne G. Ahronian³, Aparna R. Parikh³, Donna Niedzwiecki¹, Allan Andresson Lima Pereira², Matthew McKinney¹, W. Michael Korn^{4,5}, Chloe E. Atreya⁴, Kimberly C. Banks⁶, Rebecca J. Nagy⁶, Funda Meric-Bernstam², Richard B. Lanman⁶, Amir Ali Talasz⁶, Igor F. Tsigelny^{7,8}, Ryan B. Corcoran³, and Scott Kopetz²



What does this mean for patients?

- Opportunity to participate in world class research that can directly affect patient care
- Opens the door to possibilities beyond “standard of care”
- Gain a better understanding of what causes and drives cancers

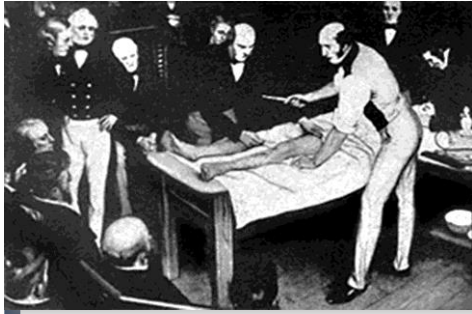


Immuno-Oncology

**BC
CAN
CER**

Provincial Health Services Authority

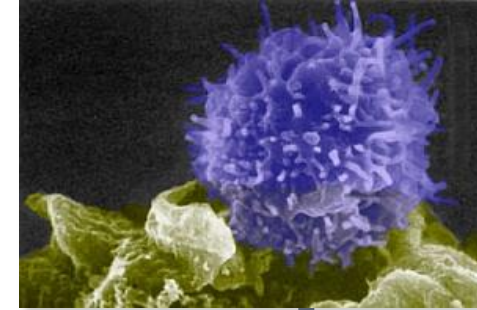
Evolution of Cancer Therapy: Treatment Modalities



Surgery
1846



Chemotherapy
1946

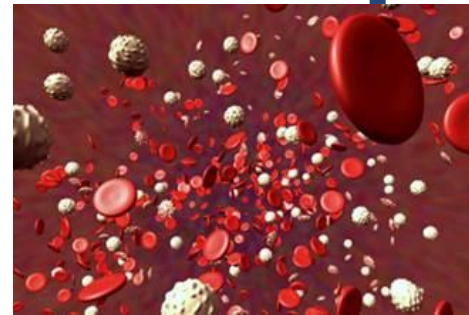


Immuno-Oncology
2011

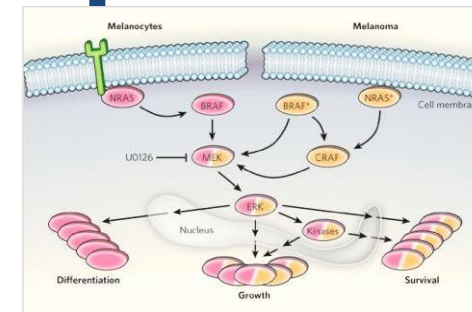
Radiation Therapy
1901



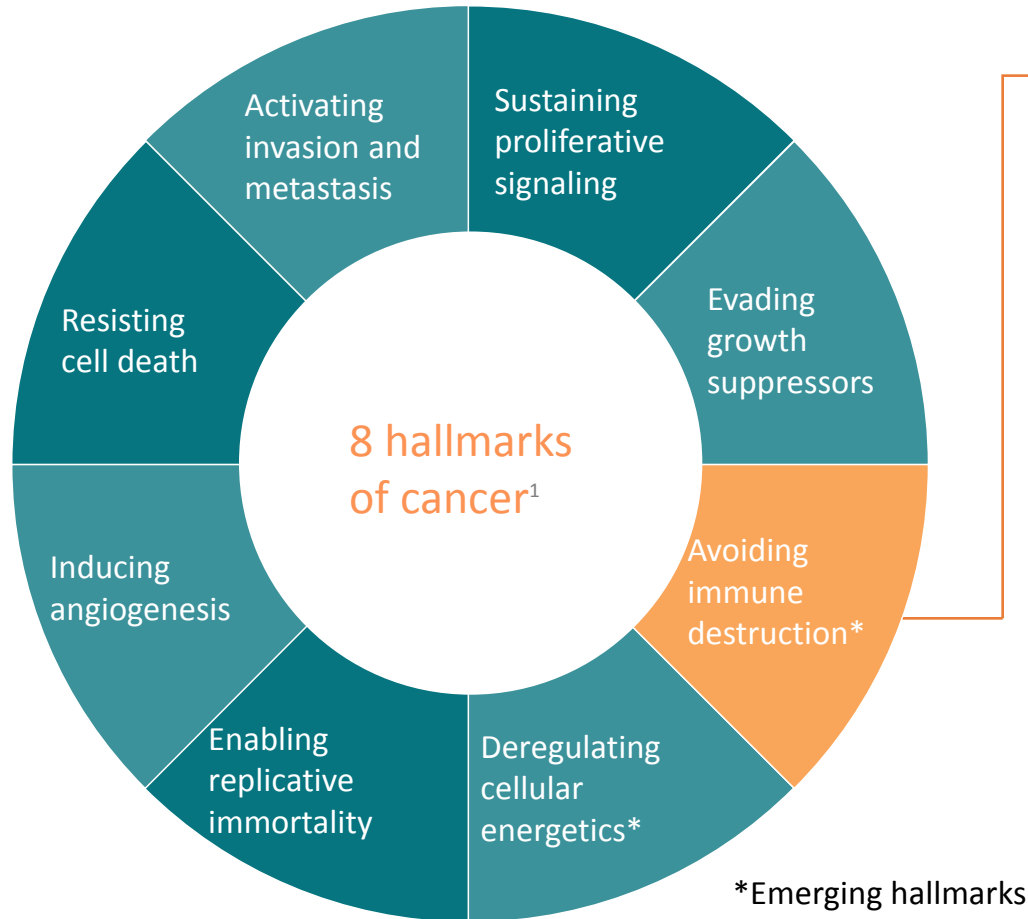
Immunotherapy
Interferon- α 1995
Interleukin-2 1998



Targeted Therapy
1997



Hallmarks of cancer



For **Immuno-Oncology therapies (I-O therapies)** to work, they generally incorporate an understanding of the *mechanisms of tumor escape*.^{2,3}

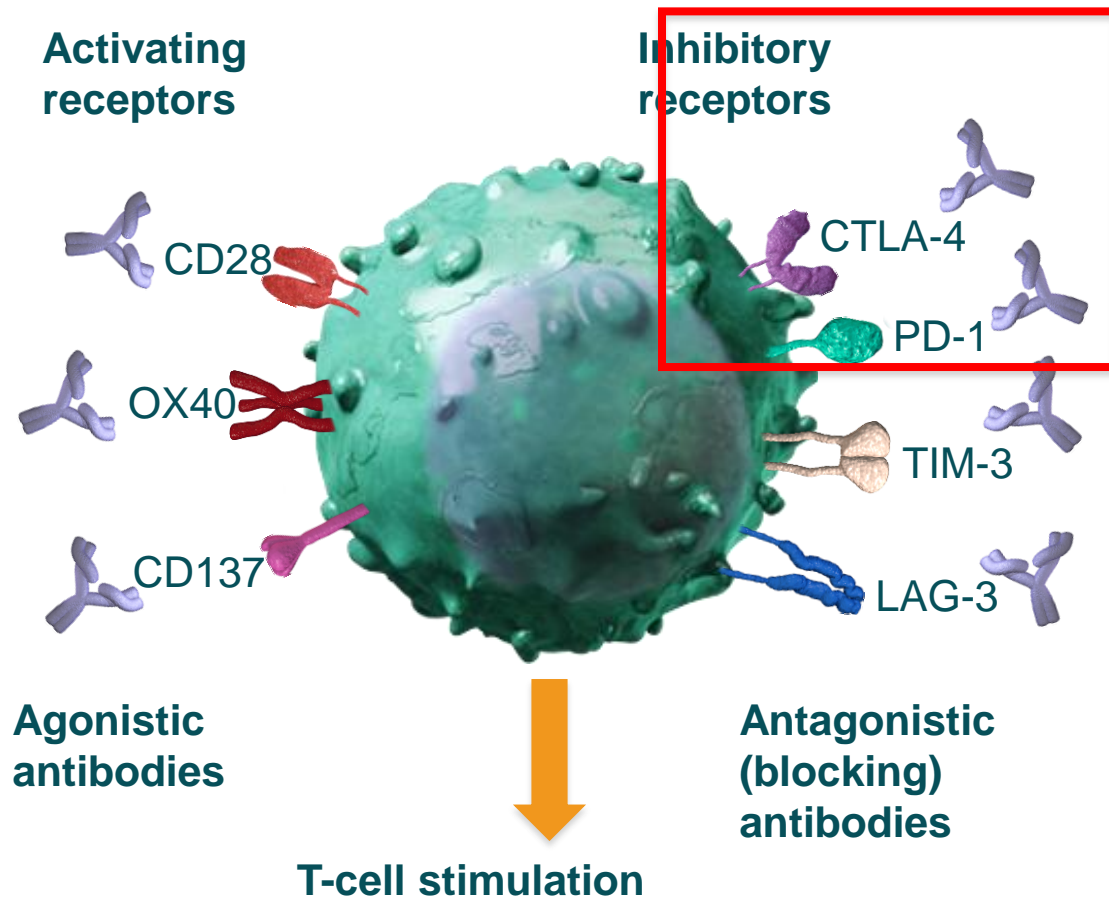
I-O therapies seek to modulate the immune system to *promote antitumor activity*, and counteract this hallmark.⁴

Introduction to the immune system

In order to protect an individual, the immune system:

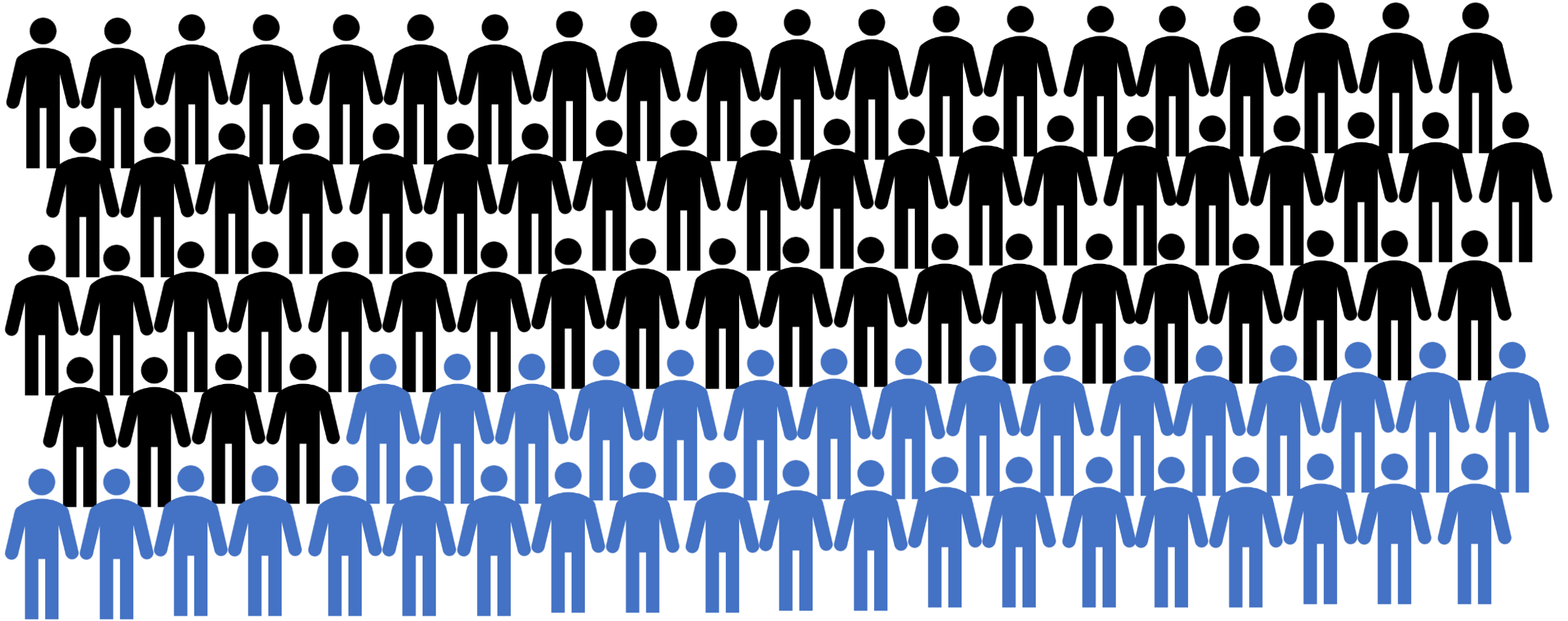
1. detects the presence of an infection or malignant cells,¹
2. carries out effector functions to contain or to eliminate the affected cells,¹
3. performs self-regulation to minimize collateral damage to healthy cells in the body,¹ and
4. generates immunological memory so that subsequent exposures to the same antigen are dealt with efficiently.¹

T-Cell Checkpoint Regulation



- T-cell responses are regulated through a complex balance of inhibitory (“checkpoint”) and activating signals
- Tumors can dysregulate checkpoint and activating pathways, and consequently the immune response
- Targeting checkpoint and activating pathways is an evolving approach to cancer therapy, designed to promote an immune response

Who should we treat with immunotherapy?



How is a trial created?

- Idea!
- Pharmaceutical compound
- Develop a protocol
- Obtain funding
- Approval from Health Canada
- Approval from Research Ethics Board
- Trial is offered to patients

Who funds these?

- Little or no institutional or government support
- Investigator Initiated Trials
- Non-profit groups
 - National Cancer Institute of Canada
 - Eastern Cooperative Oncology Group
 - South Western Oncology Group, etc.
- Pharmaceutical company
 - Funds for staffing the study (nurses, data collection) and provide the drug

Where does the money go?

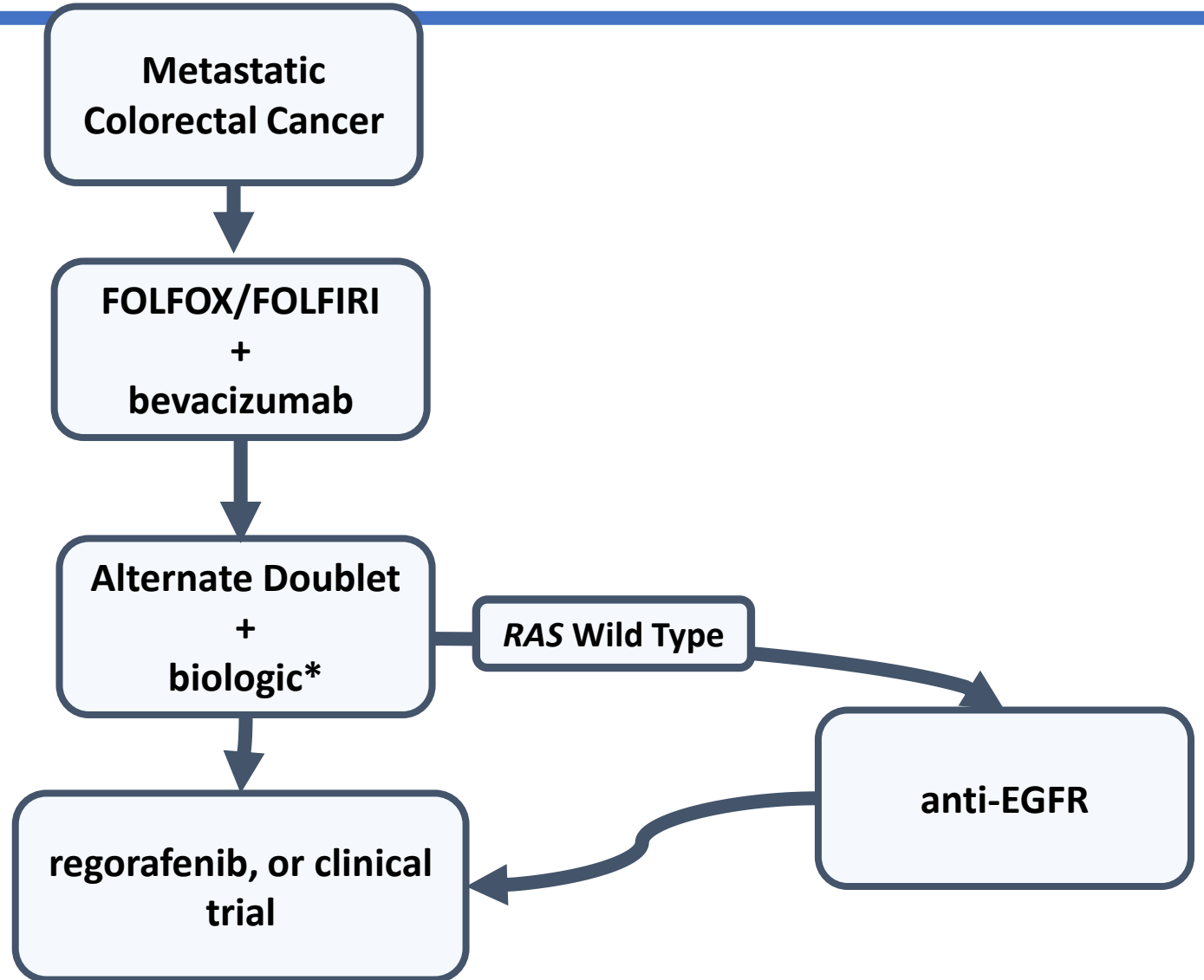
- Not a money-making venture
- Costs:
 - Nurse
 - Clerks
 - Booking
 - Data collection
 - No physician compensation
- Biological or special testing – expensive and complex

How to decide whether to participate?

- Opportunity
- Always voluntary
- Detailed discussion with doctor, nurses, friends and family
- It takes time to decide
- Advantages and disadvantages

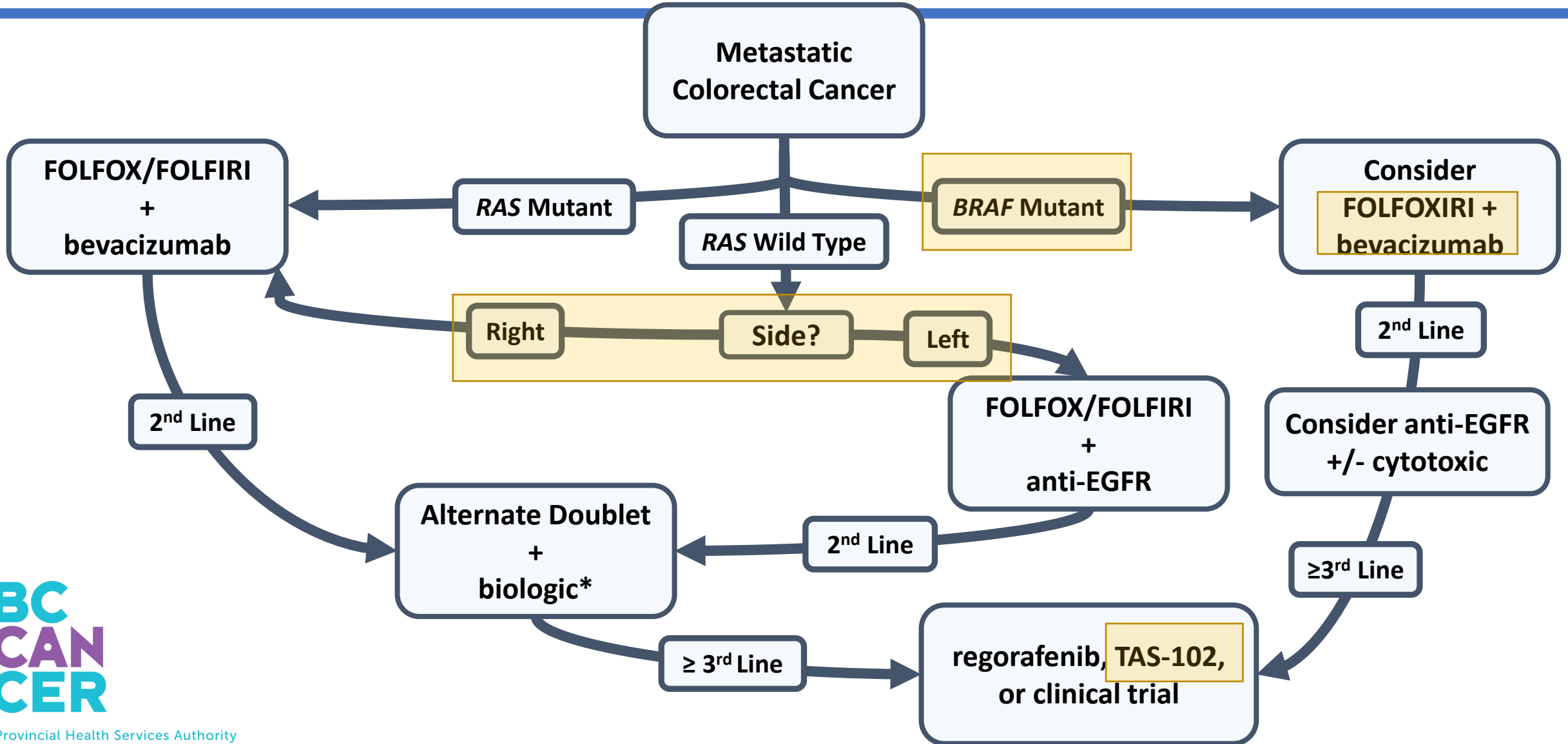
2014

Precision Medicine is Here!



2017

Precision Medicine is Here!



2018

Precision Medicine is Here!

