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L'Institut des
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The role of molecular testing in digestive cancer treatment

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Disclosure

Nothing to disclose

Personalized medicine

- There is no common definition of personalized medicine

Personalized medicine

- There is no common definition of personalized medicine
- According to the European Medicines Agency (EMA): "... give the right patient the right treatment, with each medication given the right dose, at the right time.“
- In short, an ideal medicine because it is “tailor-made”.

Personalized medicine

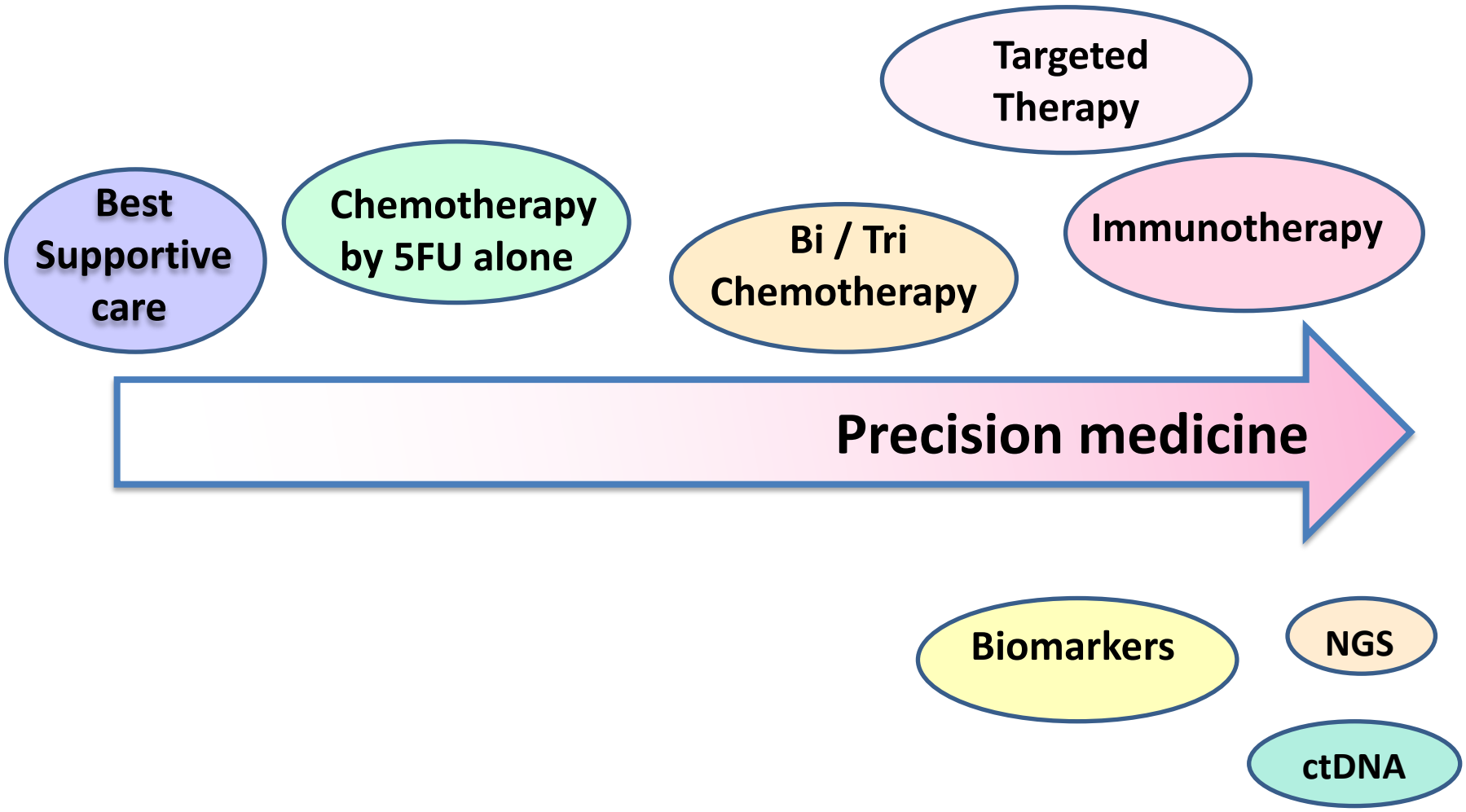
- A multi-faceted approach to patient care
  - In prevention (behavior, physical activity…)
  - In detection of the disease at early stage
  - To evaluate the risk of tumor (i.e genetic predisposition)
  - In accurate diagnosis
  - In treatment
  - In the management of treatment response and disease progression

The age of personalized medicine, Personalized Medicine Coalition

Personalized / Precision medicine

- Since 2012, opinion leaders started to abandon progressively « personalized medicine » in favor of **« precision medicine »**
- « Tailor-made » medicine was made possible by emerging technologies, in which genetics and genomics occupy a preponderant place
- A medicine wich is adapted to individual patient, taking into account **biomarkers and genetic characteristics**.

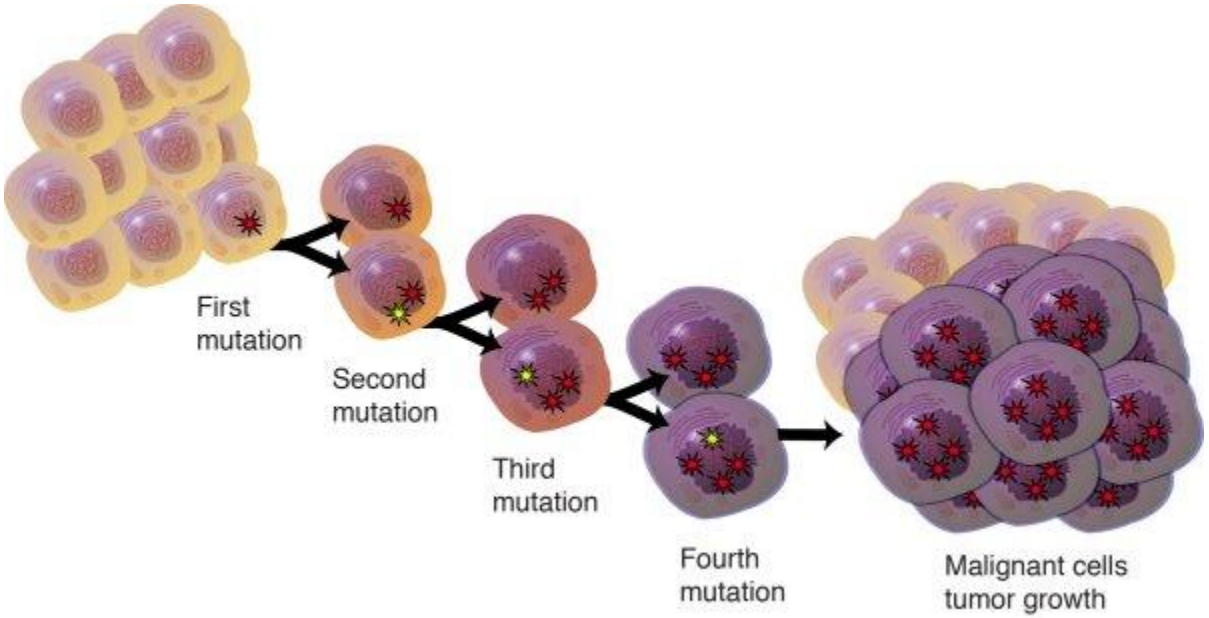
Evolution of metastatic digestive cancer‘s treatment



Precision medicine: Key points

- **Why?** Prescription of certain precision medicine treatments is conditioned by the presence of specific molecular abnormalities in tumor cells
- **Goal ?** Use of targeted therapies or immunotherapy can reduce the risk of disease progression
- **How?** Molecular testing to search for biomarkers
- **Which?** Biomarkers are biological markers which can influence therapeutic care

Tumor heterogeneity

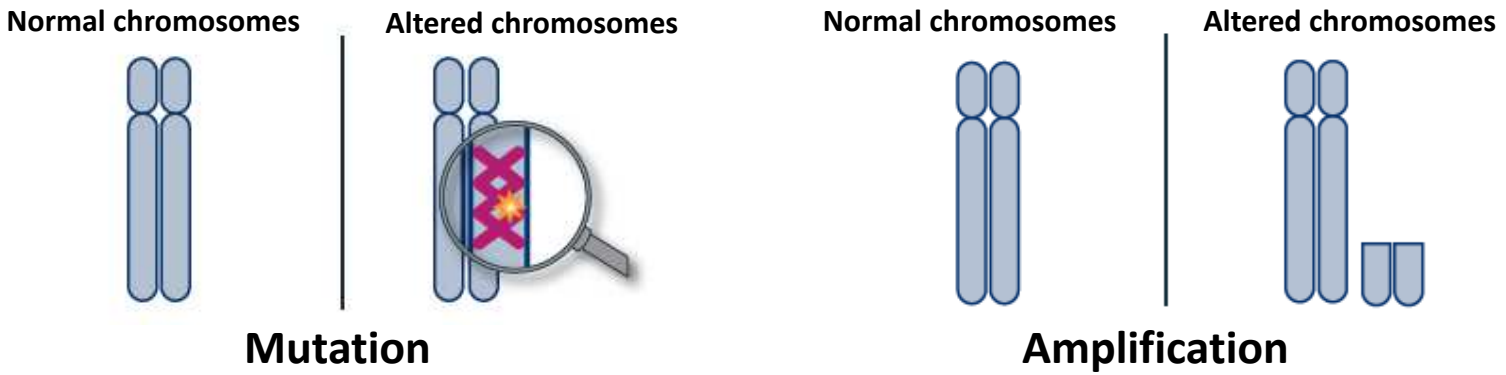


Standard model for the evolution of cancer progression with massive tumor heterogeneity

Courtesy : National Human genome Research Institute. https://www.genome.gov/about-nhgri/

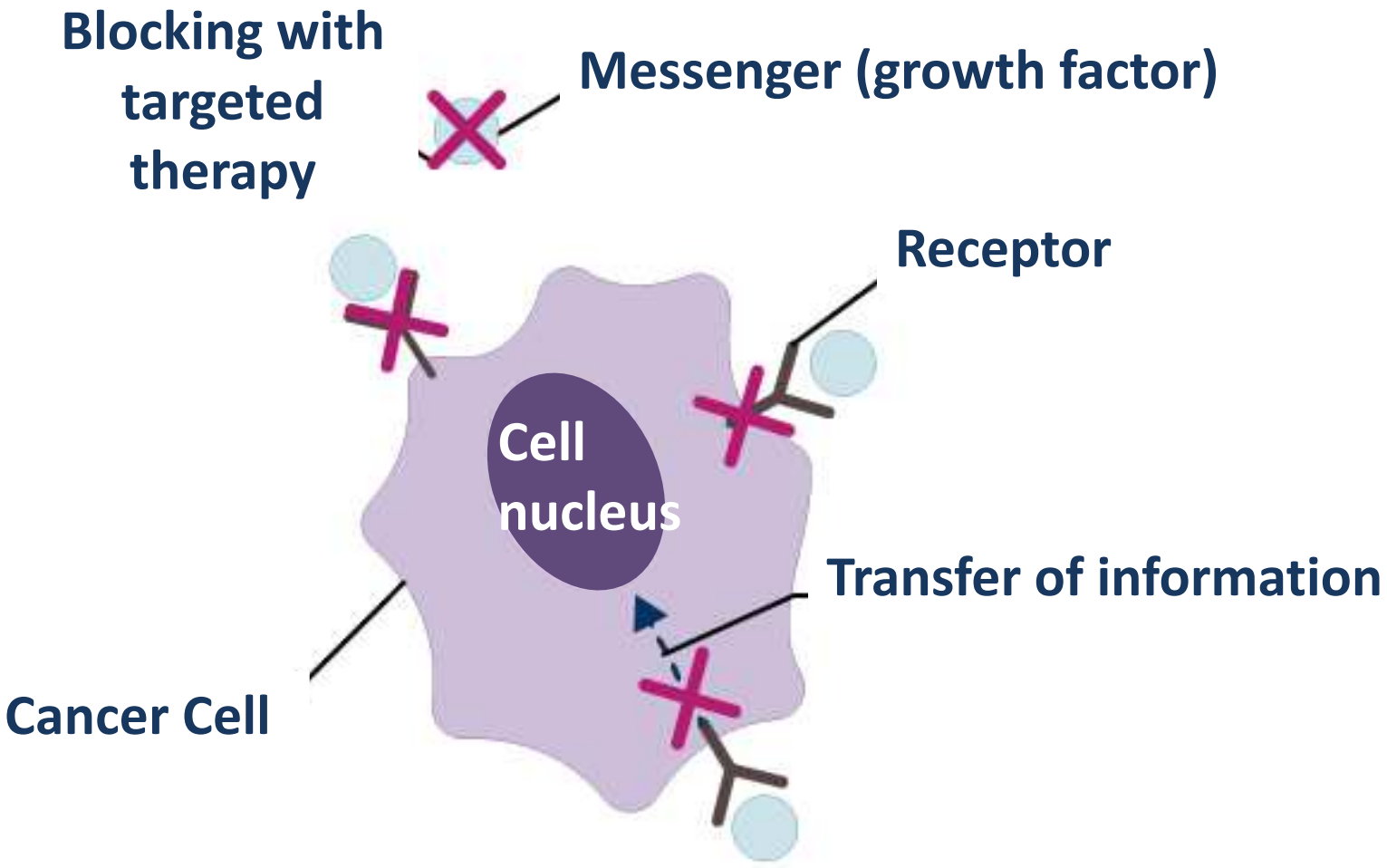
Biomarkers

- Molecular abnormalities that may occur in the form of mutation or amplification.
- Molecular tests aim to detect possible biomarkers (molecular abnormalities) in a patient's tumor.



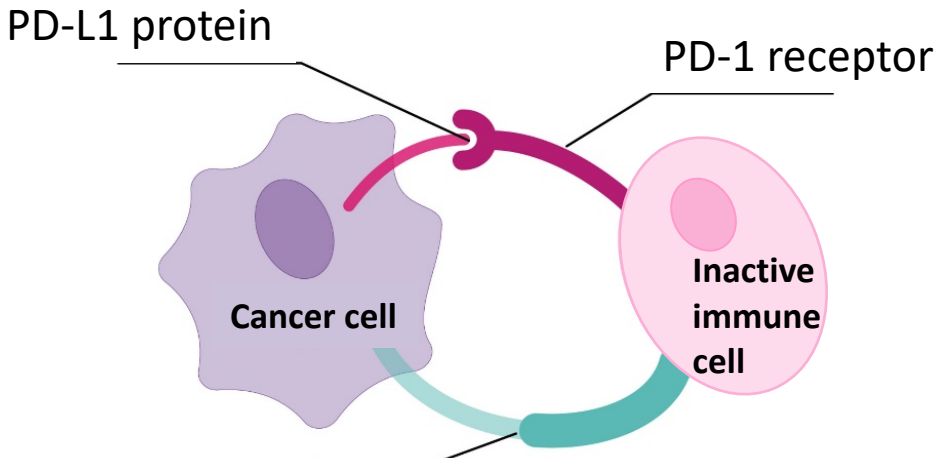
Adapted from INCa France

Targeted therapy

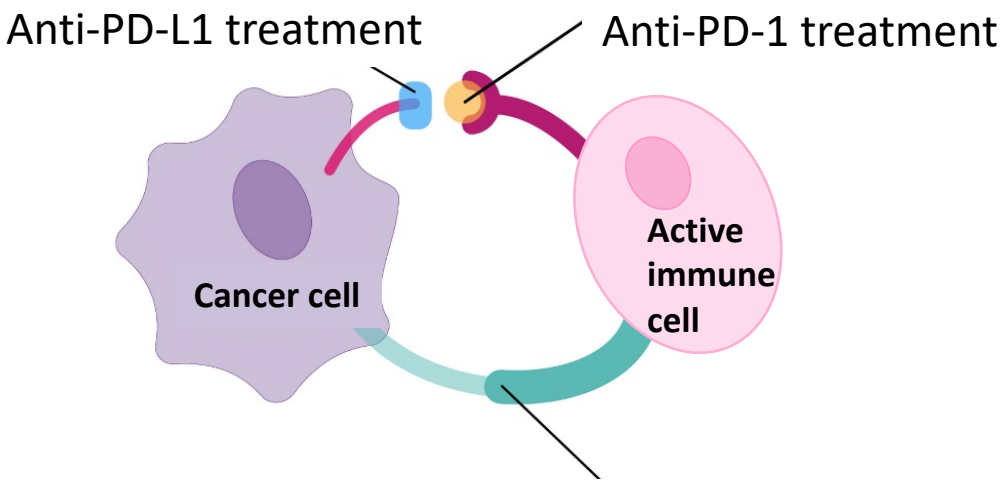


Adapted from INCa France

Immunotherapy



Normal linkage of the defense system



Normal linkage of the defense system

Adapted from INCa France

Main biomarkers in digestive tumors? Today and in future

- For colorectal cancer (RAS, BRAF, MSI…)
- For oesogastric cancer (HER2, …)
- For cholangiocarcinoma (FGFR, IDH1/2, …)
- For pancreatic cancer (BRCA 2/1, …)
- For gastrointestinal stromal tumor (GIST) (KIT, PDGFRA, …)

Great heterogeneity of colorectal cancer

- **Consensuel Molecular Subtypes**

CMS1 MSI Immune	CMS2 Canonical	CMS3 Metabolic	CMS4 Mesenchymal
14%	37%	13%	23%
MSI, CIMP high, hypermutation	SCNA high	Mixed MSI status, SCNA low, CIMP low	SCNA high
BRAF mutations		*KRAS* mutations	
Immune infiltration and activation	WNT and MYC activation	Metabolic deregulation	Stromal infiltration, TGFβ activation, angiogenesis

Guinney J *et al.* Nat Med 2015;21:1350-6

Main biomarkers in metastatic colorectal cancer

- Newly diagnosed patients and those who have progressed after the treatment.
- Tumor testing for therapeutic purposes :
  - KRAS, NRAS, BRAF analysis
  - MMR proteins, MSI
- Can detect somatic (spontaneous) mutations to identify patients for targeted treatment.
- Requires biopsy tissue.

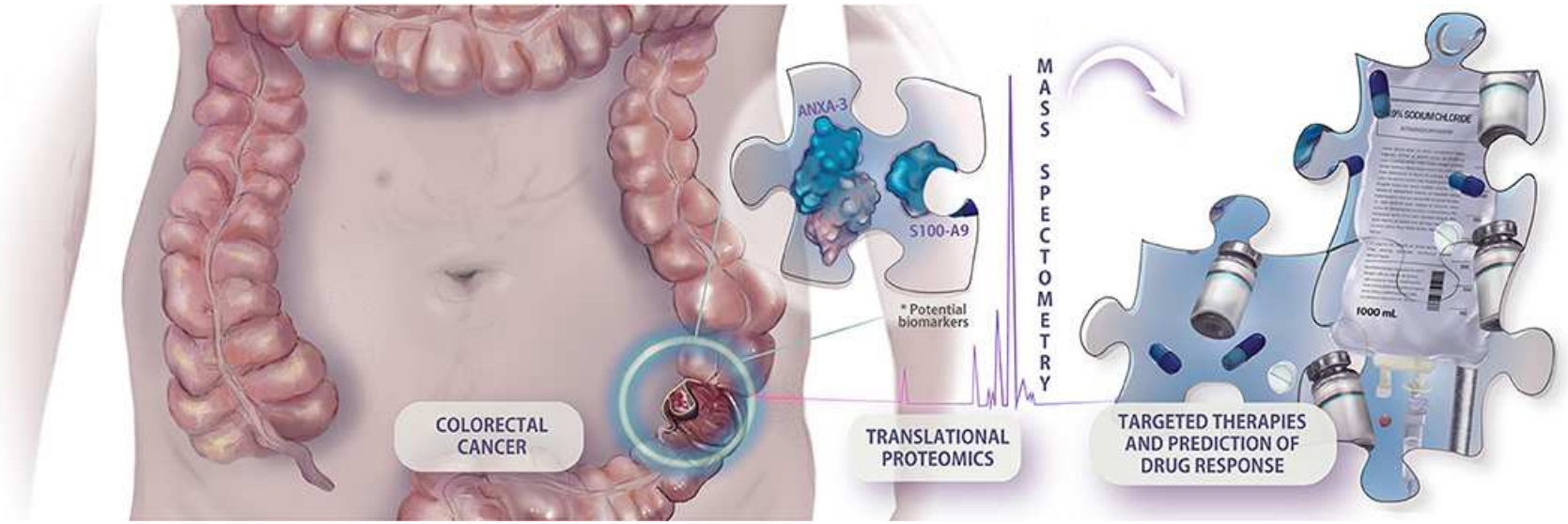
How are these analysis done?

Prescription by clinician

On tumor fragment

Transmission of material by the pathologist to the tumor genetics platform

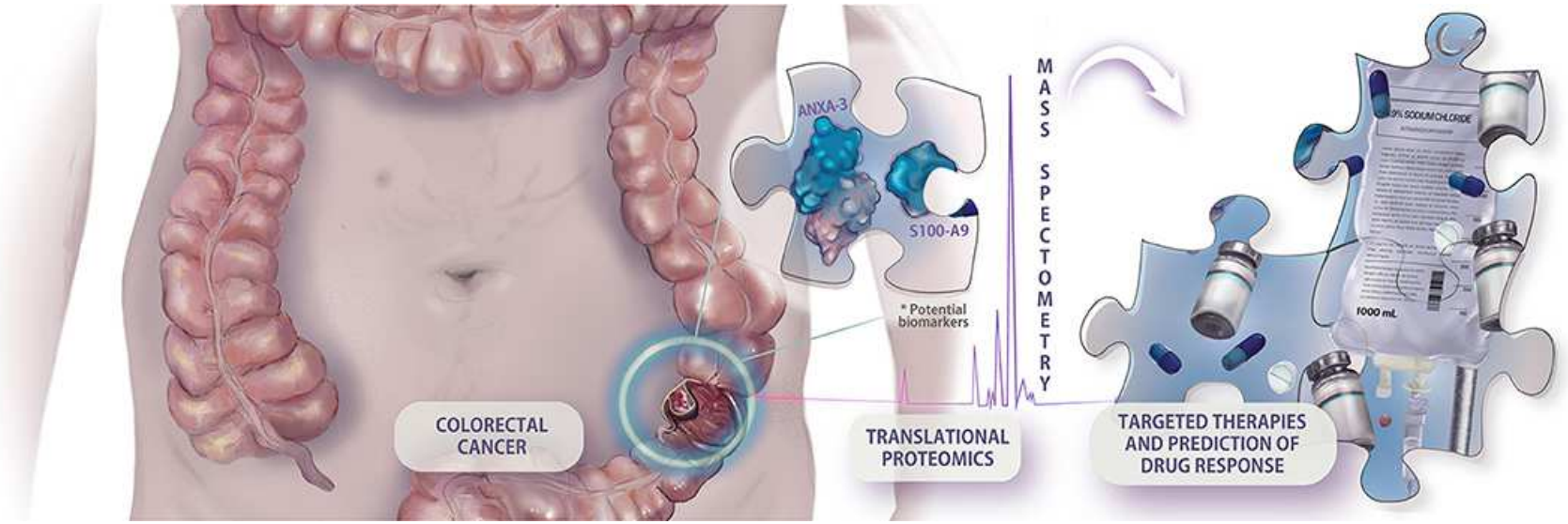
Return of results to clinician



Analysis performed in 8-10 days

Adapted from Bruno Augusto Alves Martins *et al.* Front. Oncol., 27 November 2019

How are these analyzes done?



Development of molecular analyzes from blood, circulating tumor cells or circulating tumor DNA

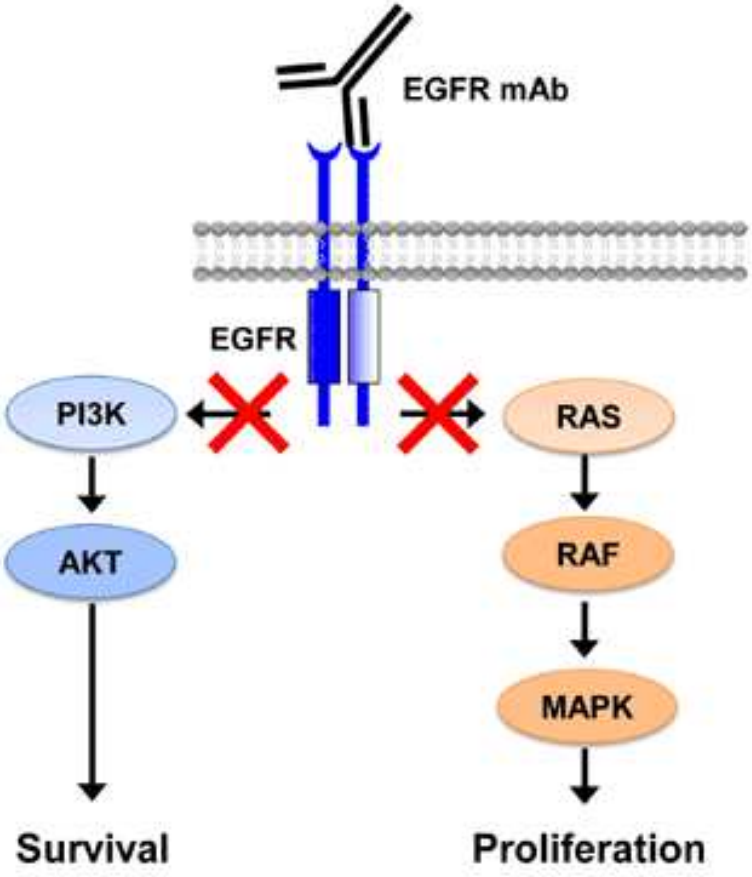
Introducing next-generation sequencers (NGS) that allow multiple mutations to be analyzed in a single time on a sample

Adapted from Bruno Augusto Alves Martins *et al.* Front. Oncol., 27 November 2019

Main biomarkers in metastatic colorectal cancer (1)

RAS mutations (KRAS, NRAS)

- ≈ 50 % of tumors
- Panitumumab or Cetuximab (anti-EGFR) are only allowed in patients with RAS wild type (non mutated) cancer
- Response rate : 30-40%



Main biomarkers in metastatic colorectal cancer (2)

BRAF Mutations (V600E is the most frequent)

- ≈ 10 % of colorectal cancer
- Poor prognostic factor
- Resistance to anti-EGFR agents
- Intensified chemotherapy without anti-EGFR
- Combinations of anti-BRAF agents (oral) and anti-EGFR therapies after 1 or 2 prior treatment (BEACON trial)

Kopetz S *et al.* NEJM 2019; 381:1632-43

Main biomarkers in metastatic colorectal cancer (3)

MicroSatellite Instability MSI

- ≈ 5 to 15% of sporadic cancer
- Almost constant in Lynch syndrome
- Patient eligible to Immunotherapy trial ?

Effectiveness of immunotherapy in MSI colorectal cancers

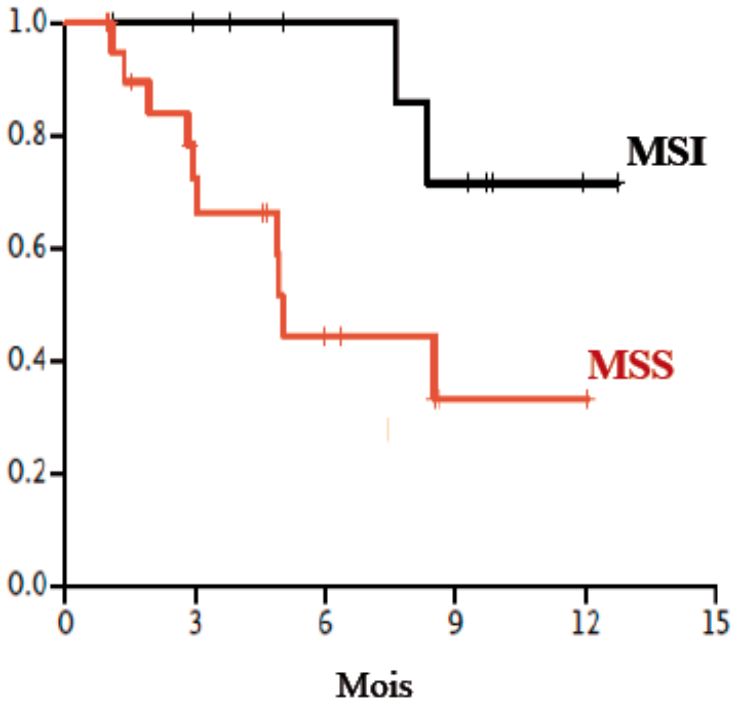
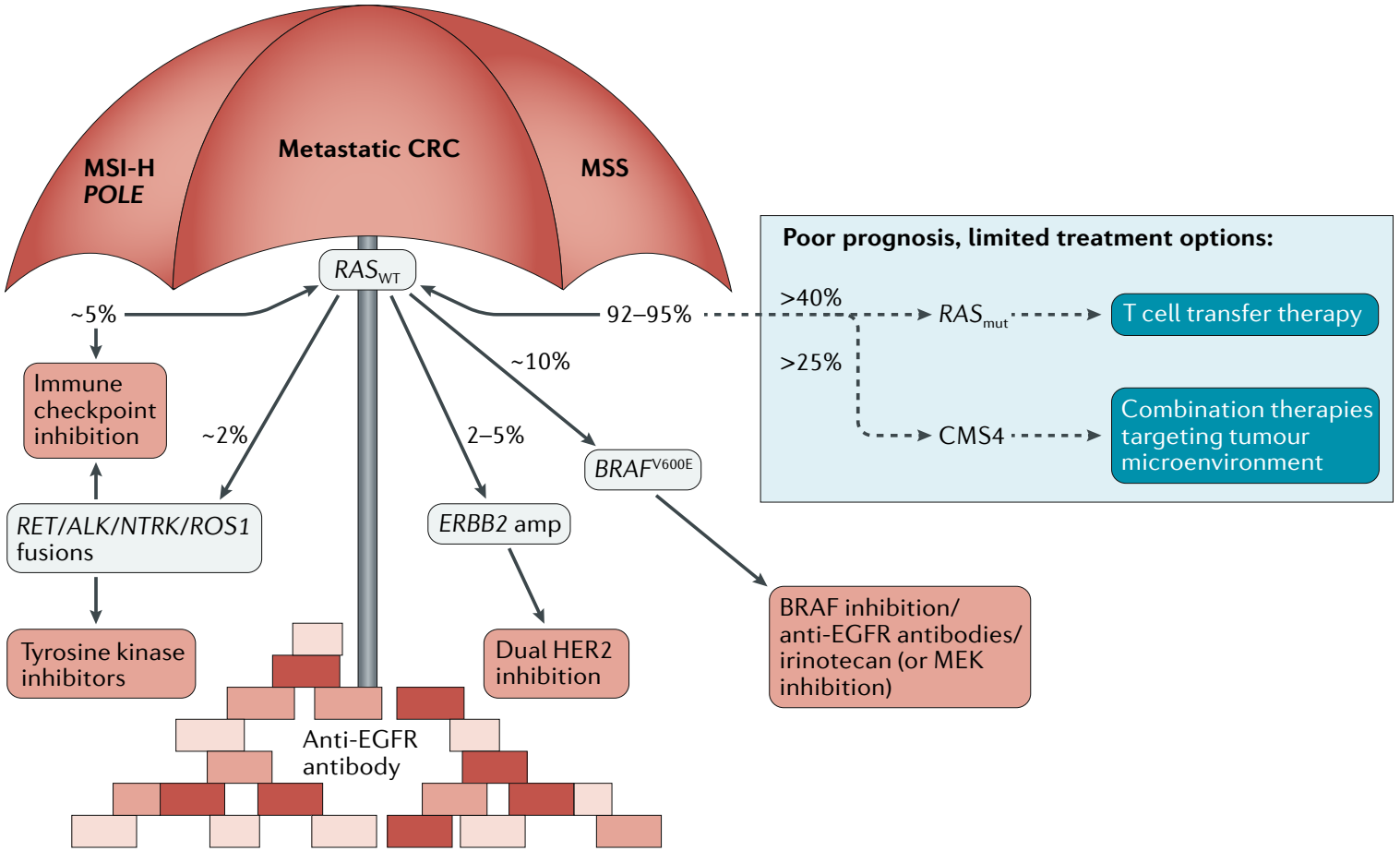


Fig . Overall survival of patients with metastatic colorectal cancer treated with pembrolizumab according to MSI status

Le Dung T *et al*. PD-1. N Engl J Med 2015;372:2509–20

Main biomarkers in metastatic colorectal cancer and therapeutic implication

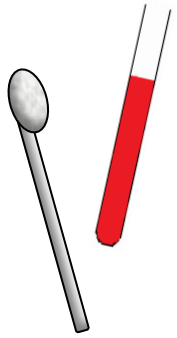


Treatment options and biomarker interactions in metastatic colorectal cancers

Adapted from Sveen A *et al.* Nat Rev 2020 : 17; 11-32

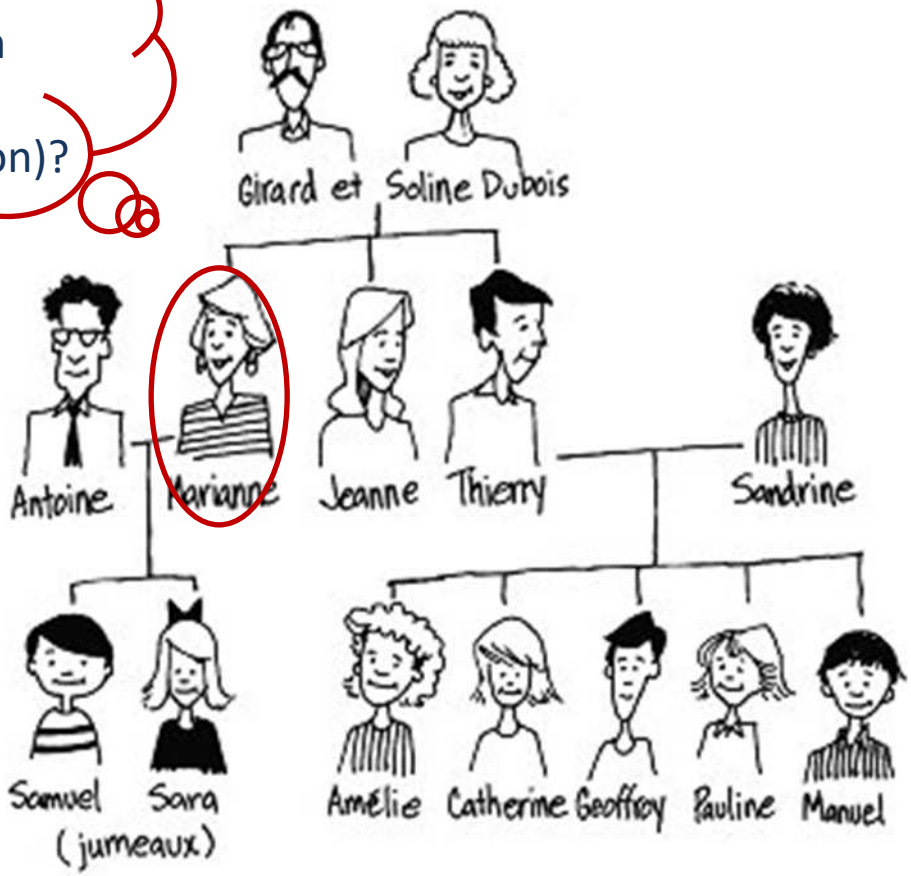
Main biomarkers in colorectal cancer
The oncogenetic approach

- If personal or family history of cancer :
  - Analysis of expression of MMR proteins
  - and/or MSI analysis
- Germline testing (digestive panel) using blood or saliva
- Can detect inherited mutations
- These inherited mutations can be transmitted to progeny (hereditary transmission)
- Can be used for testing the relatives and guide the genetic counselling in the family

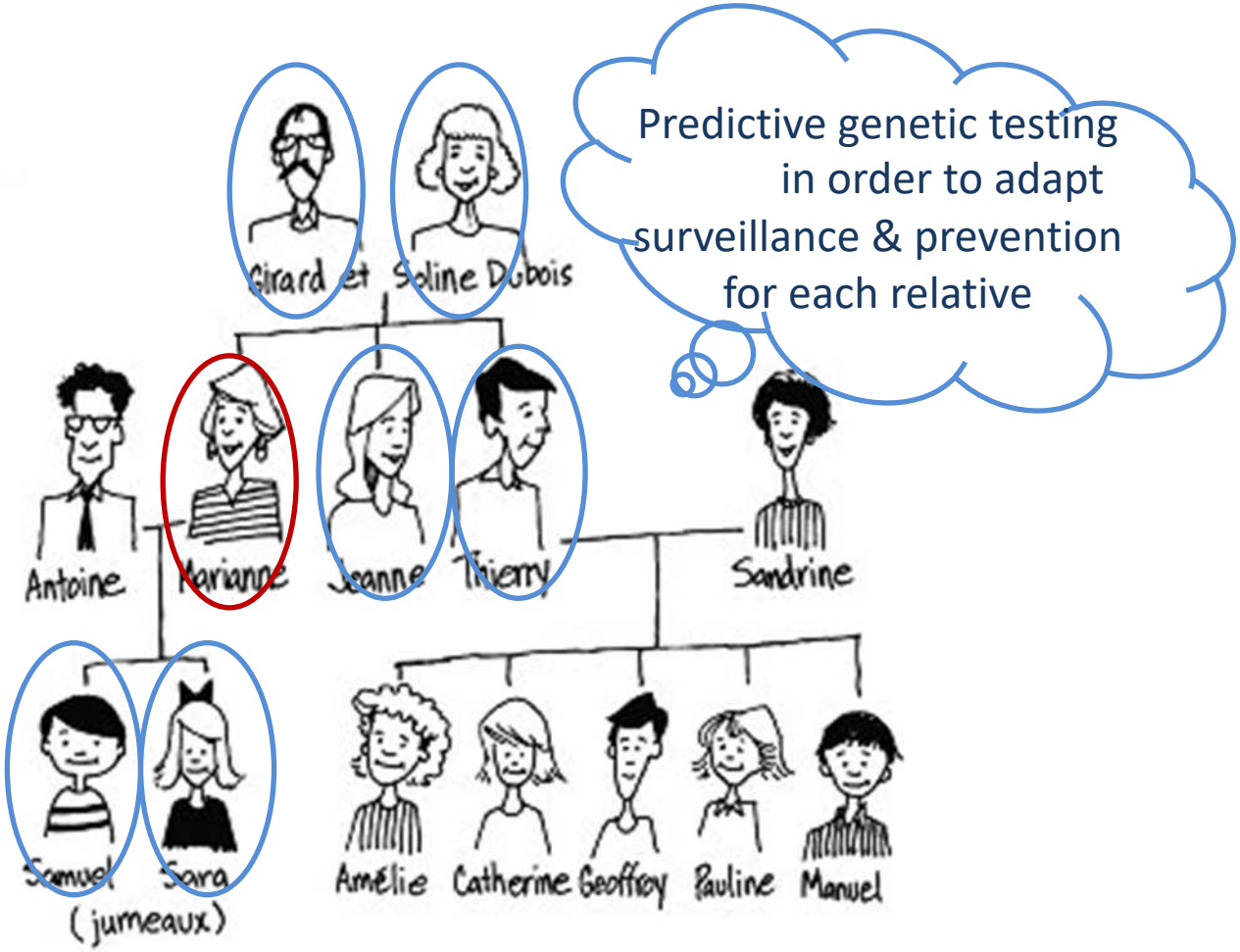


The oncogenetic approach
The genetic counselling

What is my risk of cancer if Lynch syndrome (germline mutation)?



The oncogenetic approach
The genetic counselling



Keys messages

- Only few targeted oncology drugs available in gastrointestinal cancer compared to other tumors
- Better clinical, histological, and molecular characterization of digestive cancers necessary
- Most established biomarkers have a low prevalence (HER2)
- Immunotherapy and MSI colorectal cancer
- Genetic counselling if MSI tumors
- Expected progress in the future thanks to next-generation sequencers (NGS) approach with new potential targets
- ctDNA analysis to anticipate disease progression

Thank you for your attention