![Digestive Cancers Europe logo]

DIGESTIVE CANCERS
EUROPE

MASTERCLASS SERIES

Role of the Immune response in early stage colorectal cancers:
a new era in precision medicine

By Dr Tony Dhillon
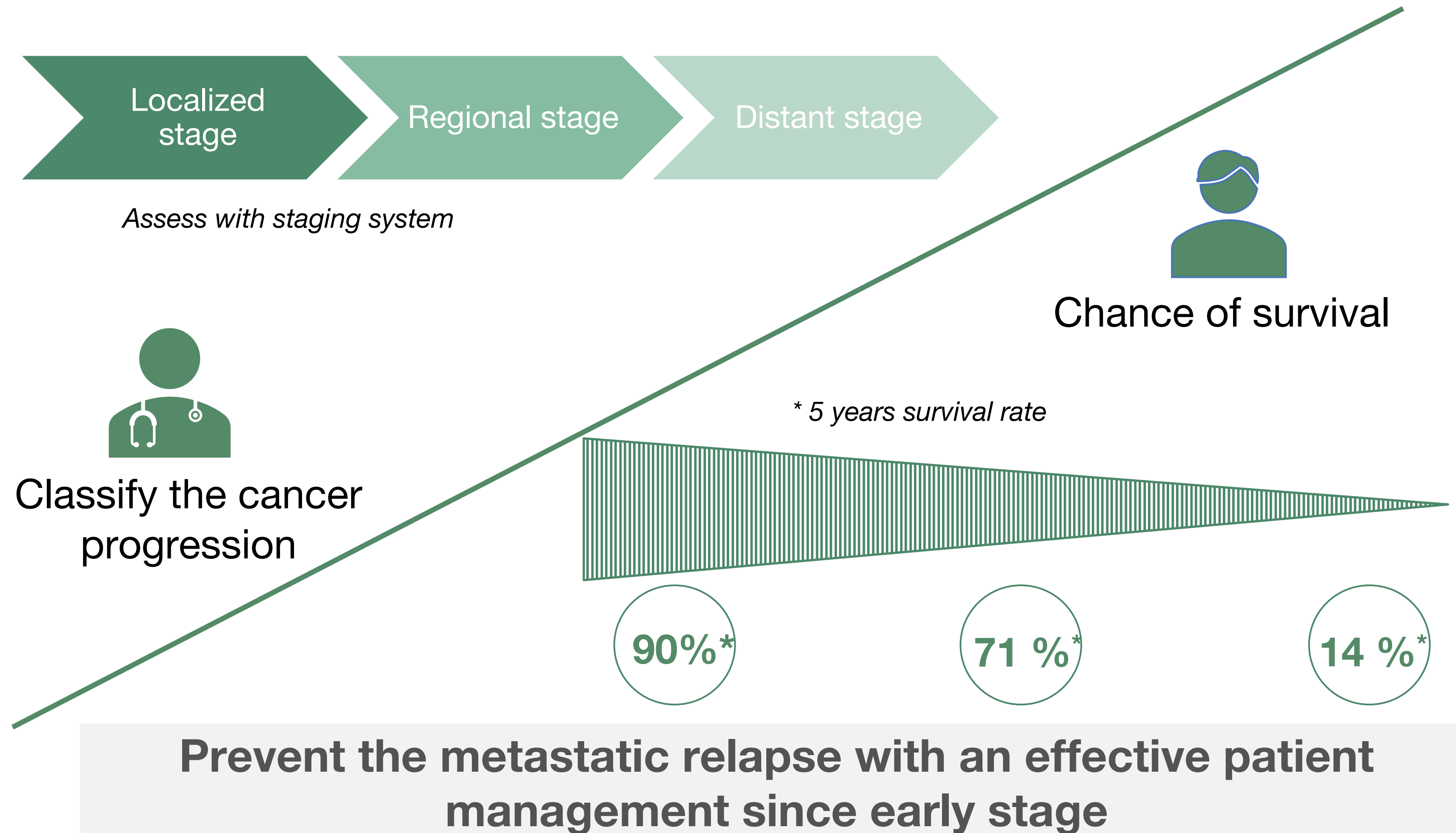**Consultant Medical Oncologist at The Royal Surrey Hospital , Guildford, UK**

Colorectal cancer- Key figures

- CRC 2nd most lethal cancer and 3rd most common cancer worldwide

- 2018 1.8 million cases worldwide

- 5 year survival is 65% and goes down to 12% for metastatic disease

- 25% present late despite widespread screening

- Early disease treated with surgery± chemo depending on stage

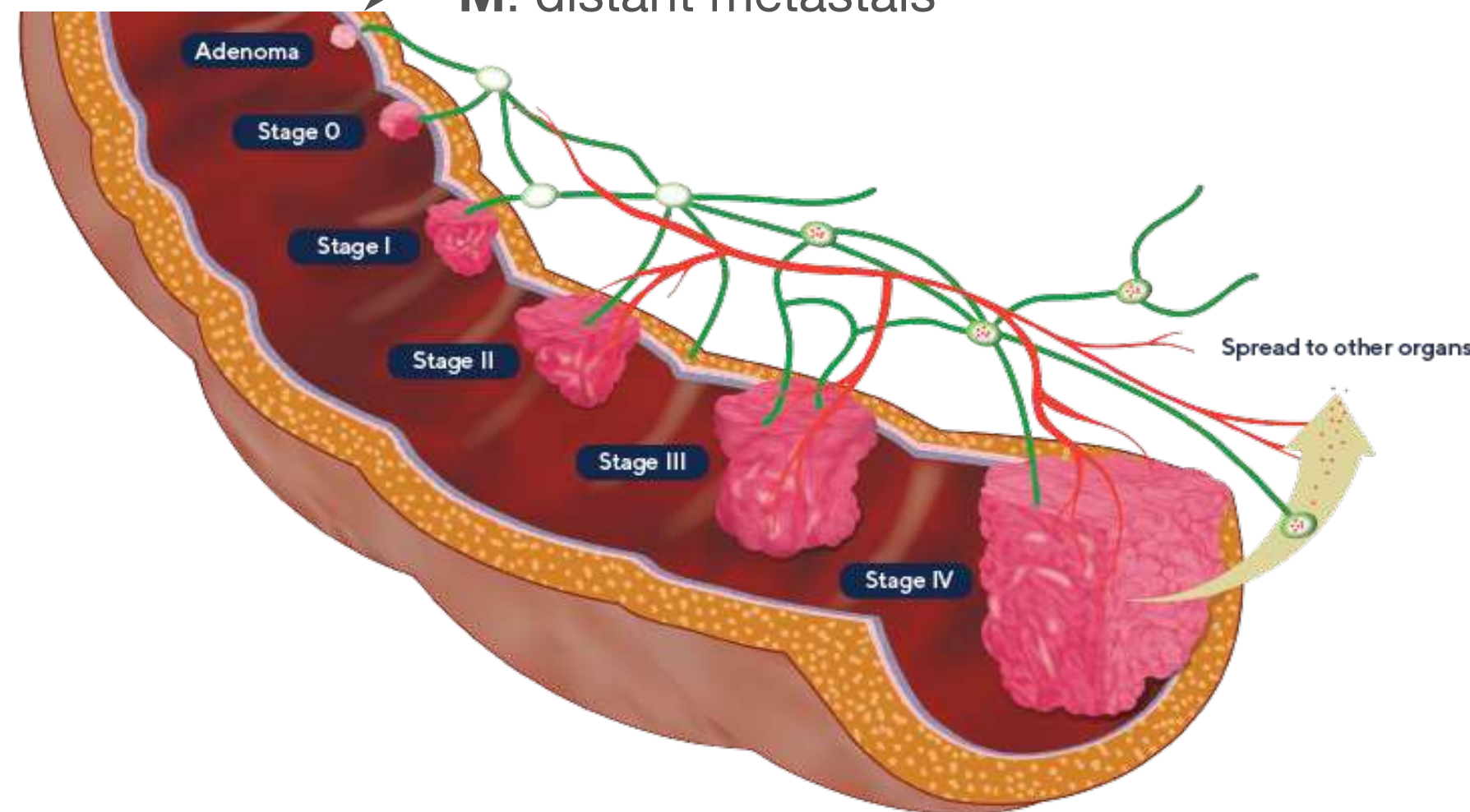**Key challenge in the early colorectal cancers is to prevent the relapse**

Colorectal cancer progression

Localized stage → Regional stage → Distant stage

Assess with staging system

Classify the cancer progression

Chance of survival

* 5 years survival rate

90%* **71 %*** **14 %***

Prevent the metastatic relapse with an effective patient management since early stage

The CRC ' therapeutic strategy is based on incomplete risk-assessment tool

**Gold standard :
TNM Classification**

> **T:** tumeur extension
> **N:** regional lymph nodes
> **M:** distant metastais

Adenoma
Stage 0
Stage I
Stage II
Stage III
Stage IV
Spread to other organs

TNM stage does not accurately reflect survival for many patients

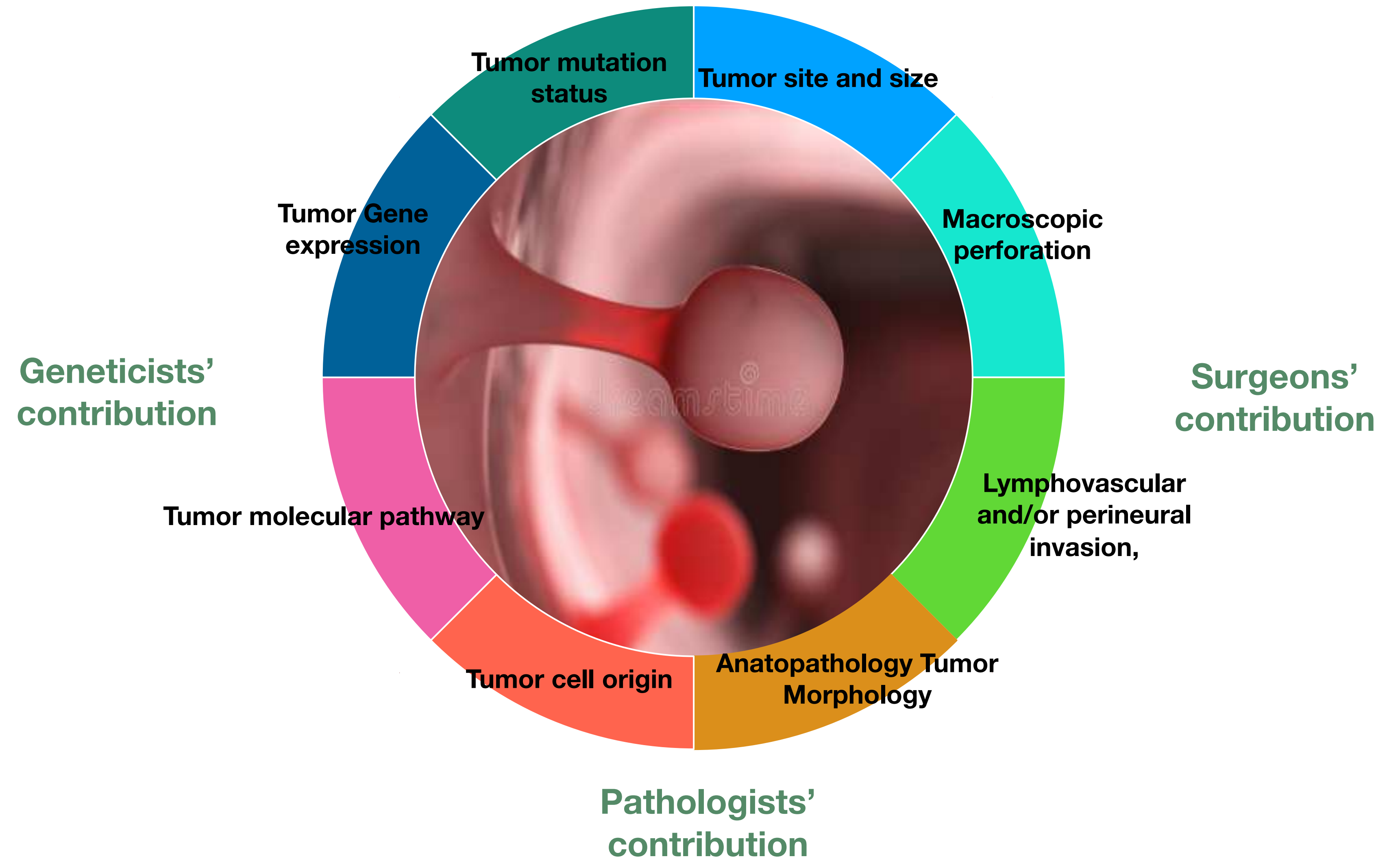**S U R G E R Y**

+/−

C H E M O

Reality for Patients based on TNM staging only

many
Over-treated

and some

Under-treated

A need for additional biomarker to OPTIMIZE adjuvant treatment decisions

Staging system has been improved by a better understanding of tumor profile

Tumor profiling improved the TNM system and cancer prognosis

Tumor mutation status

Tumor site and size

Tumor Gene expression

Macroscopic perforation

Geneticists' contribution

Surgeons' contribution

Tumor molecular pathway

Lymphovascular and/or perineural invasion,

Tumor cell origin

Anatopathology Tumor Morphology

Pathologists' contribution

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Paul Ehrlich
The Nobel Prize in Physiology or Medicine 1908

Royal Institute for Experimental Therapy,
Prize motivation: "in recognition of their work on immunity."
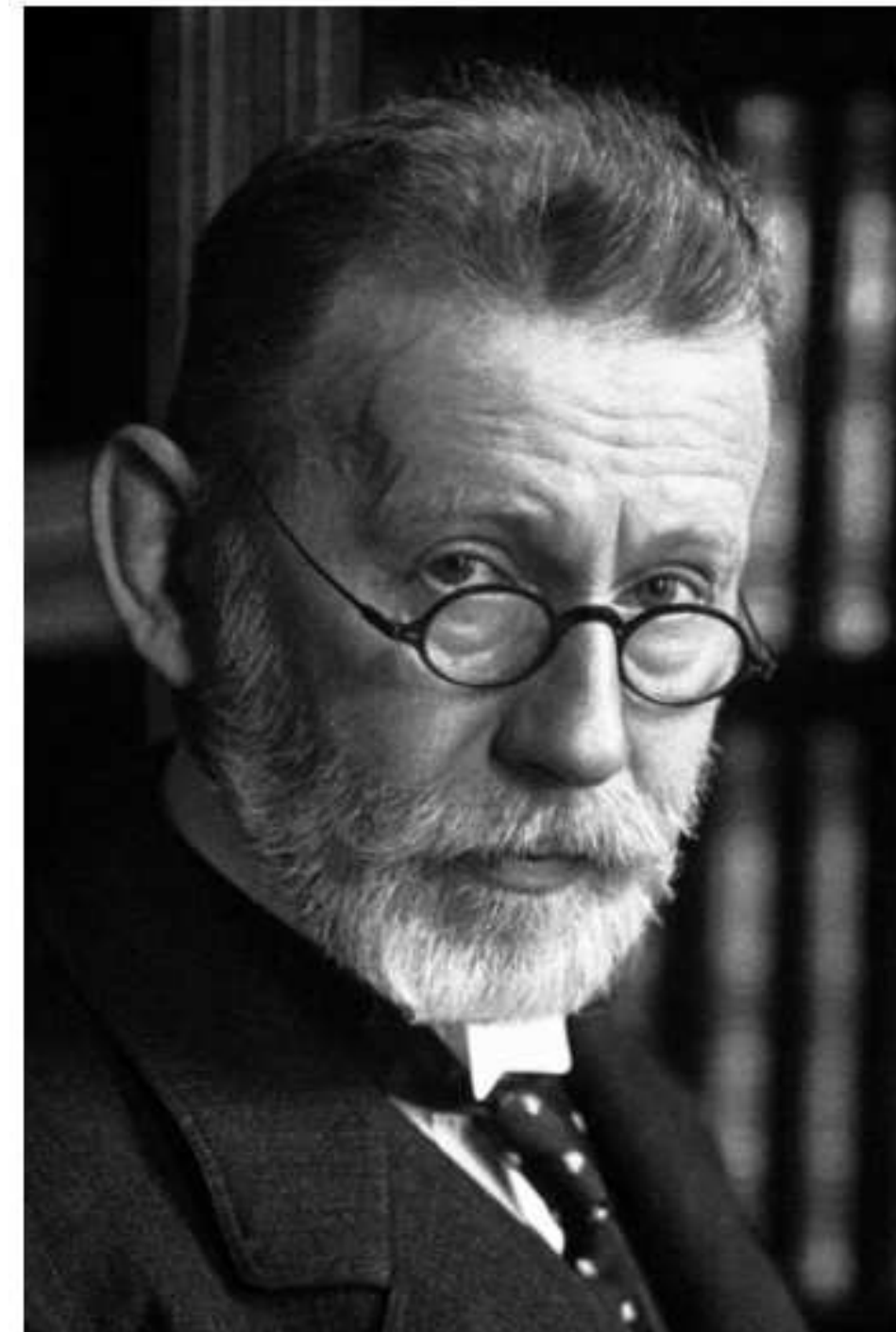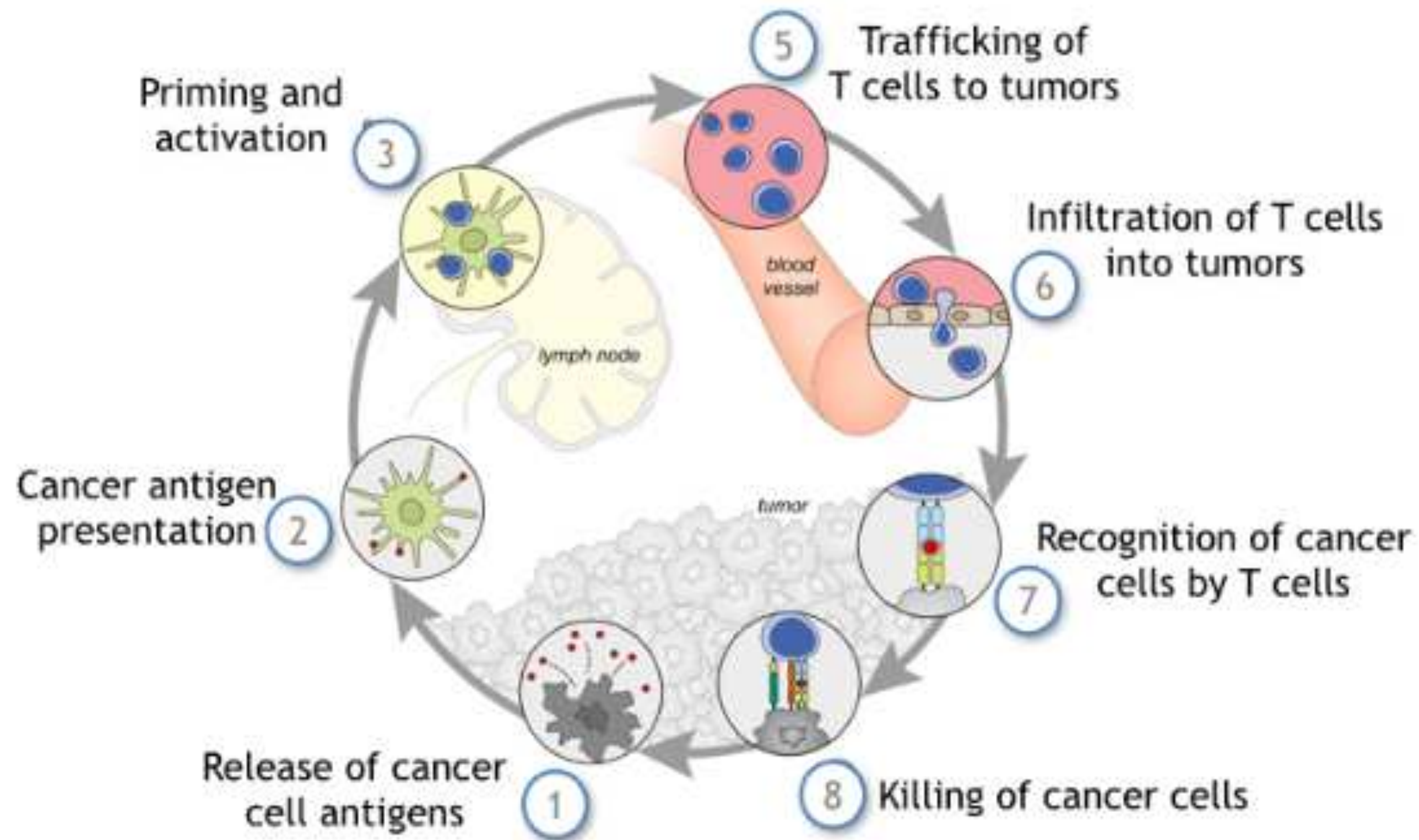Prize share: ½ Ilya Mechnikov

❖ The protective value of immunity was initially proposed by Paul Ehrlich in 1909;

❖ however, it was impossible to access the validity of the prediction

❖ limited awareness of the immune system.

Host immune assets from hope to reality… Immunomodulatory roles of nutritional, lifestyle, and pharmacological factors including omega-3 PUFA, vitamin D, physical activity

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The Cancer Immunity Cycle

- ❖ Latest discoveries of the immune system's involvement in cancer progression with the advent of immunotherapy.

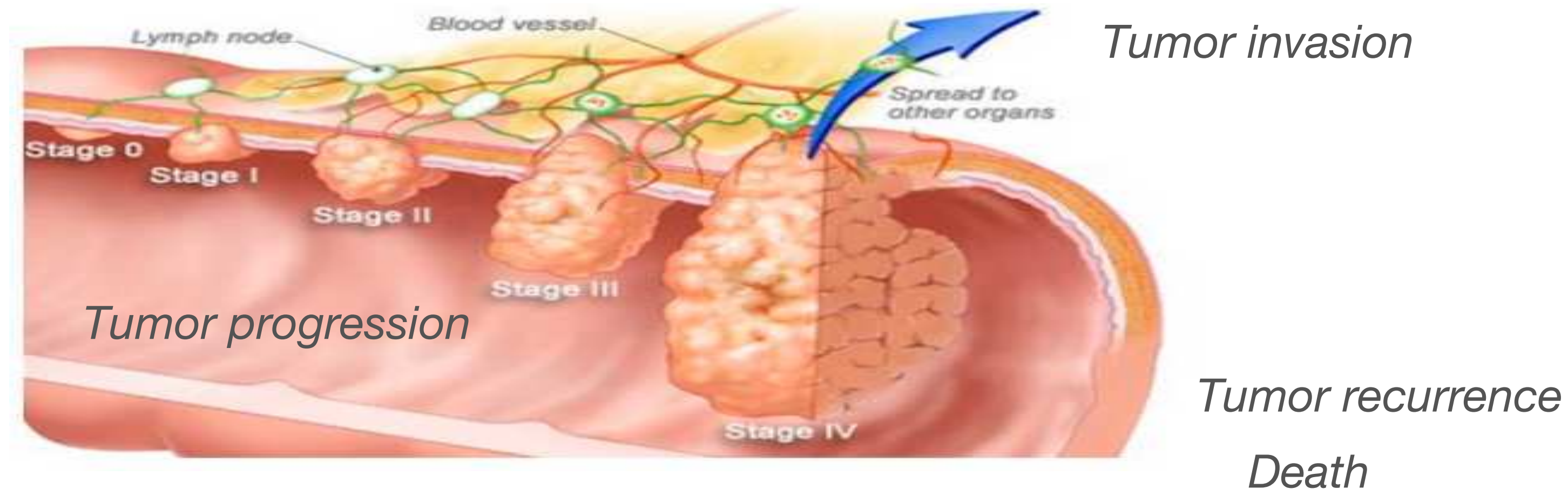- ❖ Presence of T-cells in the tumor can influence at each step of cancer progression

The lastest discoveries on the role of immune microenvironment massively changed our cancer diagnosis and treatment approach

More important than clinico-pathological feature, the survival is predetermined by pre-existing immunity
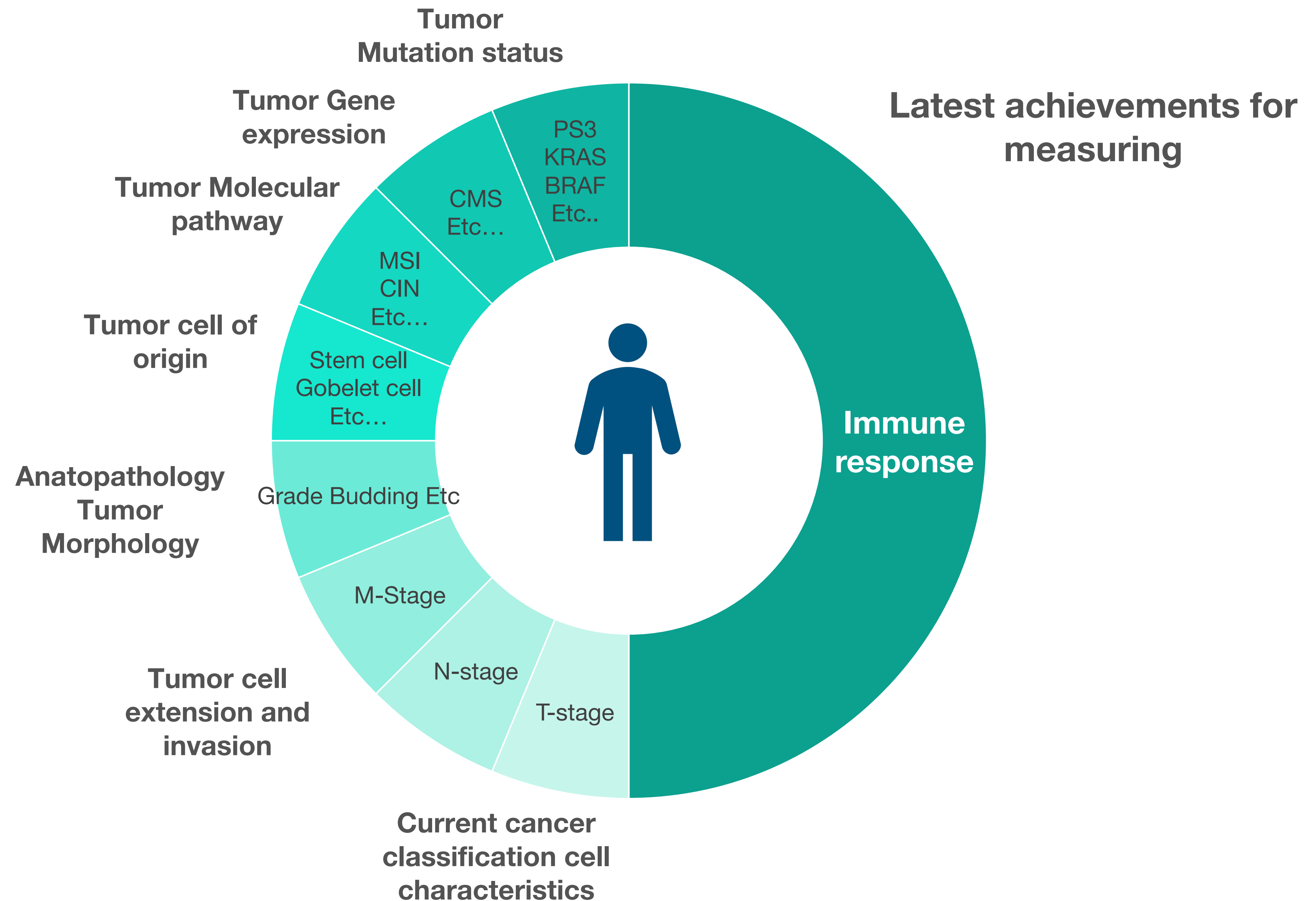
Hot
Tumor

Immune contexture

Cold
Tumor

Lymph node   Blood vessel

Stage 0

Stage I

Stage II

Spread to other organs

Tumor invasion

Stage III

Tumor progression

Stage IV

Tumor recurrence

Death

✓ Tumor progression, invasion and recurrence are dependent on pre-existing immunity
✓ Pre-existing immunity is determining the fate and survival of the patient

Include immune response, completes and refines knowledge about the patient's cancer

Tumor Mutation status

Tumor Gene expression

Tumor Molecular pathway

Tumor cell of origin

Anatopathology Tumor Morphology

Tumor cell extension and invasion

Latest achievements for measuring

Immune response

Current cancer classification cell characteristics

PS3 KRAS BRAF Etc..

CMS Etc…

MSI CIN Etc…

Stem cell Gobelet cell Etc…

Grade Budding Etc

M-Stage

N-stage

T-stage

As a key parameter now, the immune response can be measured to assess digestive tumors

WHO Blue book is the gold standard for the diagnosis of tumors with regular updates to keep up to date to innovations

This international authoritative reference book considers **now immune response as an essential and desirable diagnostic criteria** for colorectal cancer by the WHO

The tool is likely to complement the traditional staging system (cf. TNM-I claim)

Key characteristics for a good biomarker

✓**Clinically validated:** studies conducted on a large cohort of patients with consistent and similar results

✓**Accurate** : Superior to current technologies

✓**Repeatable :** same result as many times as you do the test

.

✓**Stable :** stable results for all settings

✓**Applicable and available:** in the routine practice, for all facilities

Patient journey
(precision medicine)

Difference between a prognostic and predictive diagnostic test

PREDICTIVE Biomarker

PROGNOSTIC Biomarker

Diagnosis

Will the **TREATMENT** benefit **ME**?

Treatment
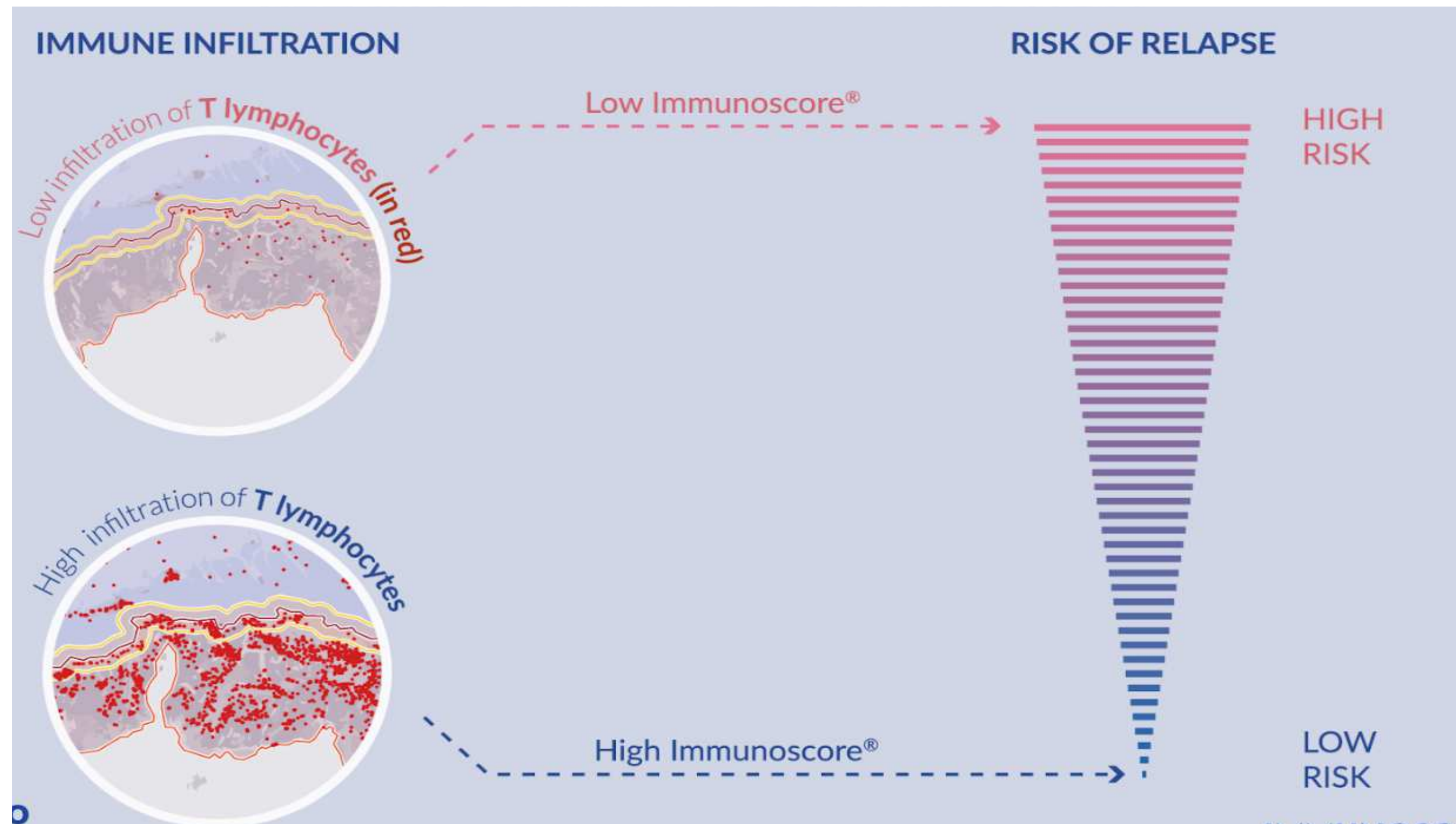
My recurrence risk can guide my doctor to take the tailored clinical decision, so that I have **the best chance of survival**

Remission

Will my tumor **RECURRE**?

Now, the immune response can be assessed and computed in a systemic scoreNew biomarker

IMMUNE INFILTRATION

RISK OF RELAPSE

Low infiltration of T lymphocytes (in red)

Low Immunoscore®

HIGH RISK

High infiltration of T lymphocytes

High Immunoscore®

LOW RISK

Driven by clinical use
A reliable estimate of the risk of recurrence in colon cancer*

* The prognostic value of Immunoscore; in patients with cancer: A pooled analysis of 10,328 patients Xingxia Zhang, IJBM2020

This new immune biomarker was validated in large international study

published in one of the most reputable peer reviewed journals

THE LANCET

Articles

International validation of the consensus Immunoscore for the classification of colon cancer: a prognostic and accuracy study

A large-scale international clinical study validates the prognostic value of Immunoscore® in colon cancer

- An international consortium confirms the strong prognostic value of the Immunoscore® assay in early stage colon cancer.
- Published in *The Lancet* on May 11, 2018, these results validate the reliability of Immunoscore® Colon in identifying patients with a high risk of recurrence, independently of the TNM[1] staging system.

Open access   Original research
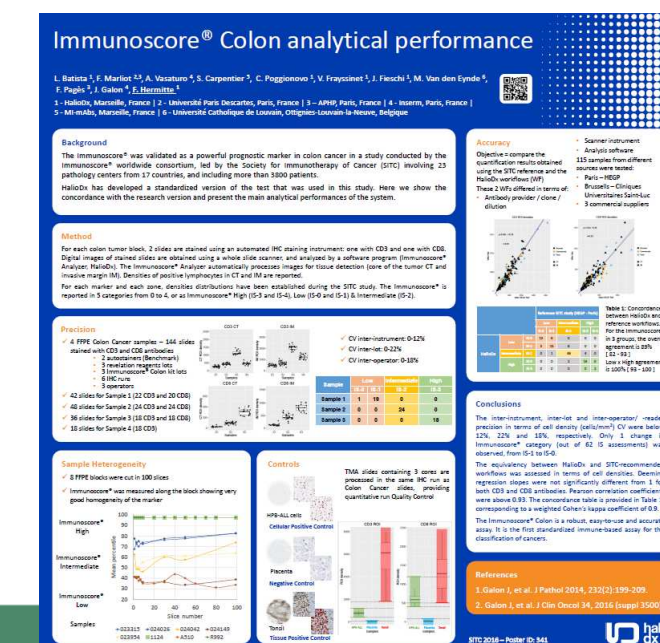
Journal for ImmunoTherapy of Cancer

Analytical validation of the Immunoscore and its associated prognostic value in patients with colon cancer

Florence Marliot,[1] Xiaoyi Chen,[2] Amos Kirilovsky,[1] Thomas Sbarrato [3], Carine El Sissy,[1] Luciana Batista,[4] Marc Van den Eynde,[5] Nacilla Haicheur-Adjouri,[6] Maria-Gabriela Anitei,[7] Ana-Maria Musina,[7] Viorel Scripcariu,[7] Christine Lagorce-Pagès,[1] Fabienne Hermitte,[3] Jérôme Galon,[1] Jacques Fieschi,[3] Franck Pagès[1]
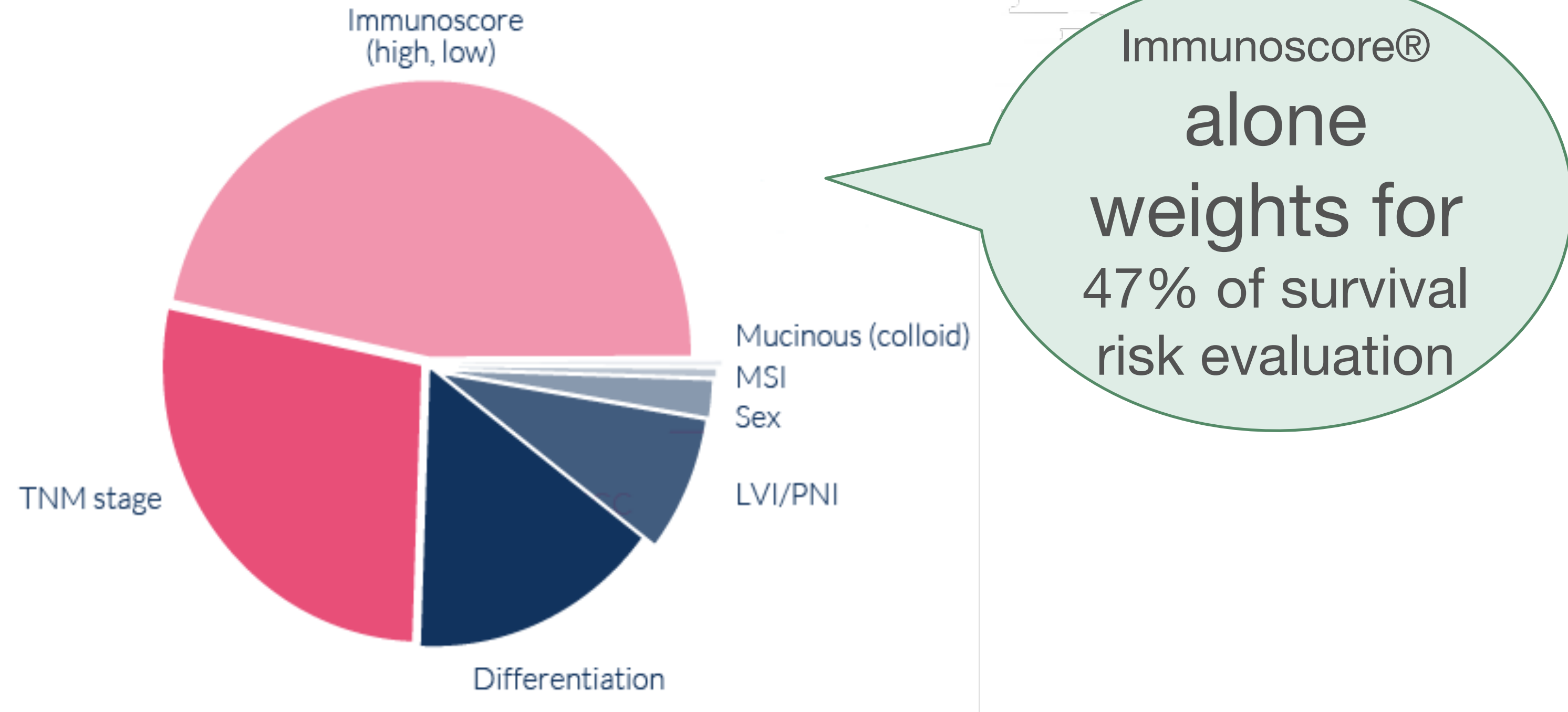
J Immunother Cancer: first published as 10.1136/jit

Key characteristics filled:

✓**Clinically validated**

✓**Accurate**

✓**Repeatable**

✓**Stable**

✓**Applicable, available**

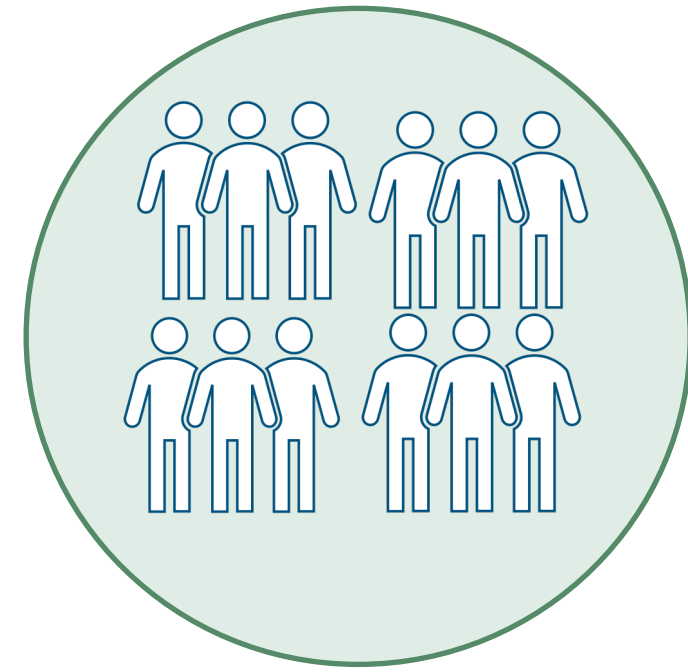DIGESTIVE CANCERS EUROPE

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Now, your doctor can know your chances of survival very early and accurately.

Relative contribution of Immunoscore® to survival risk

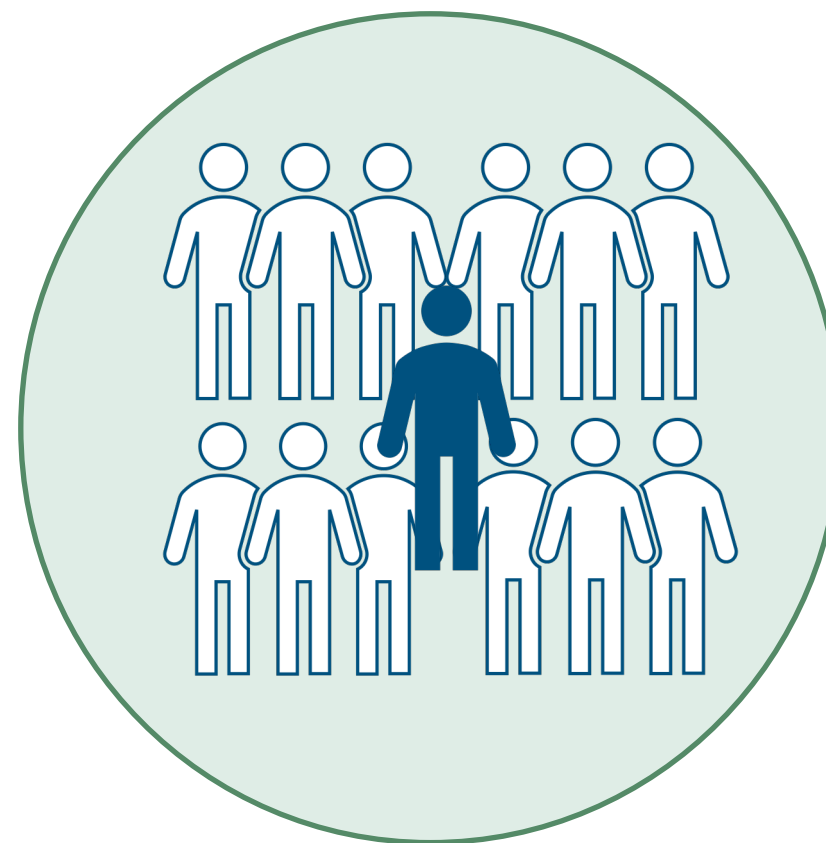Immunoscore® **alone weights for** 47% of survival risk evaluation
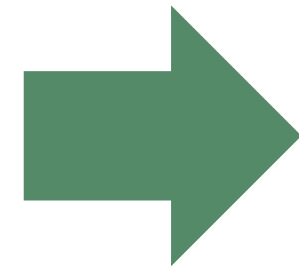
This independant parameter has the highest relative contribution to the survival risk of all clinical parameters, including the TNM classification system

Assess your immune response to maximize your survival chance

BEFORE

UP TO DATE

Your immune capital informs:

- If chemotherapy is needed for your personal case

- The efficient chemotherapy duration without unnecessarily altering your quality of life

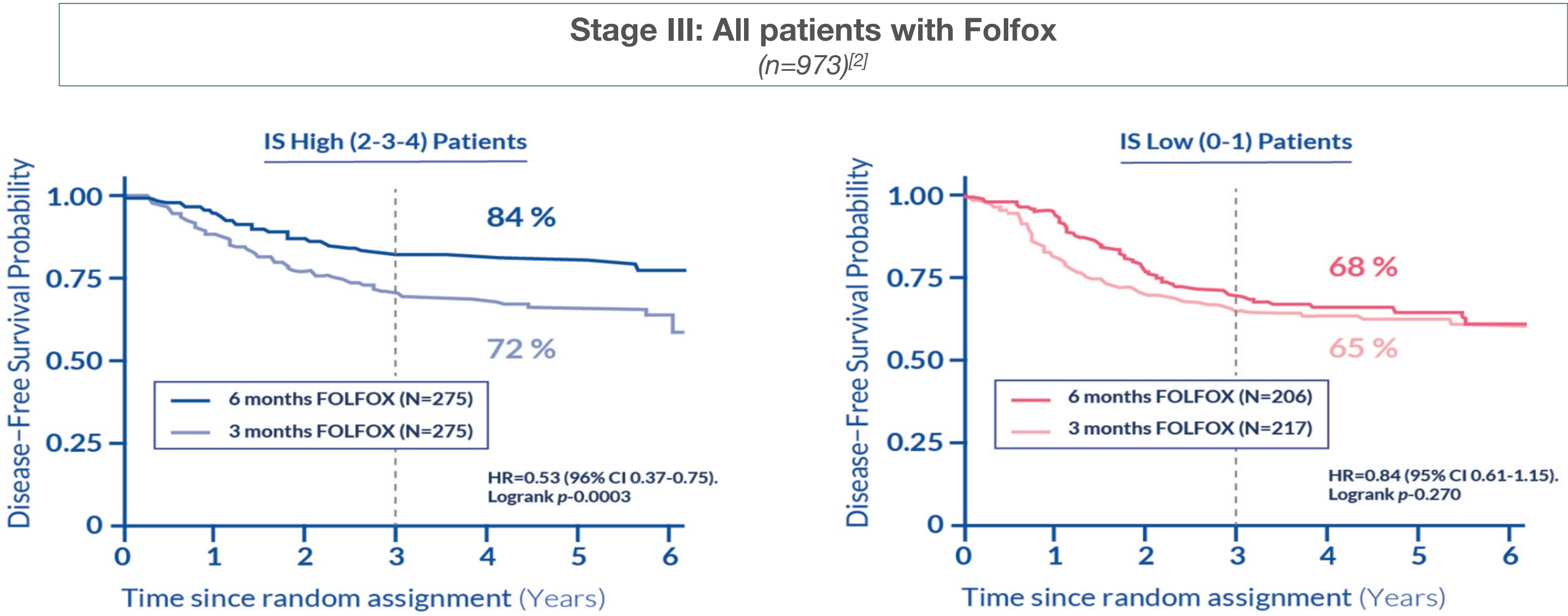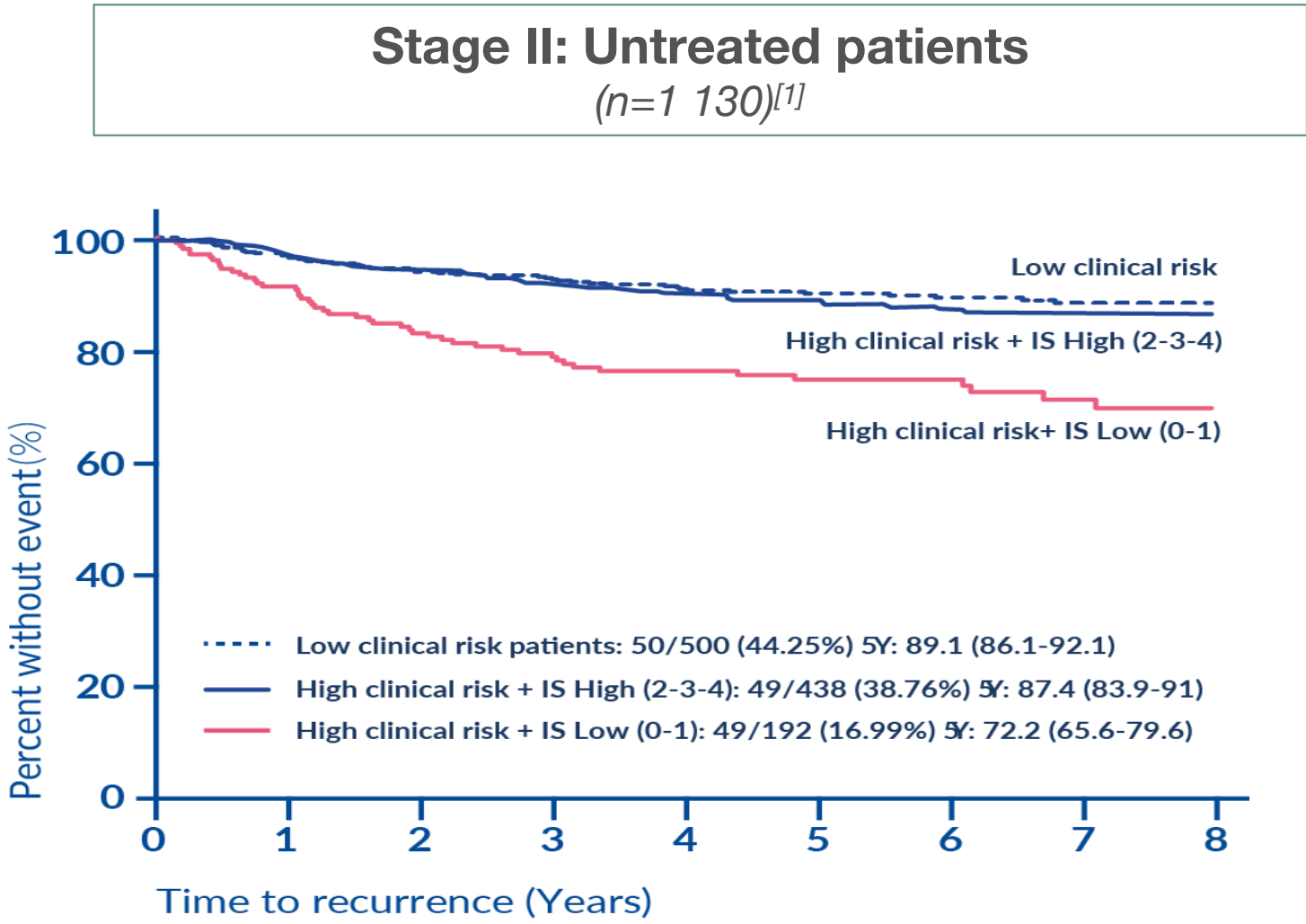# Assess your immune response to tailor your chemotherapy

STAGE II

"can I avoid chemotherapy with no risk / peace of mind ?"

STAGE III

« what is MY appropriate chemo duration

without unnecessarily altering quality of life? »

Clinical Data

Stage II: Untreated patients
(n=1 130)[1]

Low clinical risk

High clinical risk + IS High (2-3-4)

High clinical risk+ IS Low (0-1)

Percent without event (%)

Low clinical risk patients: 50/500 (44.25%) 5Y: 89.1 (86.1-92.1)
High clinical risk + IS High (2-3-4): 49/438 (38.76%) 5Y: 87.4 (83.9-91)
High clinical risk + IS Low (0-1): 49/192 (16.99%) 5Y: 72.2 (65.6-79.6)

Time to recurrence (Years)

Stage III: All patients with Folfox
(n=973)[2]

IS High (2-3-4) Patients

84 %

72 %

Disease-Free Survival Probability

6 months FOLFOX (N=275)
3 months FOLFOX (N=275)

HR=0.53 (96% CI 0.37-0.75).
Logrank *p*-0.0003

Time since random assignment (Years)

IS Low (0-1) Patients

68 %

65 %

Disease-Free Survival Probability

6 months FOLFOX (N=206)
3 months FOLFOX (N=217)

HR=0.84 (95% CI 0.61-1.15).
Logrank *p*-0.270

Time since random assignment (Years)

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With immunomics precision medicine

Paradigm change is underway

In treatment but also in prevention and control

Reveal your immune score :

- To better know your own cancer feature

- To avoid toxic unnecessary treatments

- To personalize your treatment

- To maximize your chance of survival

- To take part in your treatment decision making

Effective Clinical Experience

Patient profile:
67 Male diagnosed with T3 N0 sigmoid cancer lymphovascular and lymphatic invasion- some high risk features- ? chemo

Decided to use immunoscore® to help make decision.

Immuoscore® revealed – low risk of relapse-

Decision to not offer adjuvant chemotherapy.

Patient profile:
*52 female diagnosed with T4 N0 transverse colon cancer- emergency presentation
? Chemo*

Decided to use immunoscore® to help make decision.

Immunoscore® revealed- high risk of relapse

Decision to offer chemotherapy