OHDSI evidence in action

Personalized Oncological Surgery

The right treatment to the right patient at the right time

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Presented by professor Ismail Gögenur, DMSc
Director of the Center for Surgical Science (CSS)

Center for Surgical Science

leading an international network of excellence for personalized oncological research

- State of the art research and everyday clinical practice based on multidisciplinary collaboration.
- Innovative surgical methods with significant impact on patients' quality of life and treatment cost.
- Incorporating in its organizational structure the main scientific domains of CAG-POS:
  - Surgery
  - Epidemiology
  - Translational Research
  - Big data and personalized surgery

- Participating and leading national, European and international studies about clinical research and development.

- At CSS we emphasize on **personalized medicine being part of medicine** and has to follow the same GCP as any other medical field and
- Contribute our expertise in **multidisciplinary collaboration** to ensure the synergy between the different domains involved in personalized oncological research and lead an international network of excellence.

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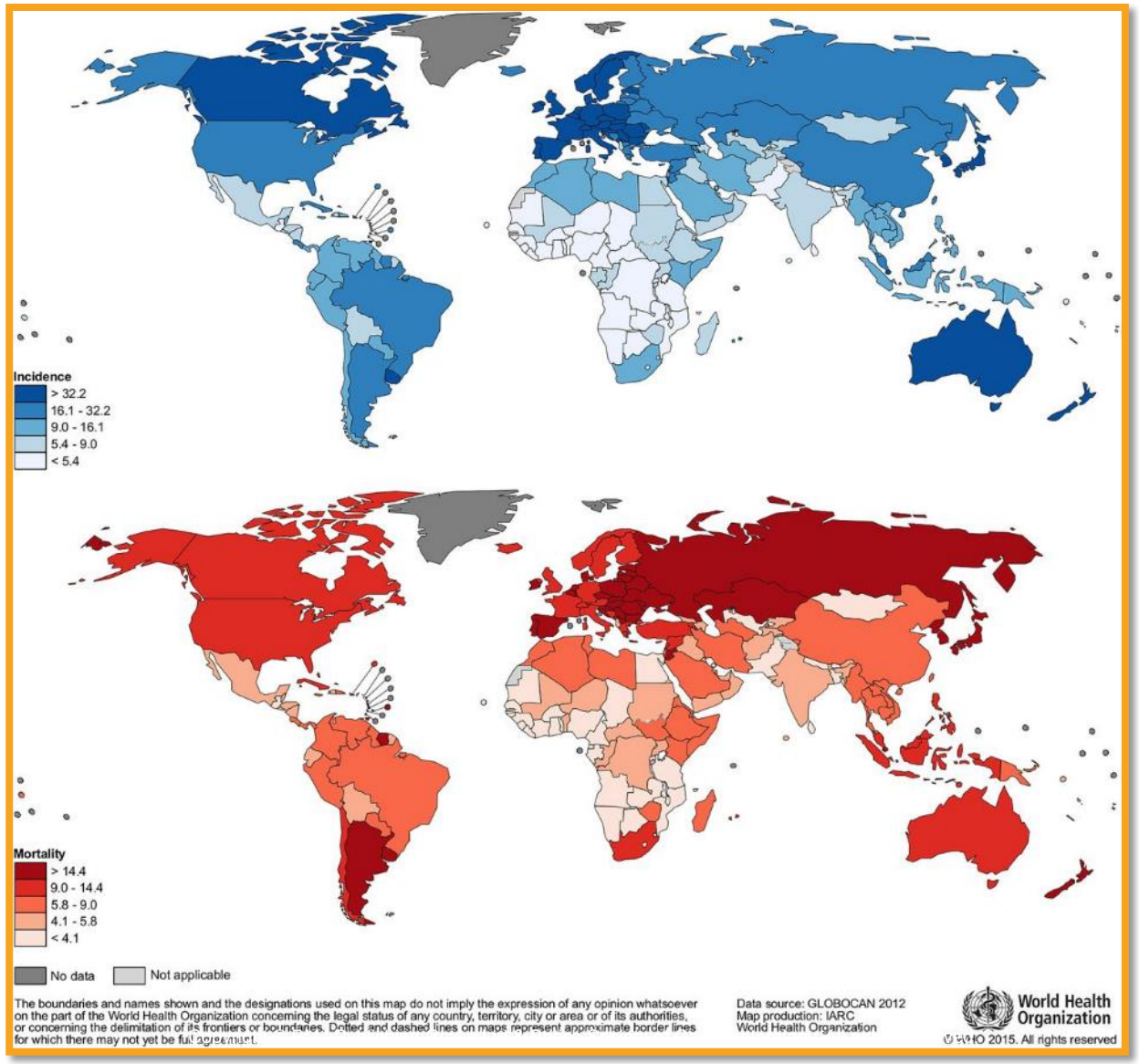
Incidence and mortality rates are increasing

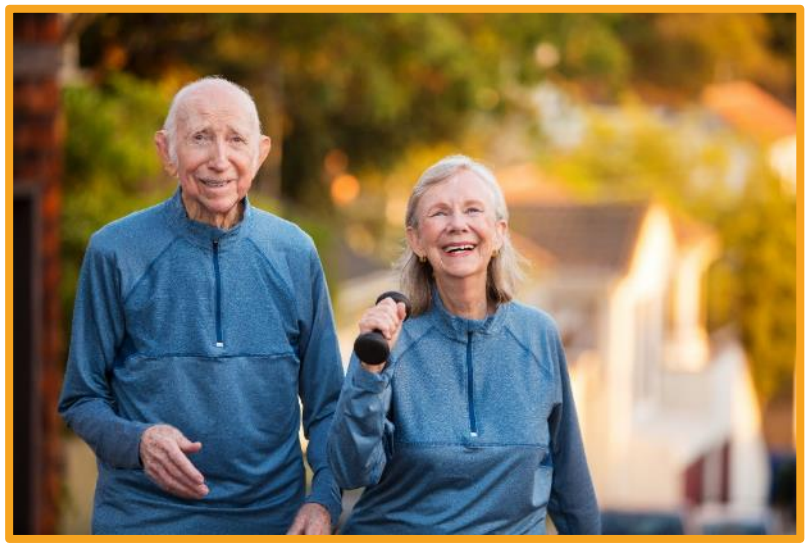


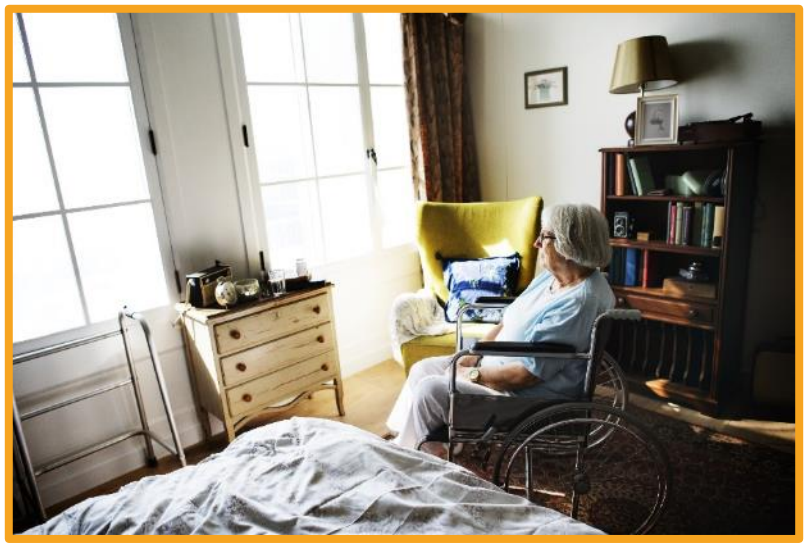
3. most common cancer

- Incidence **x 2 in 2030**
- Mortality **x 2 in 2030**

GUT Melina Arnold et al. Gut 2017;66:683-691

Phenotype is essential for prognosis





More than 1 out 3 patients dependant / frail

CRC incidence in younger age groups !

- Increasing incidence < 50 years
  - 15% of CRC
- 67% increase from age 40 to 49
- Colon cancer increased 56%
- Rectal cancer increased 94%

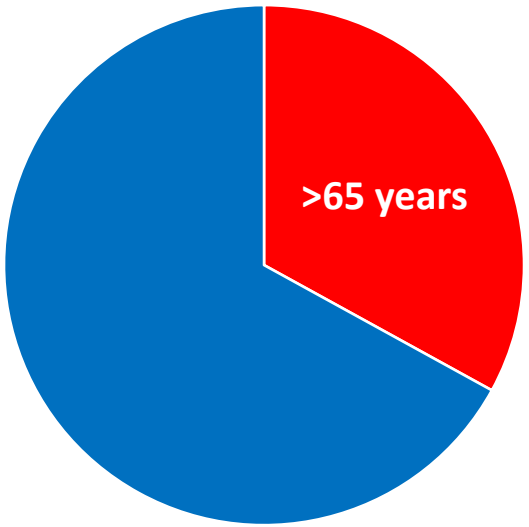
More aggressive tumors!

J Am Coll Surg 2011;213(3):352-61 (ISSN: 1879-1190) NCI, SEER Database
Cancer Epidemiol 2016;42:90-100. Prev Med 2017;105:345-9

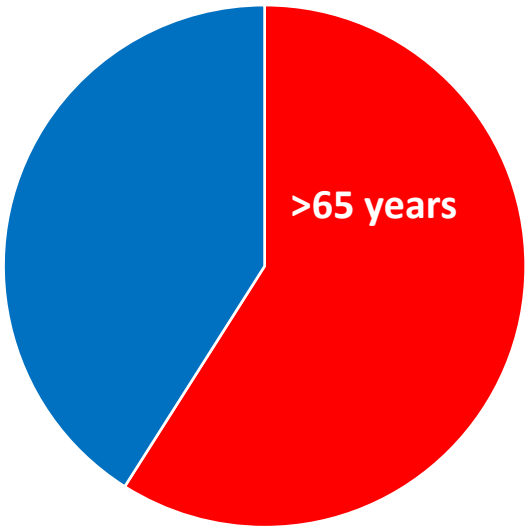
Evidence is biased!

- 24 cancer drugs approved from 2007-2010

FDA trial populations



Population with cancer



Scher and Hurria JCO 2012

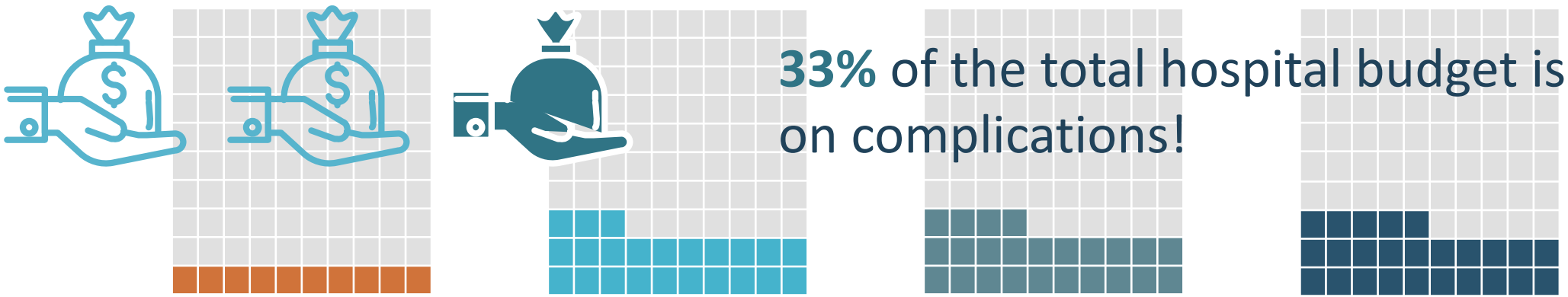
Complications are common after surgery

N = 587 CRC surgery (2015-17)

> 96 % MIS

LOS Colon = 2 days

LOS Rectum = 4 days



33% of the total hospital budget is used on complications!

10%
Reoperated

13%
Readmitted

14%
LOS > 14 days

25%
Complications

Bennedsen et al Col Dis 2018

Goveart et al EJSO 2015

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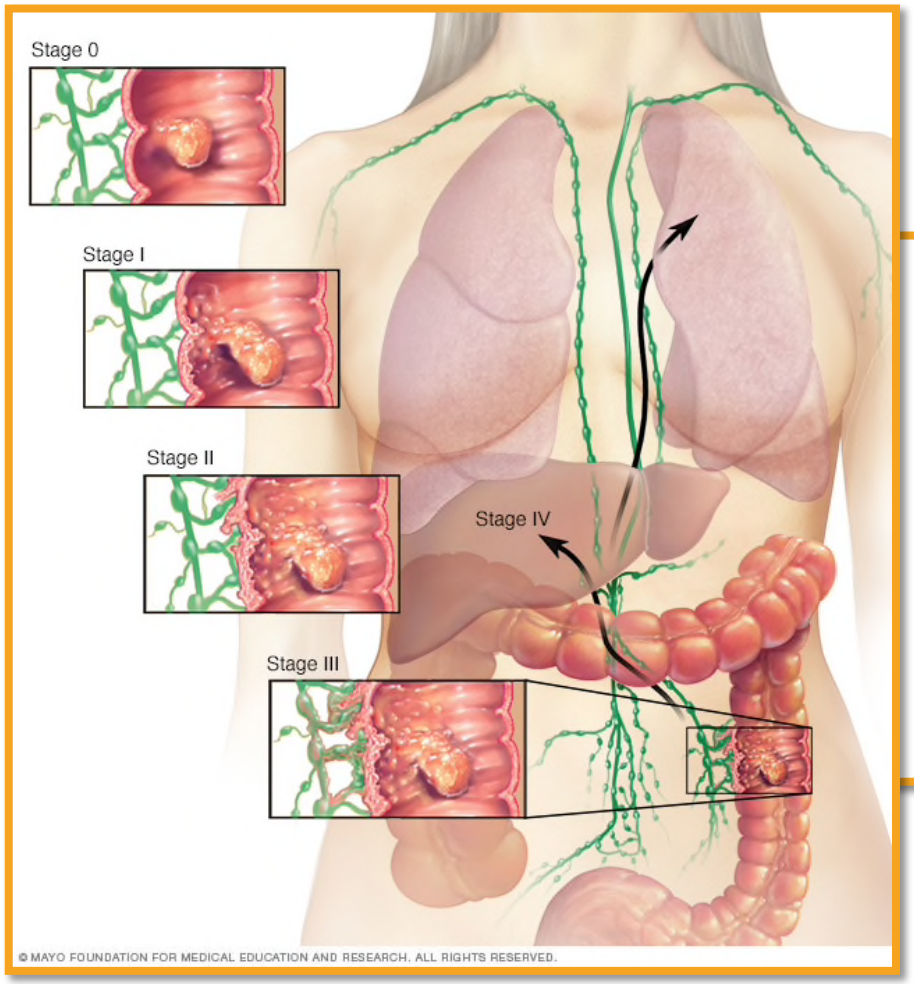
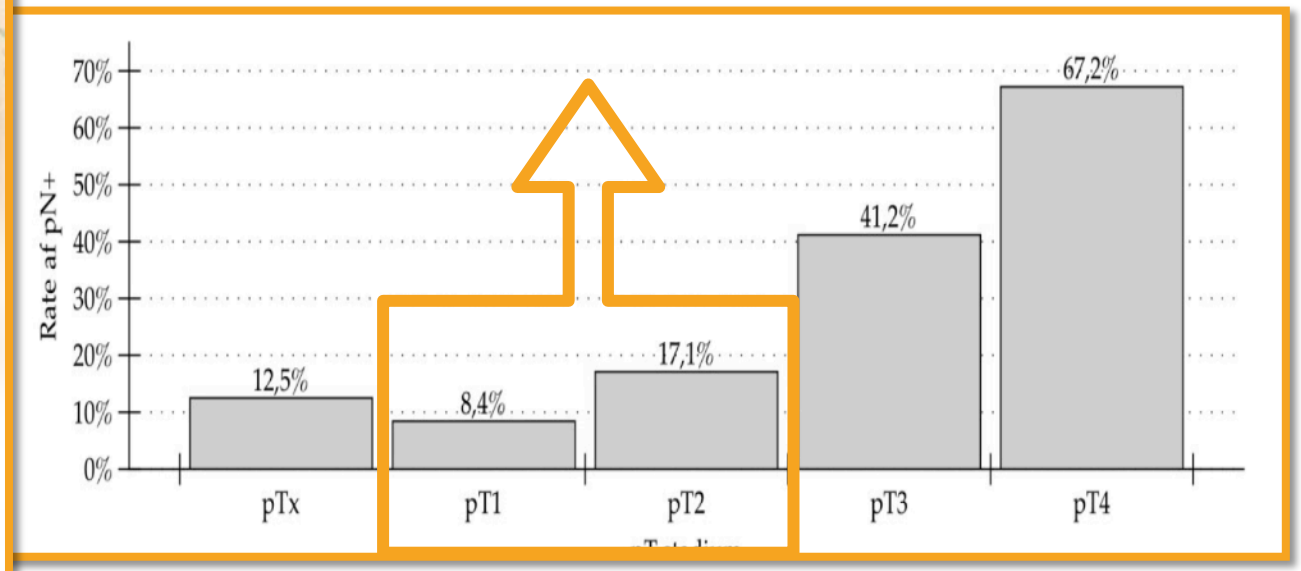
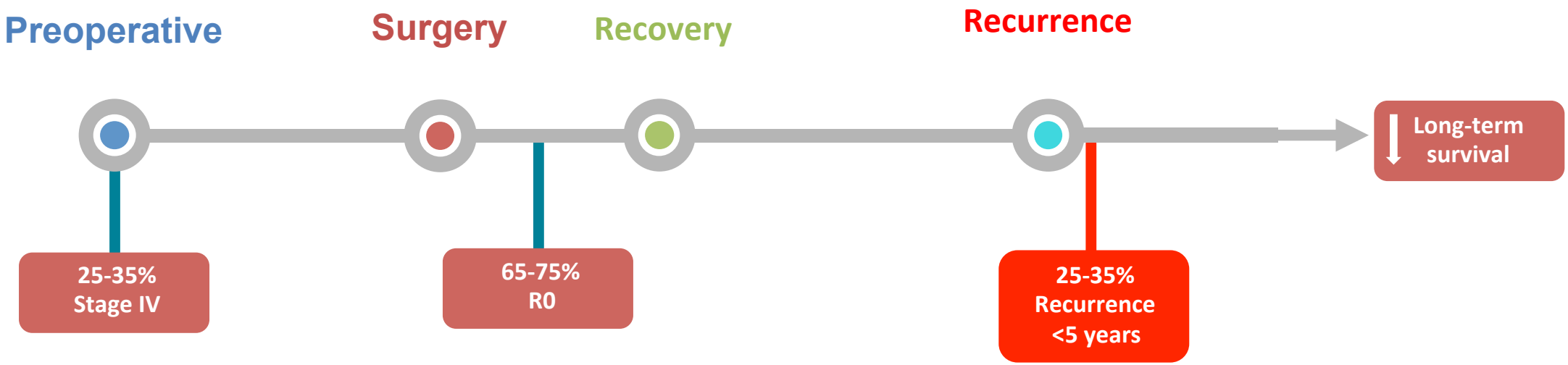
Overtreatment in CRC surgery



Overtreatment?



Cancer recurrence a huge challenge



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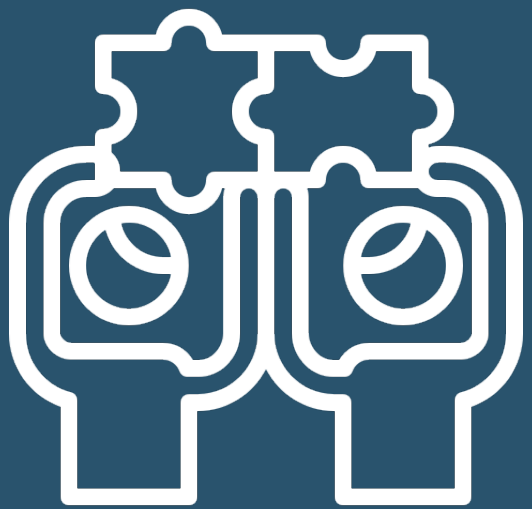
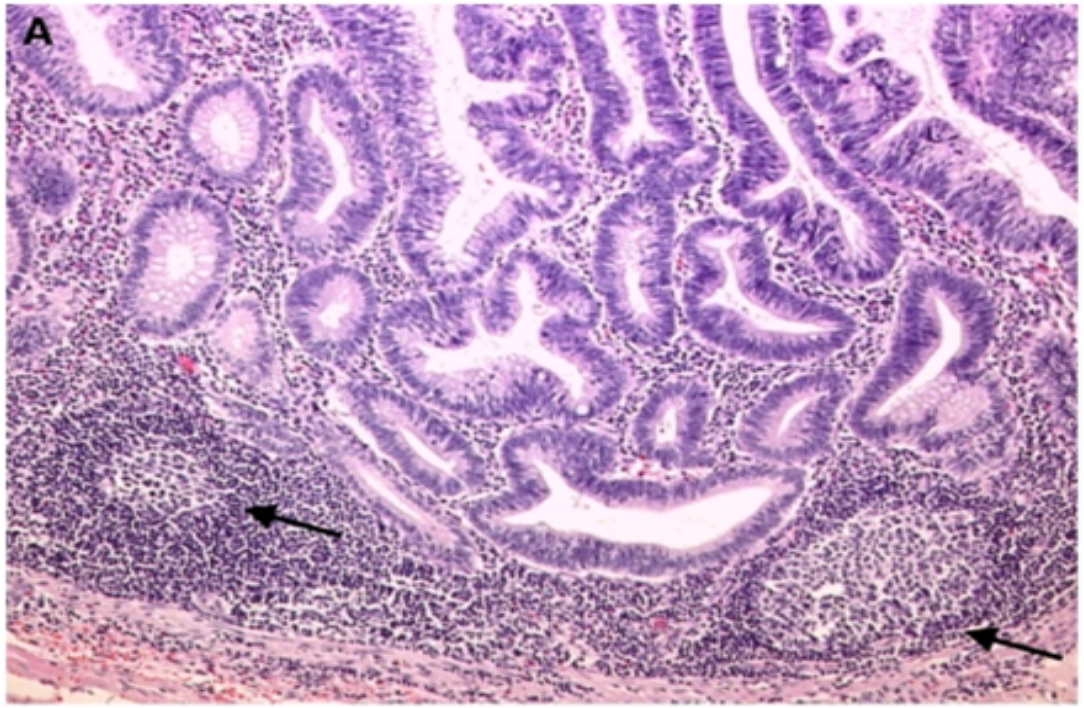
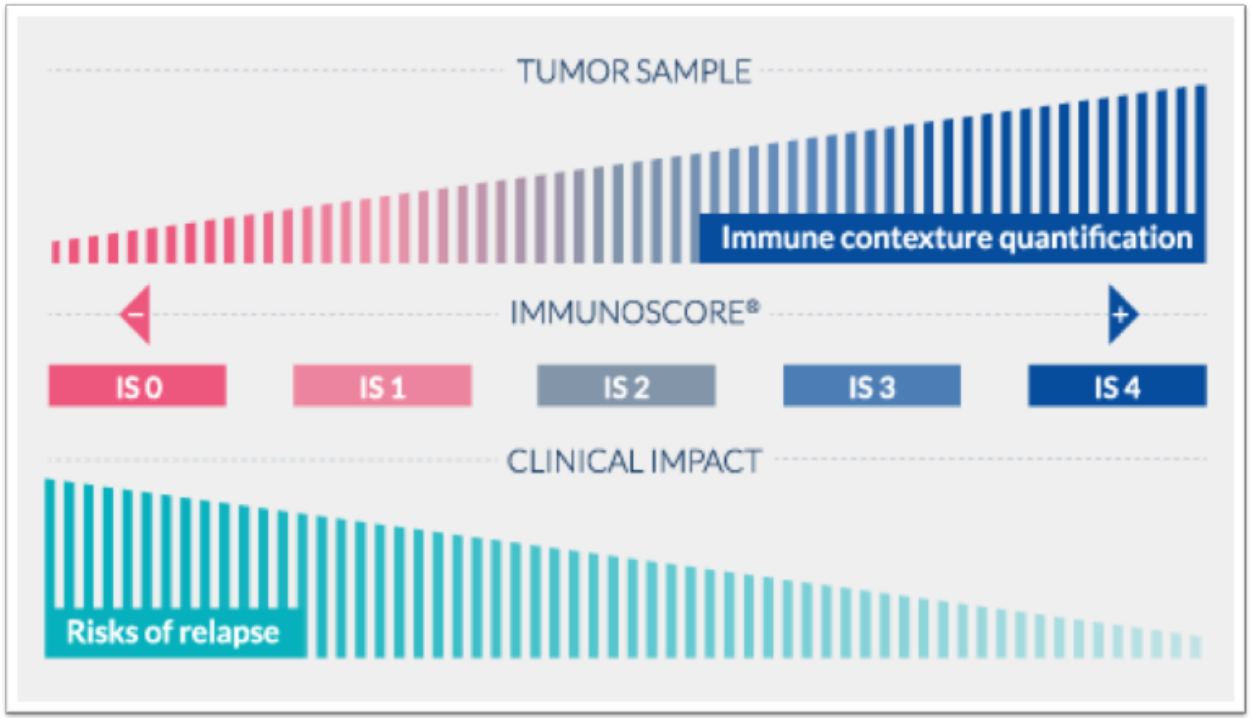
PERSONALIZED SURGERY

Major recent progress in the understanding and treatment of patients with colorectal cancer needs to be integrated in a **PERSONALIZED** surgical approach.



Immune system in CRC

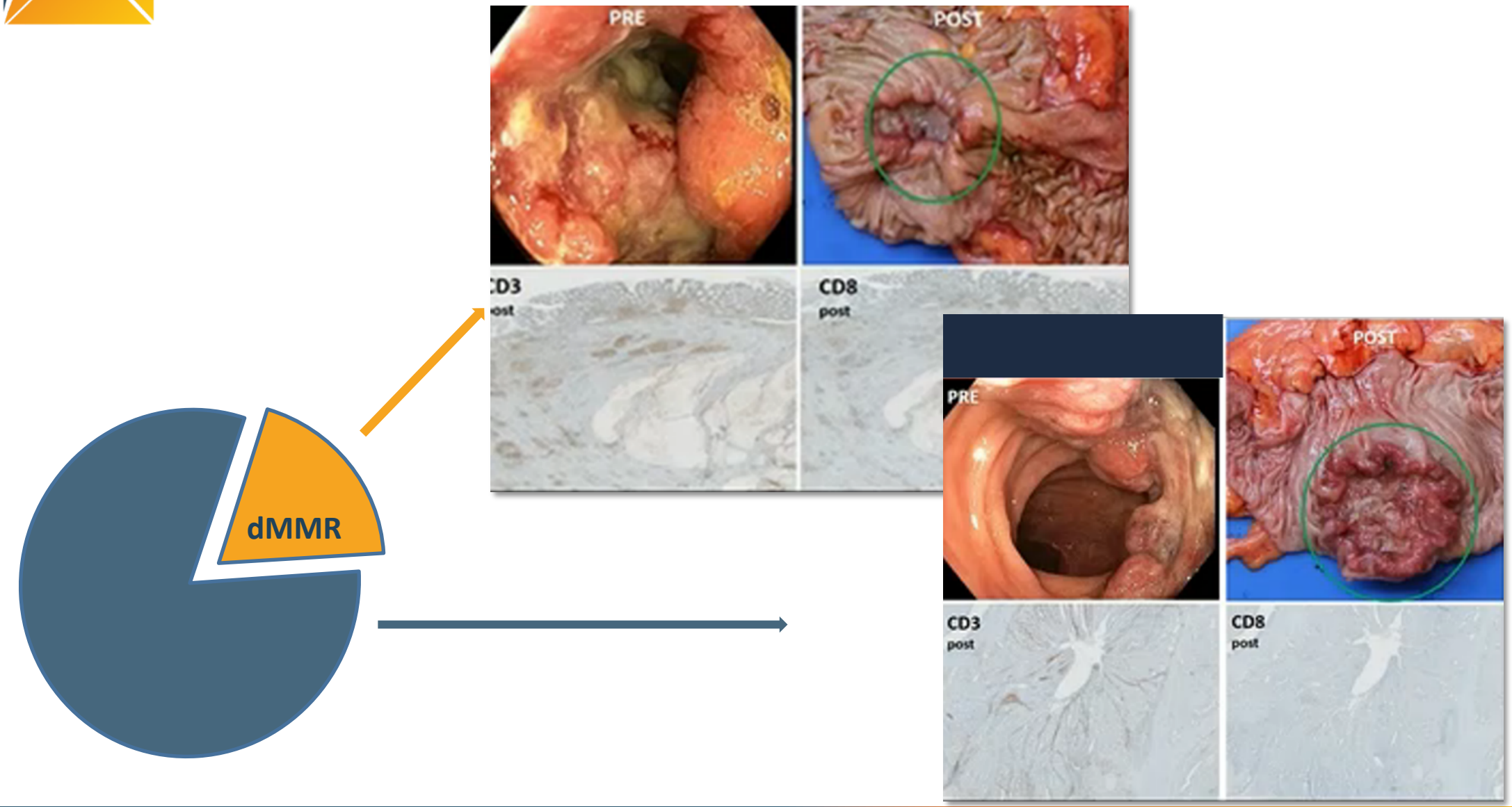




Galon et al. Science, 2006

Mlechnik et al. Journal of Clinical Oncology, 2011

Immunotherapy has a major potential

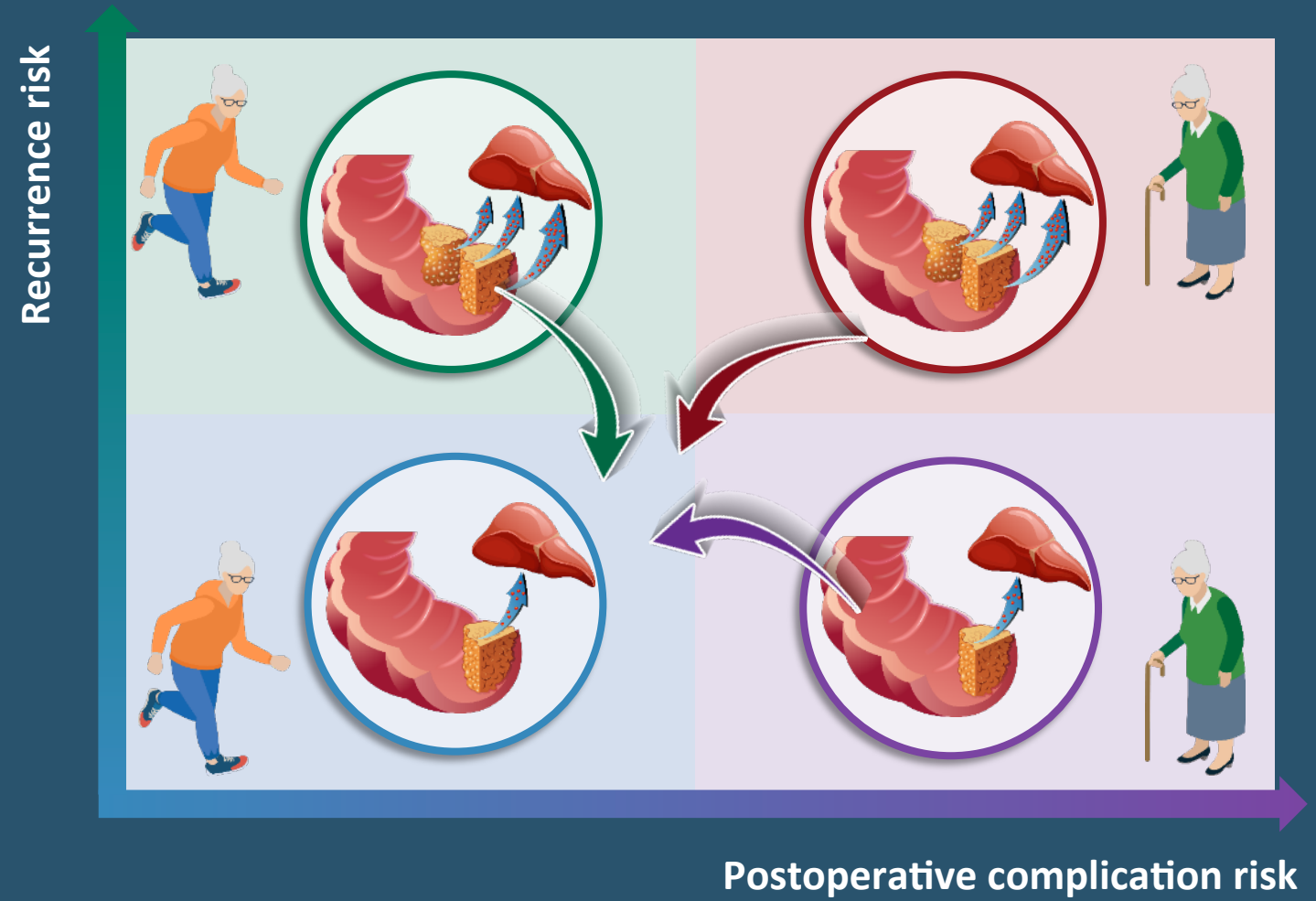


Prehabilitation

Prehabilitation

Standard treatment

Stratified approach through risk assessment



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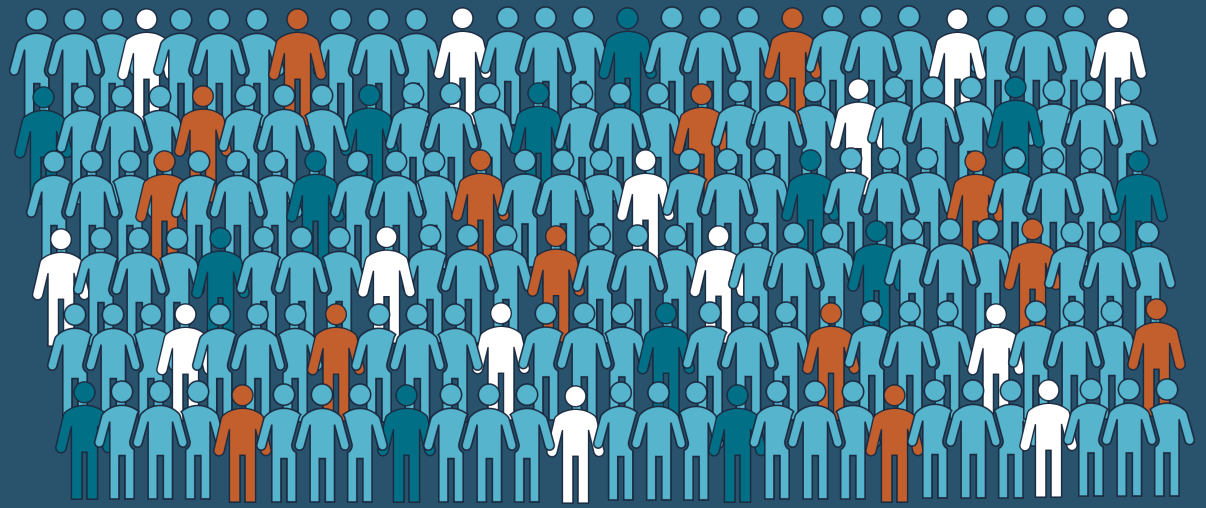
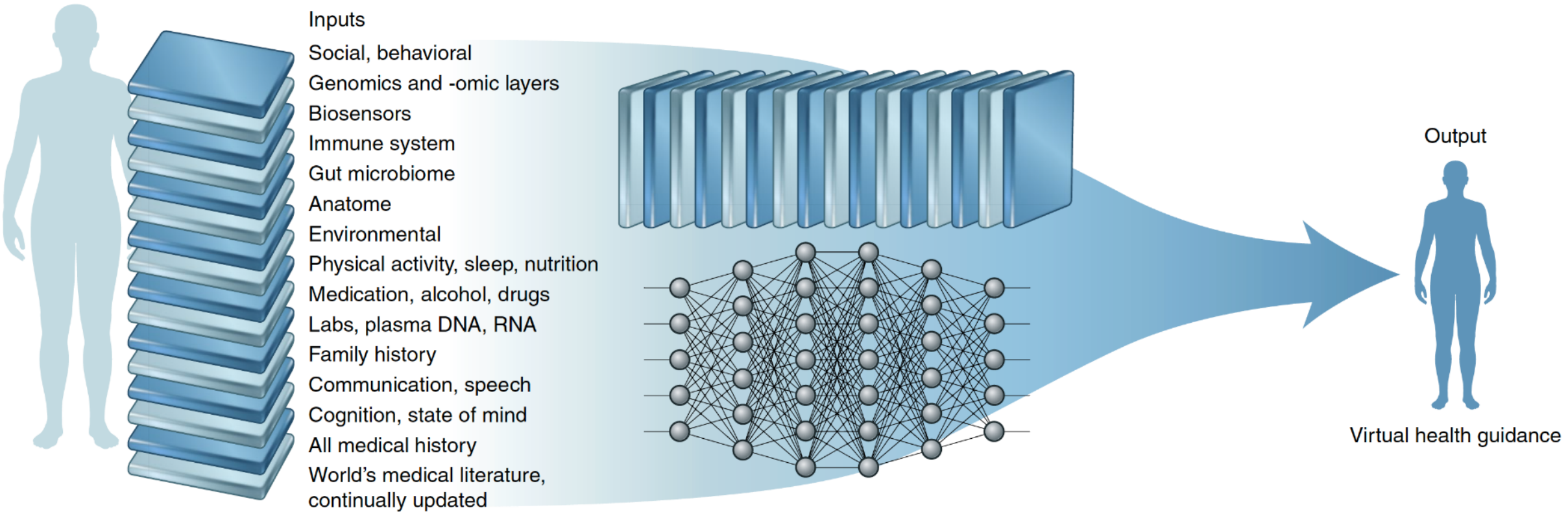
Patients like me



High quality and granularity of information leading to improved perioperative patient care?



Eric J. Topol Nat Med 2019

The Project Goal

Creating a platform where both PHENOTYPIC and OMIC data contribute to improve healthcare services.

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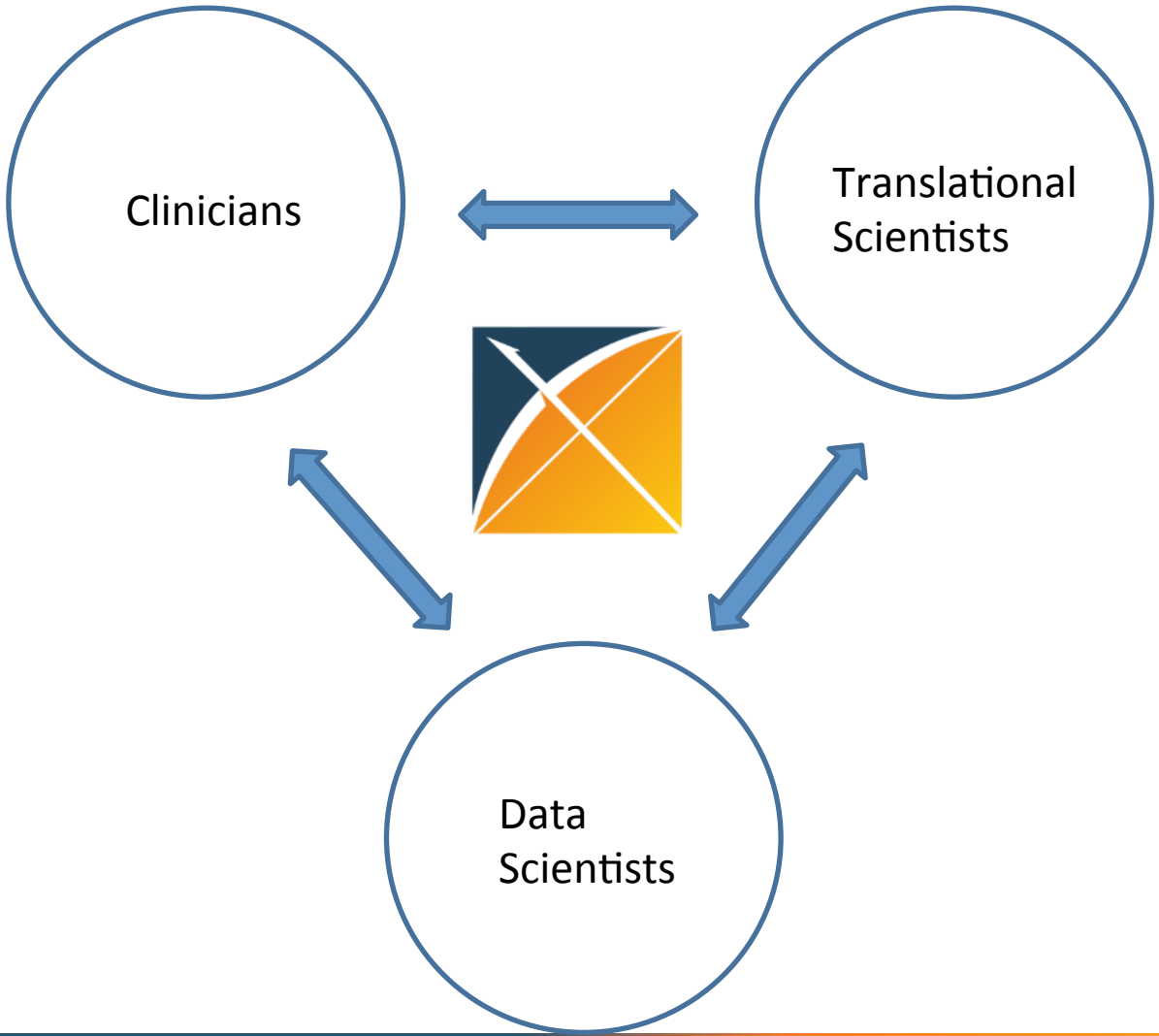
Research infrastructure



Choosing data sources for the CDM

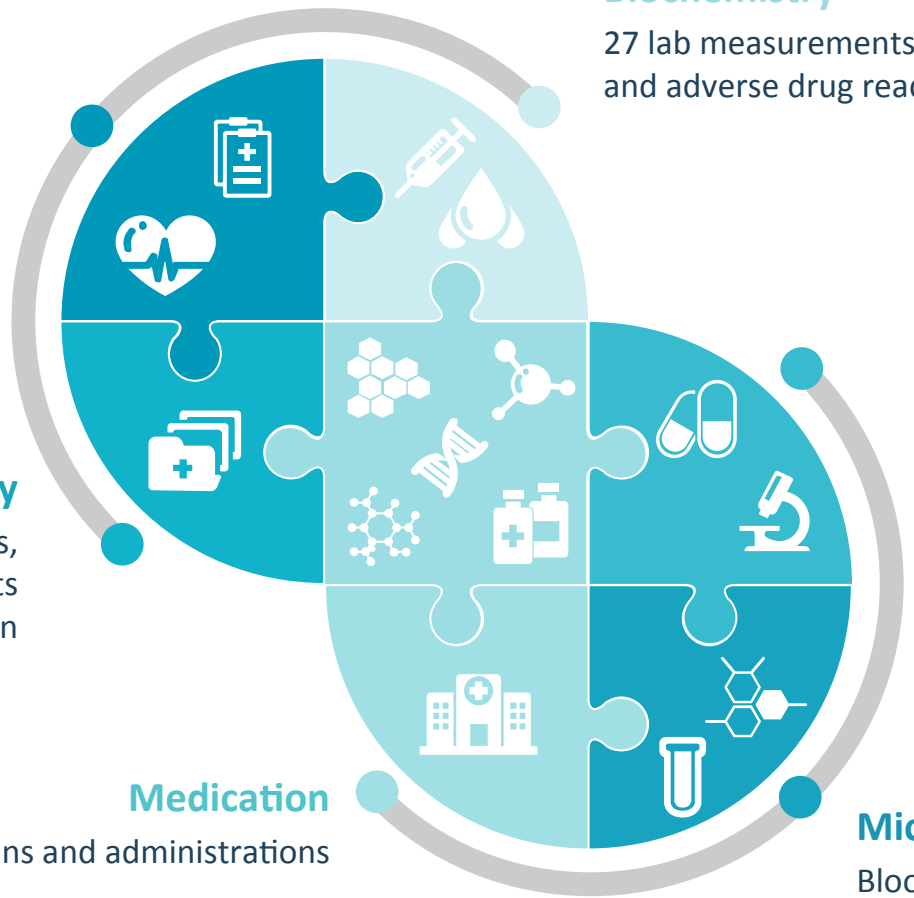
- DCCG
- DAD
- MiBa
- CPR
- LPR
- SKS
- OpusMed
- BEFUS
- BC
- BTH
- ...
- OpusMed+

Colorectal Cancer

Detailed description of all pathology aspects

Biochemistry

27 lab measurements targeting cancer and adverse drug reactions



Anesthesia

Detailed information for colorectal cancer operations

Pathology

Hospital admissions, procedures and treatments during admission

Medication

Prescriptions and administrations

Microbiology

Blood analysis results 180 days after surgery

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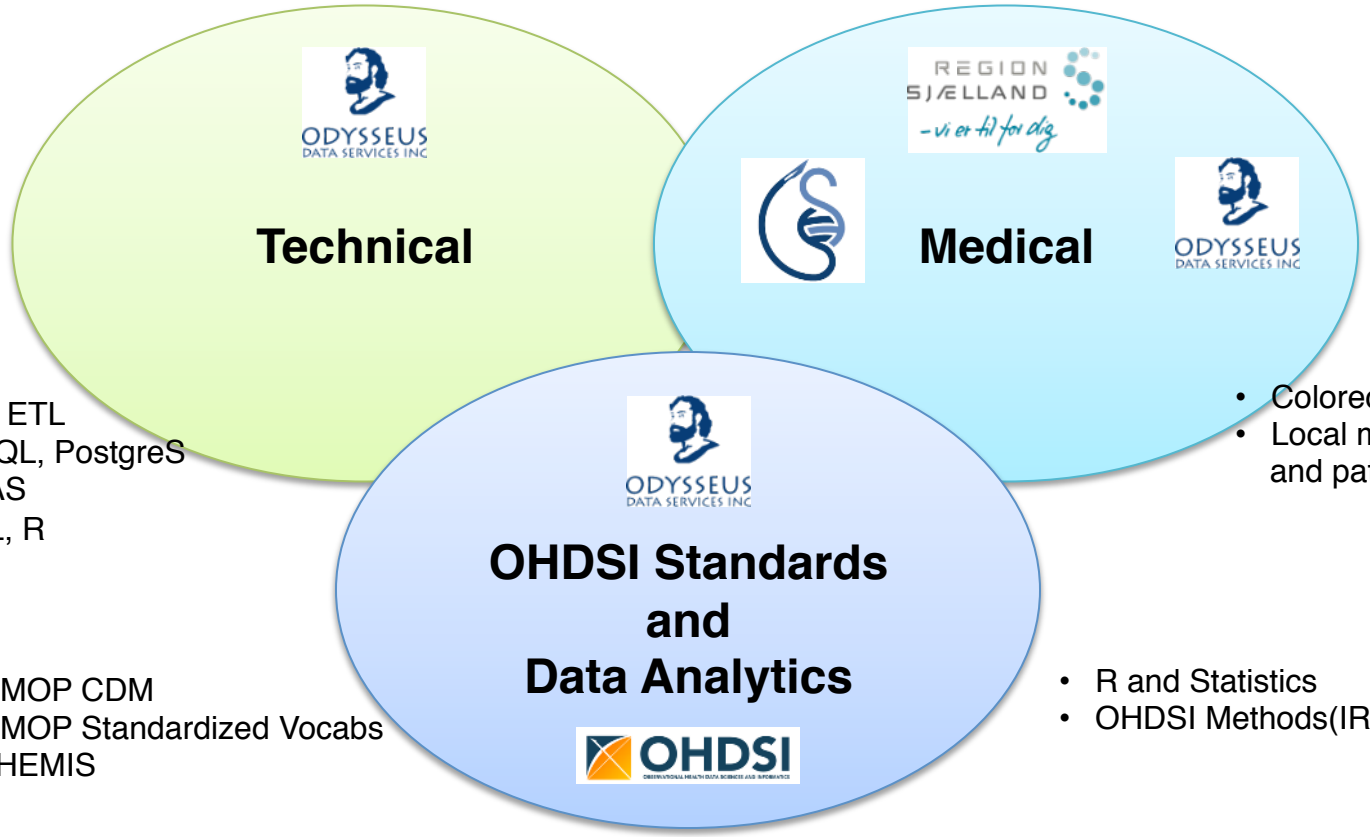
OHDSI PoC Skills

A wide range of skills and knowledge lead to a tight collaboration



OMOP CDM ETL
- Python, SQL, PostgreS

OHDSI ATLAS
- Java, SQL, R

- Colorectal Cancer Surgery
- Local medical processes and patient data

- OMOP CDM
- OMOP Standardized Vocabs
- THEMIS

- R and Statistics
- OHDSI Methods(IR, PLE and PLP)

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2018 OHDSI PoC

A few known challenges :

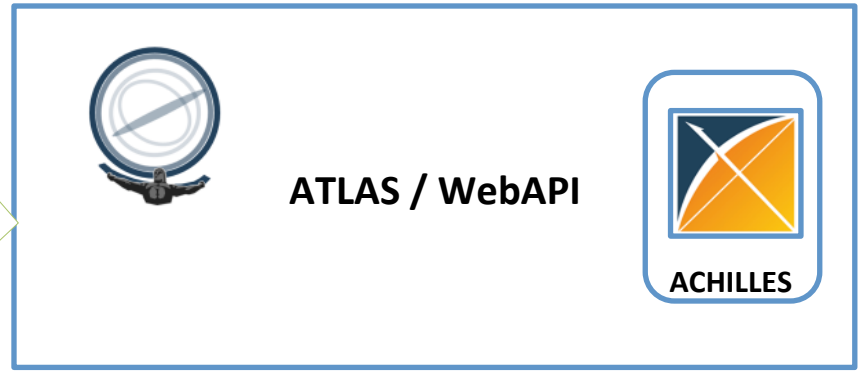
- Unfamiliar clinical data with unknown quality and data… What is DCCG? DAD? LPR?
- Danish registry uses Danish medical coding system (SKS), including for diagnosis, procedures, observations - needs custom mappings / vocabularies…
- Multiple data sources (DCCG, BigTempHealth) will be integrated and interlinked…
- 4 - 6 weeks to a completion of the POC
- Highest quality expected

PoC study	Data-source name	Targeted data domain	Variables of interest *(approximation)*	Number of Records
Colorectal Cancer	Danish Colorectal Cancer Group Database (DCCG)	See table 3 for DCCG data details	350	50.000
Colorectal Cancer	Danish Anaesthesia Database (DAD)	Anaesthesia during CC operations	200	50.000
Colorectal Cancer	Danish National Database of Reimbursed Prescriptions	Anti-diabetic medication and Statins for CC patients	50	50.000
Colorectal Cancer	Danish Civil Registration System	Mortality information for CC patients.	50	50.000
Colorectal Cancer	Danish Pathology Registry (Patobank)	CC recurrence	50	50.000
Colorectal Cancer	Danish Cancer Registry	CC related information	50	50.000
Colorectal Cancer	Danish National Patient Registry	Demographics, diagnosis, treatment, procedure for CC patients	50	50.000
Colorectal Cancer	The Danish Microbiology Database (MiBa)	Microbiology lab values for CC patients	50	50.000
BEFUS	The BEFUS population study	See table 3 for BEFUS data details	350	22.000
BigTempHealth	The BigTempHealth population study	Adverse Drug Reactions	100	200.000

A typical project of this type takes 3-4 calendar months w/ 4-5 FTE resources!!!

CSS OHDSI Tool stack

- ACHILLES database level characterization
- Vocabulary search
- Database level statistics (Achilles)
- Patient profile
- Cohort definitions
- Incidence Rate Analysis tool
- Population-level Estimation (PLE)
- Patient-level Prediction (PLP)
- TxPathways



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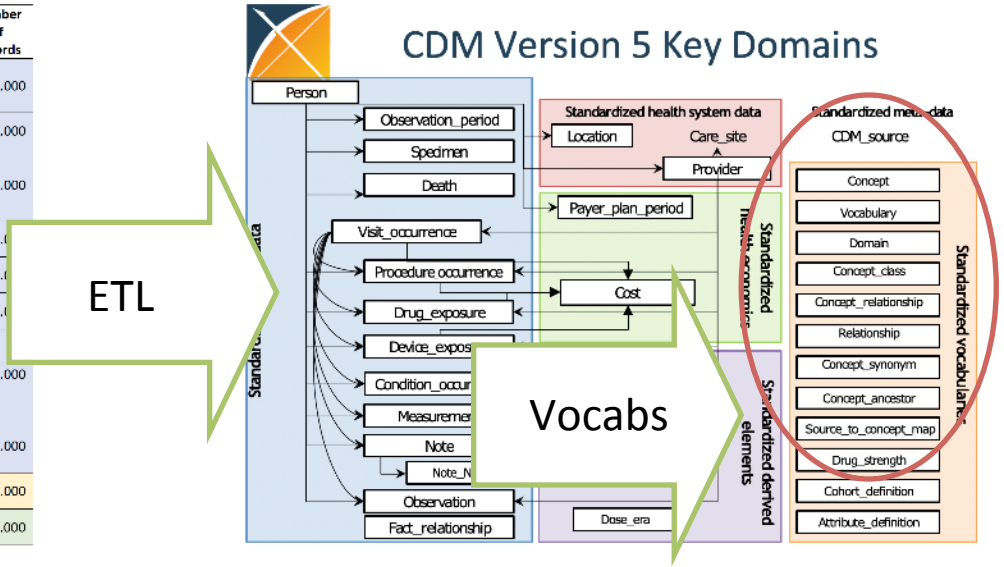

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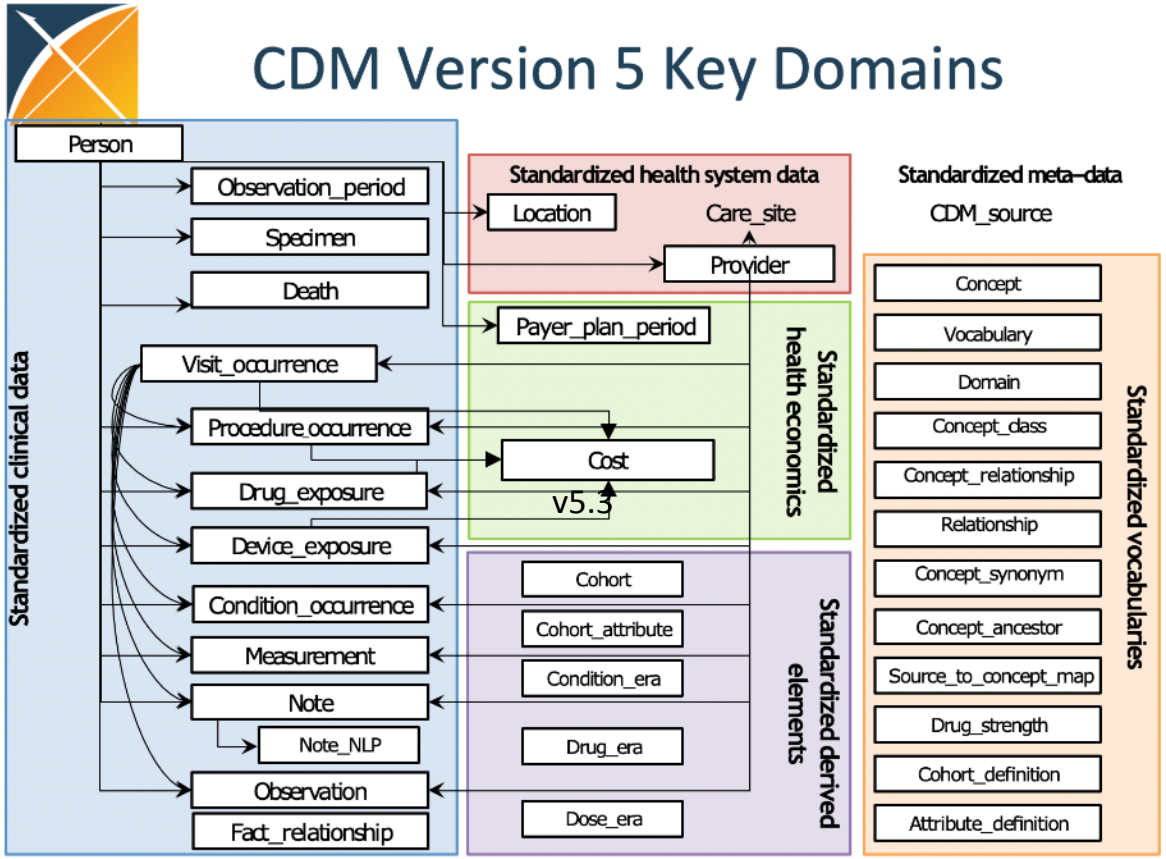
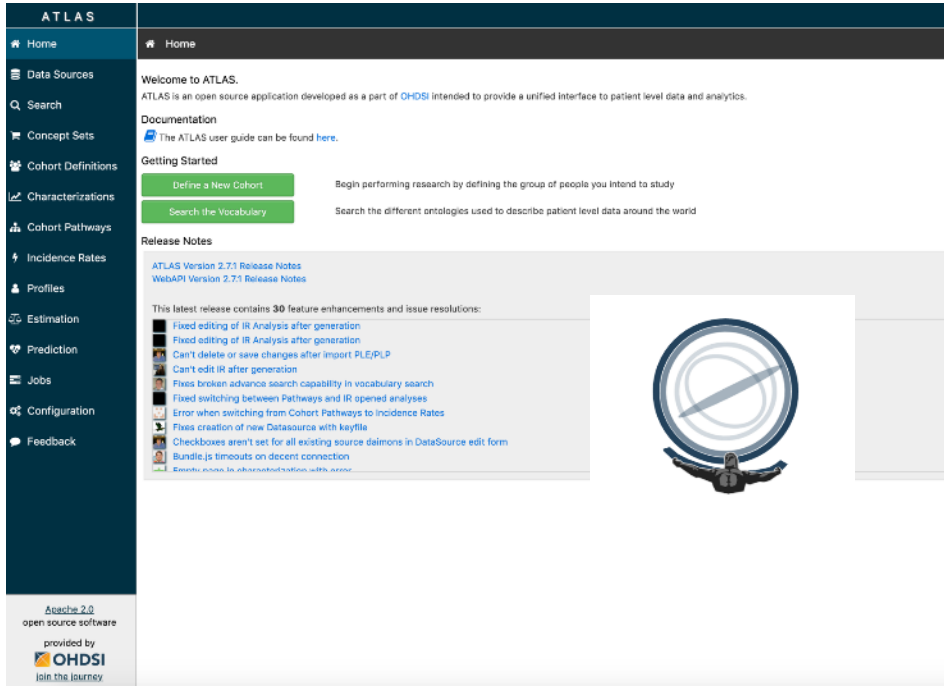
OMOP CDM V5.3.1



- **ATLAS 2.x only supports OMOP CDM 5.x**
- **OMOP CDM and vocabularies still have gaps in supporting rich oncology data**

OHDSI ATLAS

- Supports complex cohorts building and analytical designs (Characterization, Prediction and Estimation) on OMOP CDM
- Execution of the analytics against local OMOP CDM data
- Installed at most of the OHDSI Network sites



- **Enabled PLP/PLE execution from ATLAS with ARACHNE Execution Engine**
- **OHDSI Team work on making sure ATLAS 2.7.3 is a stable version**

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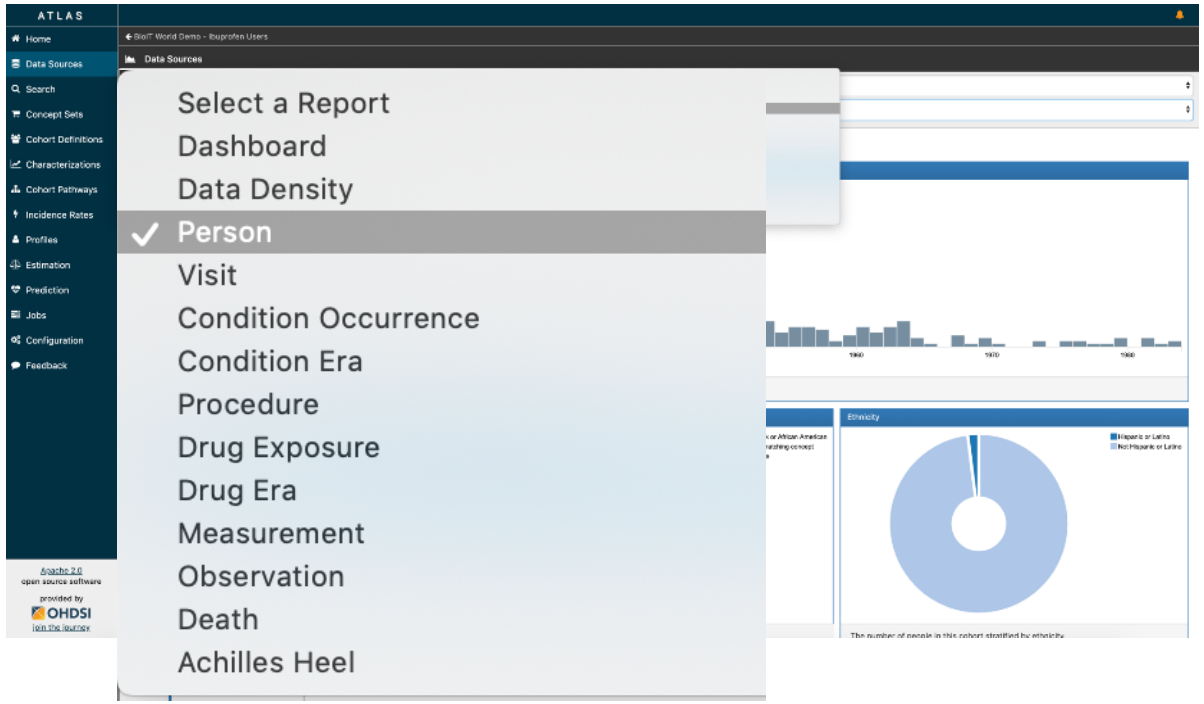
OHDSI Achilles (ATLAS Data Sources)

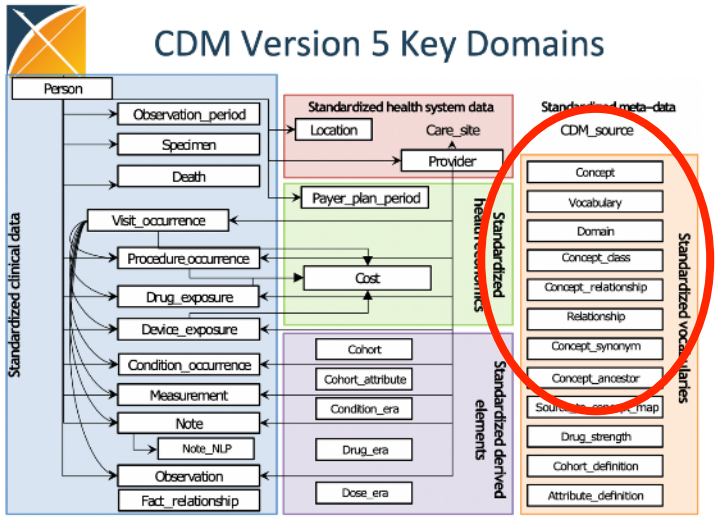
- Provides characterization, quality assessment and visualization of observational health databases.

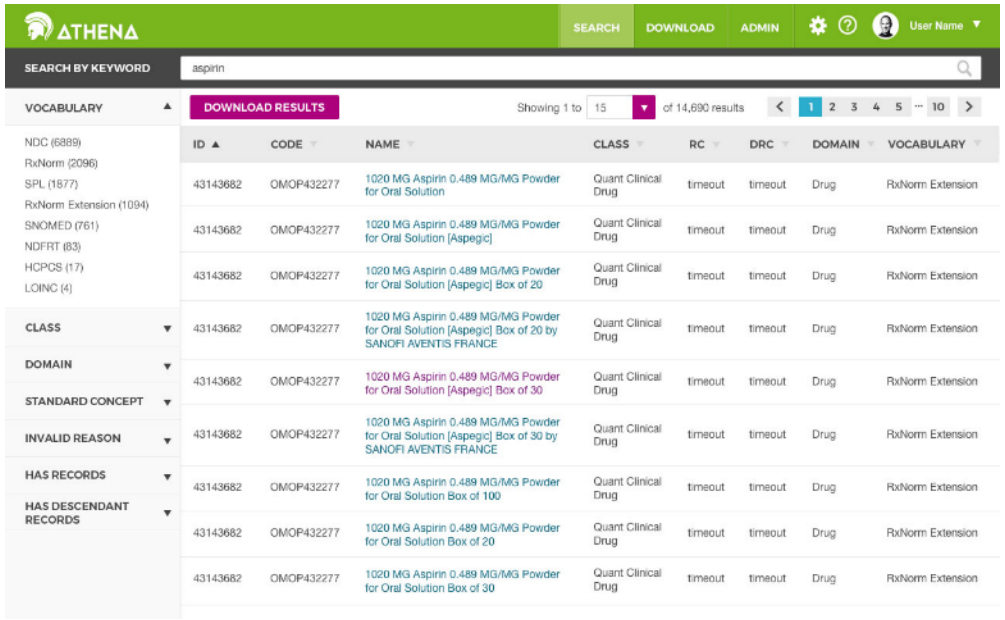


- **Used extensively during testing and for data validation**

ATHENA

Allows search, navigation and distribution of the OMOP Standardized Vocabularies





OHDSI

- **Used extensively during concept mapping process**

2018 OHDSI PoC results

PoC completed in record times by mid-September, 2018

- OMOP CDM version 5.3 populated with Danish colorectal cancer data
- ~2,000 custom concepts created and mapped
- 13,500 total concepts mapped
- ATLAS 2.5.2 installed (upgraded to 2.7.3 in June 2019)
- Enabled ARACHNE Execution Engine to run PLE/PLP studies

Done!!! **Nope, it is just a beginning ….**

Interesting Challenge #1

"Computed" Custom Concepts

To address research needs, we created a number of custom concepts that were computed.

> ***"Neutrophil-to-Lymphocyte Ratio" = ratio of " Neurophils" and "Lympocytes"***

Used for cohort creation as well as a covariate in PLP. Such concepts may be subject to further proposal for adding them into official vocabularies (like LOINC).

Opportunity (pros and cons):

Should it be an enhancement enhancement in ATLAS?

Or

should these be precomputed during the ETL CDM?

Interesting Challenge #2

Storing "Negative information" e.g. absence of off

"No diabetes mellitus"

Introduced a new approach storing all negative information in OBSERVATION table by mapping the source entities to 'No evidence of' (Maps to) and the entity itself (Maps to value, can be disorder, procedure, observation or any other domain).

Interesting Challenge #3

Storing rich Oncology data

Oncology data is complicated and sometimes obscure. The granularity of our datasets didn't allow us to map it to the existing concepts without losing important aspects of disorders.

neurofibrosarcoma, relapse
malignant schwannoma, direct spread
malignant schwannoma, uncertain whether primary or metastatic
precursor B-lymphoblastic lymphoma / leukemia relapse [<1.1.04]
T-cell chronic lymphocytic leukemia, relapsed
Hodgkin lymphoma in incomplete remission

How to store cancer stages??

Opportunity:

OMOP CDM Oncology Extension
Richer oncology vocabularies

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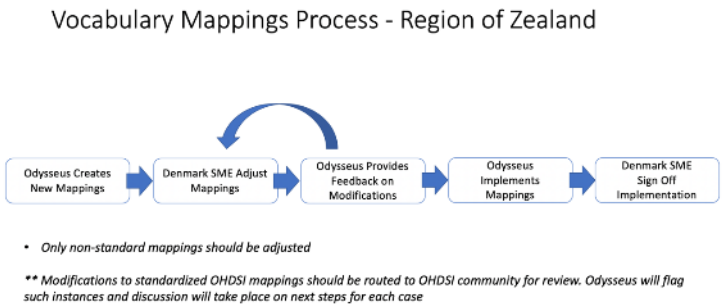
PoC Learnings

- Strict QA/QC and validation is a must
- Vocabulary mappings “done right” is critical. Agree on “mapping review and validation” process. And yes - there are sometimes errors and gaps in OHDSI Vocabularies too!
- Sometimes there is no “black and white” in mapping a concept. ~11% were wrong, ~35% with less granularity



- OHDSI components must be harmonized and up to date – it’s about a full stack
  e.g. OMOP CDM, ATLAS, Method Packages, latest vocabularies, R libraries /R
- Disciplined delivery approach and ongoing communication

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Hackathons

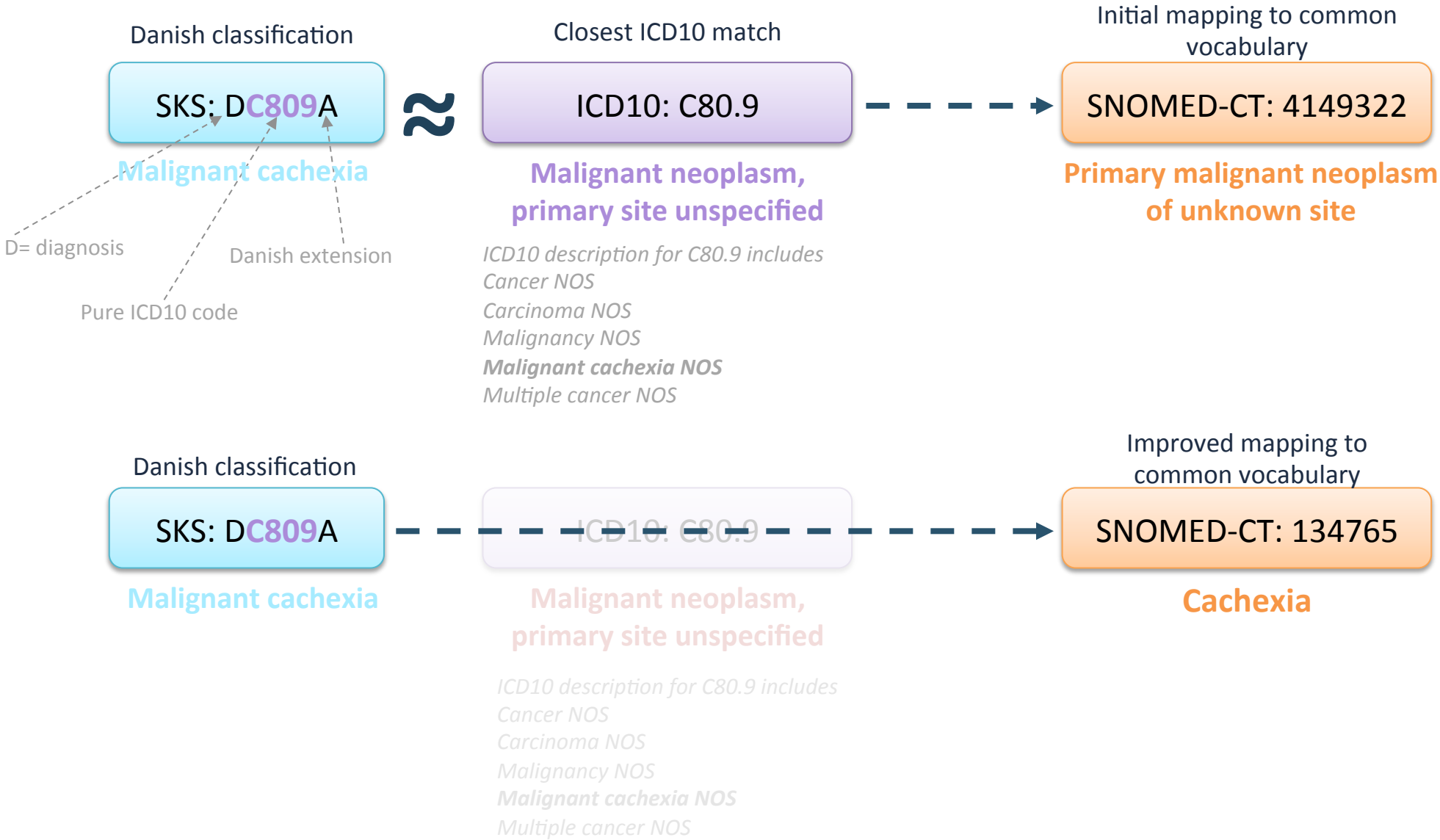
- 7 sources: 1) colorectal cancer, 2) anesthesia, 3) pathology, 4) microbiology, 5) causes of death, 6) biochemistry, 7) in-hospital medication
- 13,683 concepts (54,761 patients)
- 4 months (March – June 2019)
- 12 Medical doctors + 2 Data scientists in two teams:
  - A great team of 12 MDs sweeping through the mapping files
  - A task-force of 6 MD with more experience in medicine and OMOP, finetuning and approving the corrections
- 46% improvements in mapping quality identified:
  - 11% concepts mapped completely wrong
  - 35% concepts mapped with granularity loss
- 73% of the erroneous mappings corrected
  - 76% of the wrong mappings corrected
  - 72% of the granularity lass retrieved

Hackathons

56	Souce	Maps to	Target
Vocabulary	DCCG		SNOMED
Variable (code)	Anastomose_teknik 1		
ID	2000047024		4120001
Text.dk	en anvendte anastomoseteknik (håndsyet-staplet-anden)		
Text.en	Anastomosis technique: hand-stitched		Internal fixation using staple
	Tag 1		**Tag 2**
Choice	Wrong		Wrong
Comment	Hånsyet anastomose, ikke stapler		
New Choice	Wrong		Wrong
New Comment	Hånsyet anastomose, ikke stapler		
	Solution		**Status**
Coice	Map to new concept		Approved
New ID	4191857		
New Concept			
Comment	replace		new tag
New Choice	Map to new concept		Approved
New New ID	4191857		
New N. Concept	Multi-layer hand sewn intestinal anastomosis		
New Comment	replace		new tag

Hackathons

50	Souce	Maps to	Target
Vocabulary	DCCG		SNOMED
Variable (code)	Anastomose_orientering 4		
ID	2000046444		4078639
Text.dk	Angivelse af anastomosens orientering		
Text.en	Anastomosis orientation: page-to-page		Type of anastomosis
	Tag 1		Tag 2
Choice	OK		OK
Comment	Engelsk oversættelse forkert (page)		
New Choice	OK		OK
New Comment	Engelsk oversættelse forkert (page)		
	Solution		Status
Coice	Not needed		Approved
New ID			
New Concept			
Comment			
New Choice	Not needed		Approved
New New ID			
New N. Concept			
New Comment			



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Patient X

- Gender: Female
- Age: 64
- Colon tumour
- Stage 2
- Is having a primary malignant neoplasm of unknown site. Colon tumour may be considered secondary condition.

≠

Patient X

- Gender: Female
- Age: 64
- Colon tumour
- Stage 2
- Experiencing discomfort and weight loss because (cachexia) of cancer

A network of excellence for Personalized Oncological Surgery

AIM

A network for excellence aiming to establish a research platform for **personalized medicine in surgery** through a collaboration between scientist and stakeholders in the clinical pathway of the surgical oncological patient in order to **reduce morbidity and increase cancer survival.**

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One-week workshop in Personalized Oncological Surgery

June 2019

Kusadasi, Turkey

27 medical professionals + 7 data scientists + 7 days

= **EDUCATION - INFRASTRUCTURE - RESEARCH**

- Study design & cohort definition using ATLAS
- Standardized population level estimations & patient level predictions
- Validation of the PM infrastructure of CAG-POS
- Clinical questions & hypotheses validation in real-time
- 4 + 1 research papers

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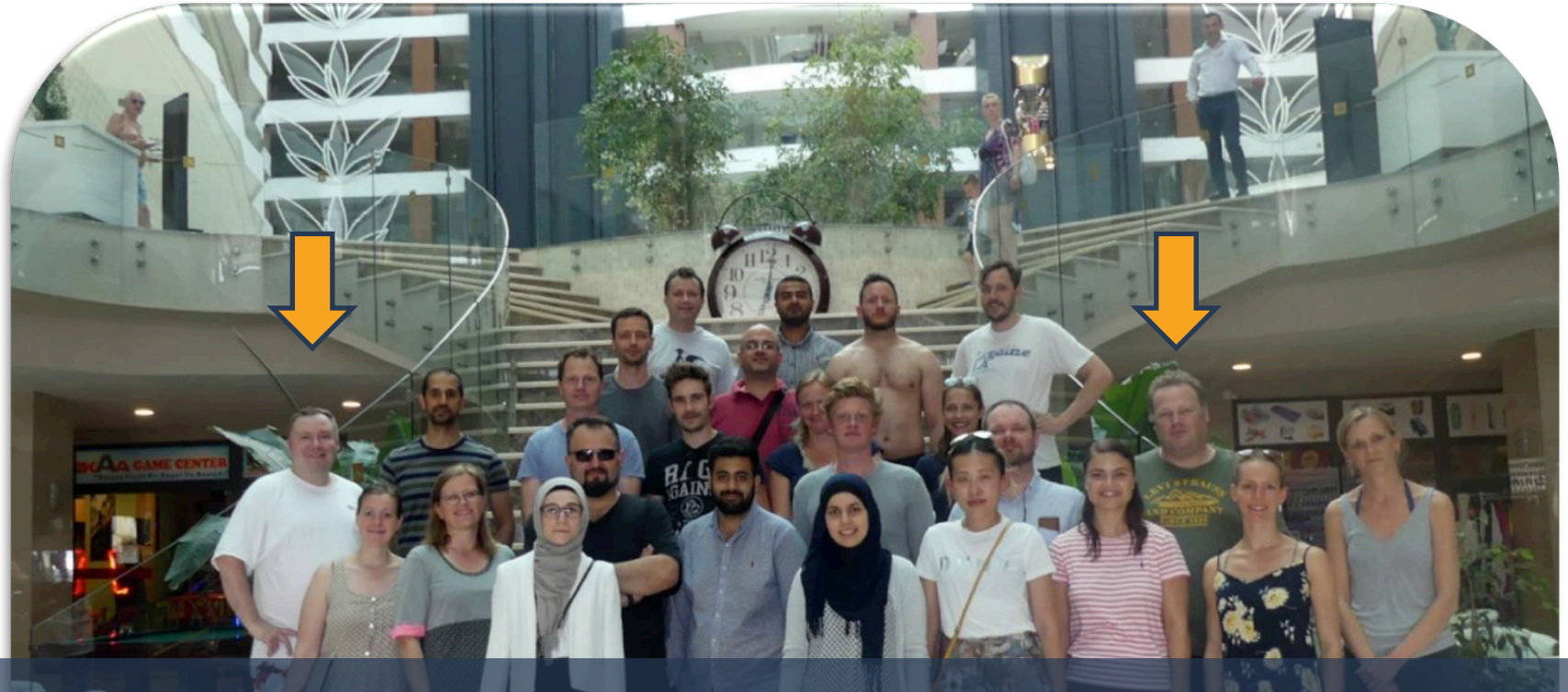
Penelopes, Ulysses' and Hommers



- Adile Orhan, Center for Surgical Science
- Anna Ostropolets, Columbia University
- Alexander Davydov, Odysseus
- Andreas Rosen, Center for Surgical Science
- Betul Okutan, Center for Surgical Science
- Camilla Grube, Center for Surgical Science
- Dunja Kokotovic, Center for Surgical Science
- Eldar Allakhverdijev, Odysseus
- Ellen Bjerrum, Center for Surgical Science
- Emma Hølmich, Center for Surgical Science
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- Kirsten Wahlstrøm, Center for Surgical Science
- Luyi Cai, Center for Surgical Science
- Mahdi Alamili, Center for Surgical Science
- Maria Pozhidaeva, Odysseus
- Morten Hartwig, Center for Surgical Science
- Nicolas Dérian, Center for Surgical Science
- Patrick Ryan, OHDSI
- Pavel Grafkin, Odysseus
- Peter Rijnbeek, OHDSI
- Puk Kristiansen, Center for Surgical Science
- Rasmus Bojesen, Center for Surgical Science
- Rasmus Vogelsang, Center for Surgical Science
- Rune Hasselager, Center for Surgical Science
- Rune Trangbæk, Center for Surgical Science
- Sofie Møller, Center for Surgical Science
- Thea Degett, Center for Surgical Science
- Tina Fransgård, Center for Surgical Science
- Ali Shaker, Center for Surgical Science
- Jawad Ahmad Zahid, Center for Surgical Science

Study 1

Exposure to inhalation anesthesia and risk of mortality for patients undergoing surgery for colorectal cancer

Rune Petring Hasselager, MD[1], Andreas Weinberger Rosen, MD[1], Tina Fransgaard, MD, PhD[1], Mahdi Alamili, MD, PhD[1], Johanne Gormsen, BSc[1], Thea Helene Degett, MD, PhD[1], Nicolas Derian, PhD[1], Pavel Grafkin, MSc[6], Peter Rijnbeek, PhD[2], Patrick Ryan, PhD[3,4,5], Ismail Gögenur, MD, DMSc[1], Iannis Drakos, PhD[1]

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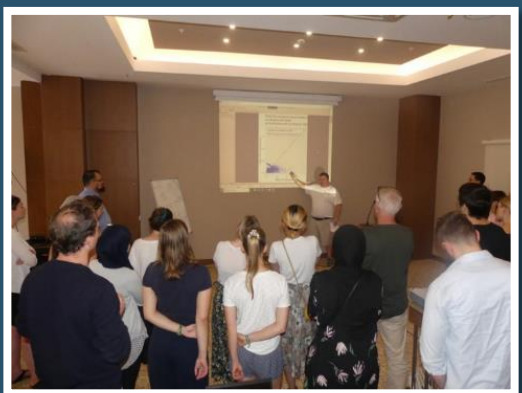
[2]Erasmus Universitair Medisch Centrum, Rotterdam, Netherlands,
[3]Observational Health Data Sciences and Informatics (OHDSI), New York, New York, USA,
[4]Department of Biomedical Informatics, Columbia University, New York, New York, USA,
[5]Janssen Pharmaceuticals, New Jersey, USA
[6]Odysseus Data Services Inc., Cambridge, Massachusetts, USA



Study 2

Prediction of 90-day mortality after colorectal cancer surgery through standardized perioperative data analysis

Rasmus Vogelsang MD[1], Rasmus Bojesen MD[1], Emma Hoelmich BMSc[1], Adile Orhan BMSc[1], Fatima Buzquurx BMSc[1], Luyi Cai BMSc[1], Camilla Grube BMSc[1], Jawad Zahid BMSc[1], Hans Raskov MD[1], Gregory Klebanov, MSc[6], Iannis Drakos PhD[1], Nicolas Derian PhD[1], Patrick Ryan PhD[3,4,5], Peter Rijnbeek PhD2, Ismail Gögenur MD, DMSc[1]

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[4]Department of Biomedical Informatics, Columbia University, New York, New York, USA,
[5]Janssen Pharmaceuticals, New Jersey, USA
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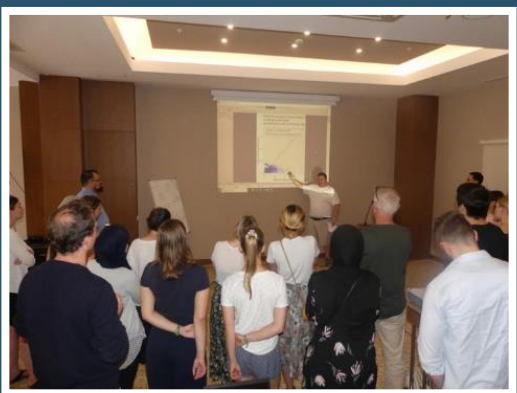

Study 3

Data driven hypothesis generation using the OMOP Common Data Model

Andreas Rosen[1], Nicholas Derian, PhD[1], Anna Ostropolets, MSc[6], Peter Rijnbeek, PhD[2], Patrick Ryan, PhD[3,4,5], Ismail Gögenur, MD, DMSc[1], Iannis Drakos, PhD[1] & the Center for Surgical Science Consortium[1]

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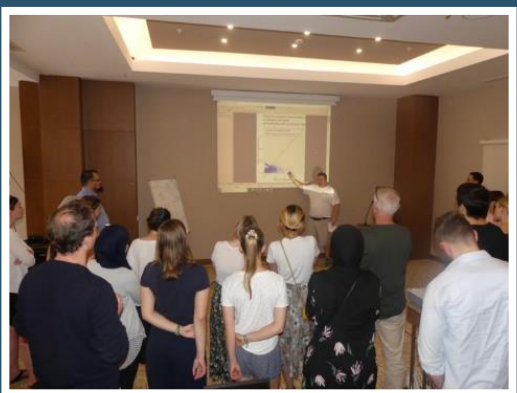
[6]Odysseus Data Services Inc., Cambridge, Massachusetts, USA



Study 4

Characterization of anemic and non-anemic colorectal cancer patients undergoing cancer surgery

Ali Abbas Shaker, MD[1], Rune Petring Hasselager, MD[1], Andreas Weinberger Rosen, MD[1], Tina Fransgaard, MD, PhD[1], Mahdi Alamili, MD, PhD[1], Johanne Gormsen, BSc[1], Thea Helene Degett, MD, PhD[1], Eldar Allakhverdiiev, MSc[6], Iannis Drakos, PhD[1], Peter Rijnbeek, PhD[2], Patrick Ryan, PhD[3,4,5], Ismail Gögenur, MD, DMSc[1], Nicolas Derian, PhD[1]

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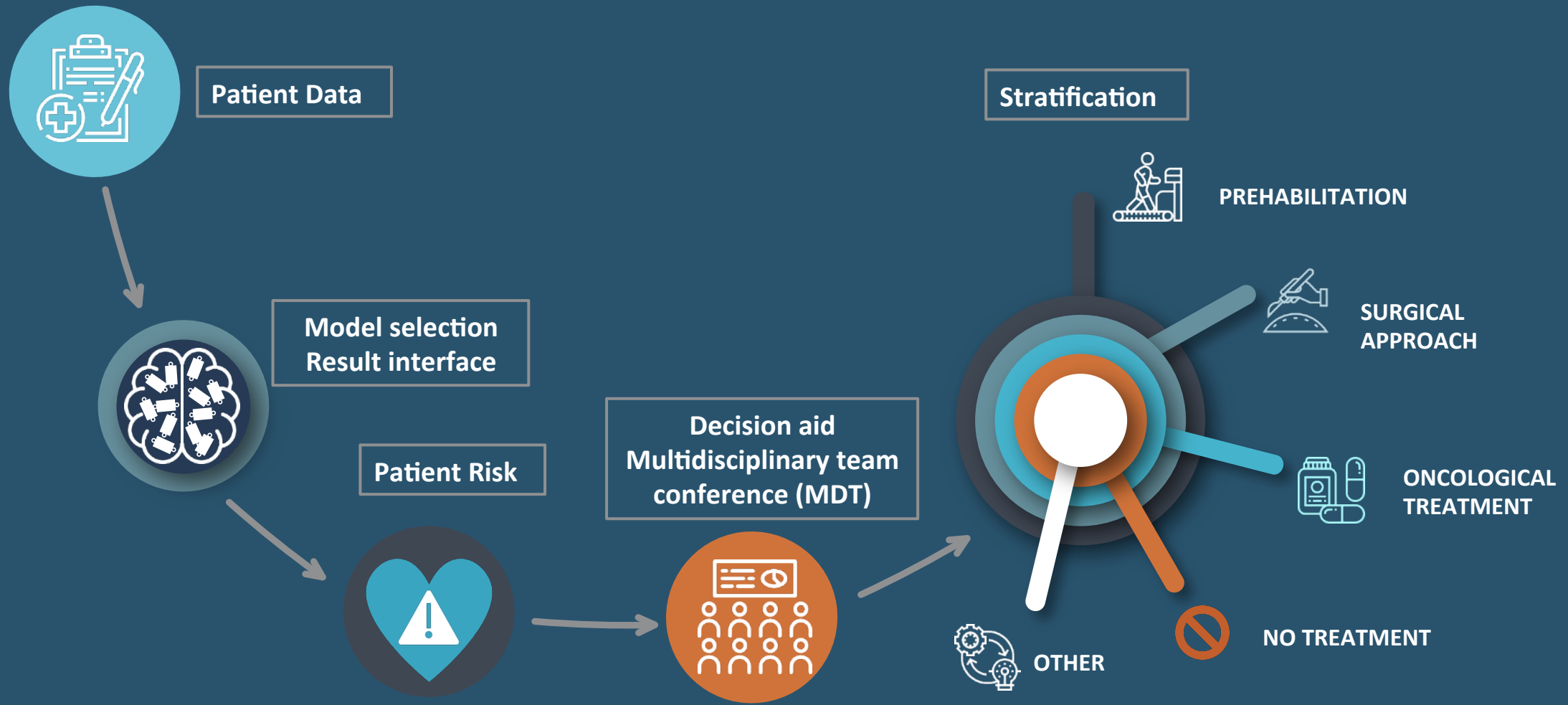
The patient pathway



Professor Ismail Gögenur, CSS, Zealand, Denmark
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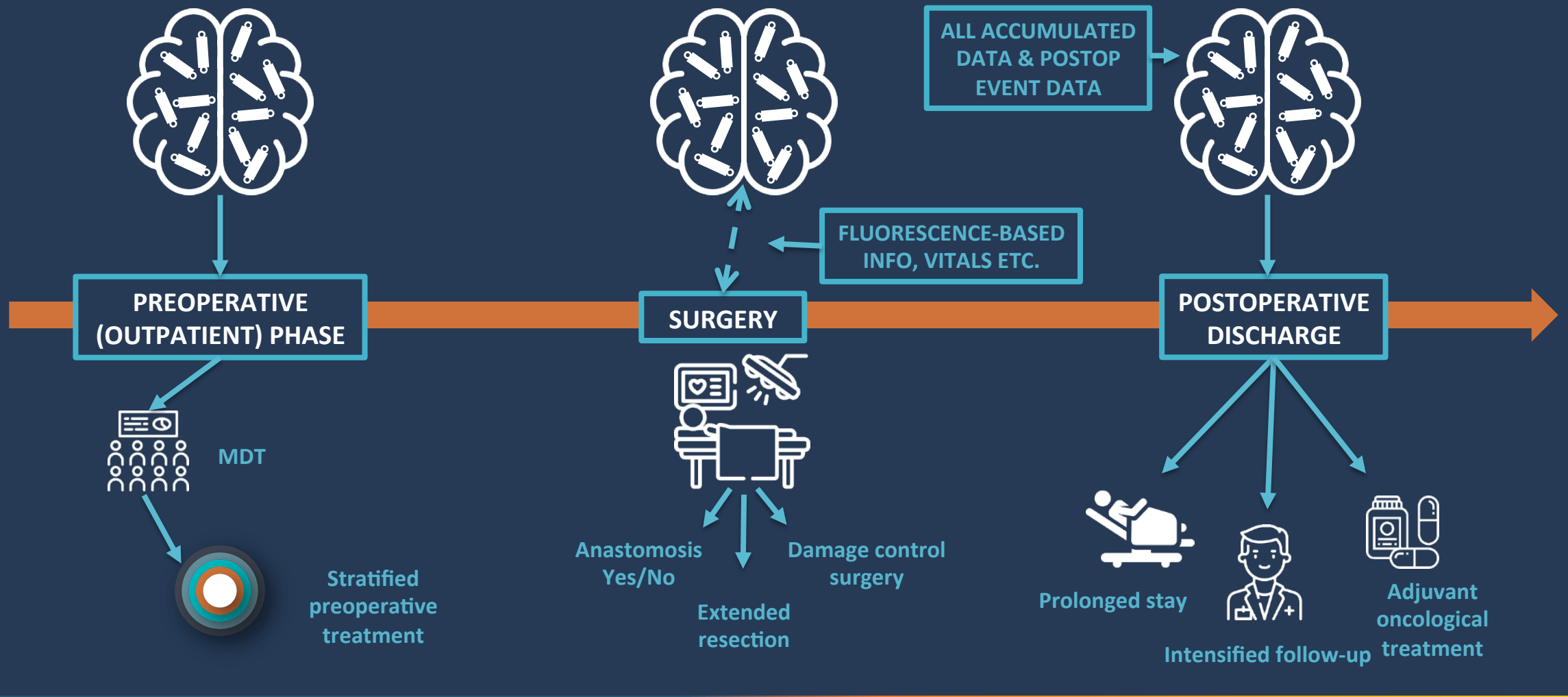
Critical phases of the patient journey



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The best OHDSI slide ever!

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Loosing a bet on the OHDSI journey!

Professor Ismail Gögenur, CSS, Zealand, Denmark igo@regionsjaelland.dk

The many faces of mapping!

The pleasures on the OHDSI journey!

Personalized Oncological Surgery
The right treatment to the right patient
at the right time

Thank you for your attention!

CENTER FOR SURGICAL SCIENCE

Presented by Prof. Ismail Gögenur, DMSc
Director of the Center for Surgical Science (CSS)