Real-world data at scale:

How machine learning can enable learning from all patients

Discussion Leader:
Lotte Steuten, PhD

Discussants:
Maarten Ijzerman, PhD
Corey Benedum, PhD
Natalia Kunst, PhD

Panelists

Lotte Steuten, PhD

Moderator
Deputy Chief Executive,
Office of Health Economics

Maarten Ijzerman, PhD

Discussant
Dean, Professor,
Cancer Health Services Research
Erasmus School of Health Policy and Management

Corey M. Benedum, PhD

Discussant
Quantitative Scientist,
Machine Learning
Flatiron Health

Natalia Kunst, PhD

Discussant
Associate Professor,
Department of Health Management and Health Economics,
University of Oslo

Agenda

1. The Challenge of Data Linkage to Analyse Complete Episodes of Care
2. Machine Learning Extraction and RWD Generation at Scale
3. Improving Medical Decision Making: Evidence And Uncertainty Consideration

Erasmus School of Health Policy & Management

THE UNIVERSITY OF MELBOURNE

The Challenge of Data Linkage to Analyse Complete Episodes of Care

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Acknowledgement

PRIMCAT
PREDICTING THE IMPACT OF CANCER TREATMENT

Fanny Franchini, Karen Trapani, Sallie Pearson

“Predicting the Population Health Impact of New Cancer Treatments”

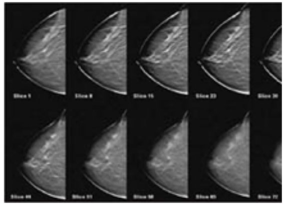
Medical Research Future Fund, Australia

The Opportunity of Big Data in Numbers

10 Mb

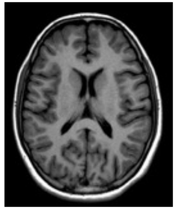
radiography

27 Mb



digital mammography

100 Mb

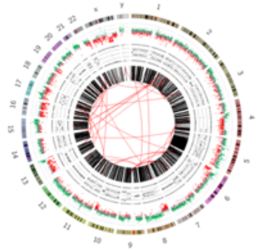


CT scan

6,000 Mb

digital pathology

180,000 Mb



whole-genome sequencing

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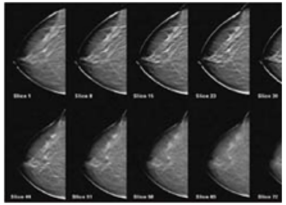

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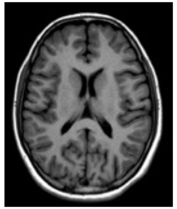

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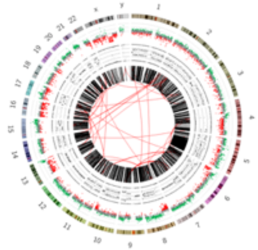

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US$ 8 billion

global market (2026) for
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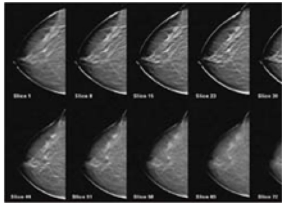

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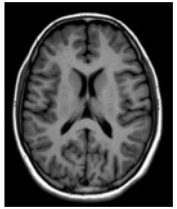

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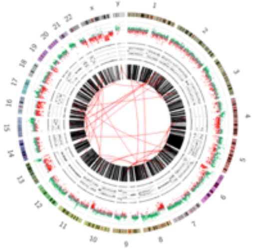

whole-genome sequencing

US$ 8 billion

global market (2026) for
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US$ 35 billion

global market (2028) for
electronic health records

The Opportunity of Big Data in Numbers

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radiography

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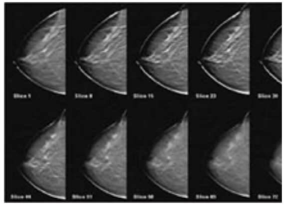

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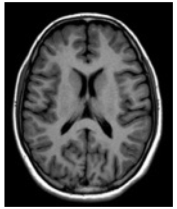

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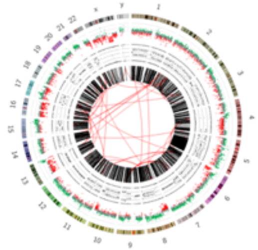


whole-genome sequencing

US$ 8 billion

global market (2026) for **healthcare data storage**

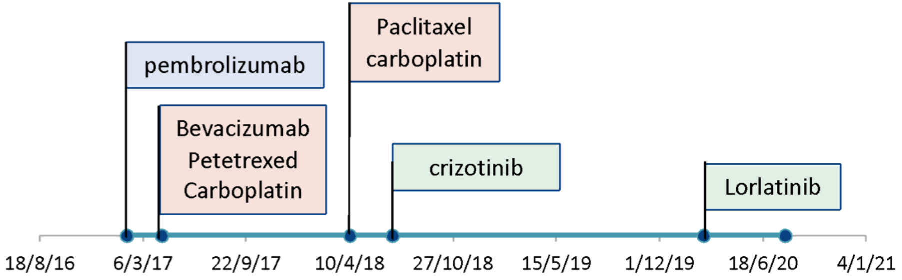
US$ 35 billion

global market (2028) for **electronic health records**

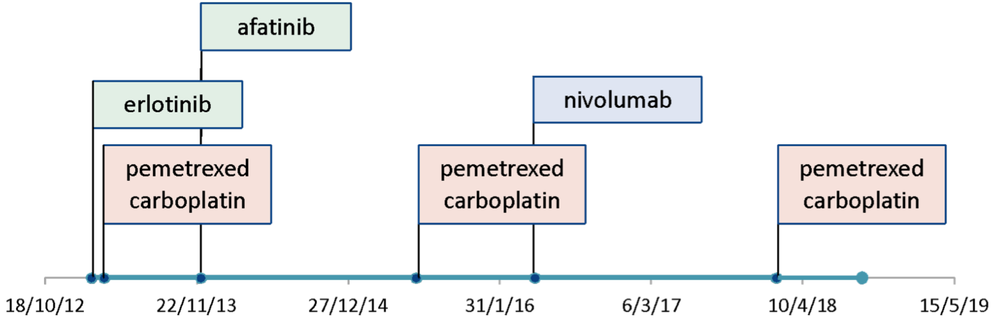
US$ 56 billion

global market (2025) for **checkpoint inhibitors**

Listing new treatments: ALK+ NSCLC



NSCLC, stage IV, ALK+ and EGFR+



NSCLC, stage IIIb, EGFR+

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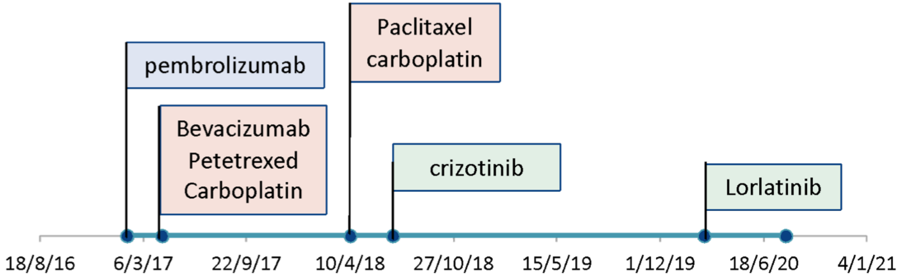

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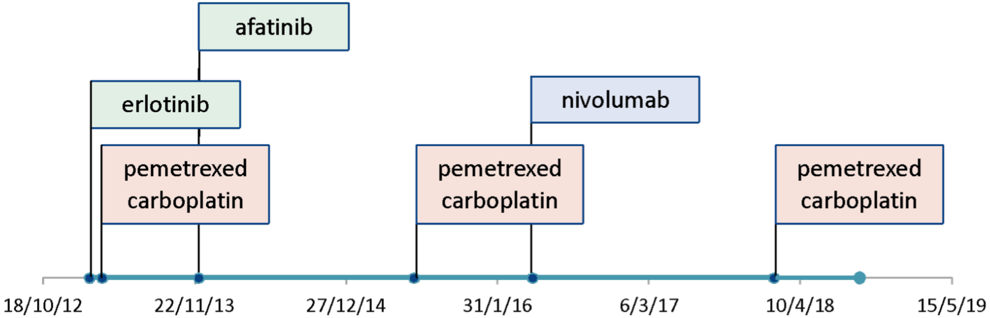

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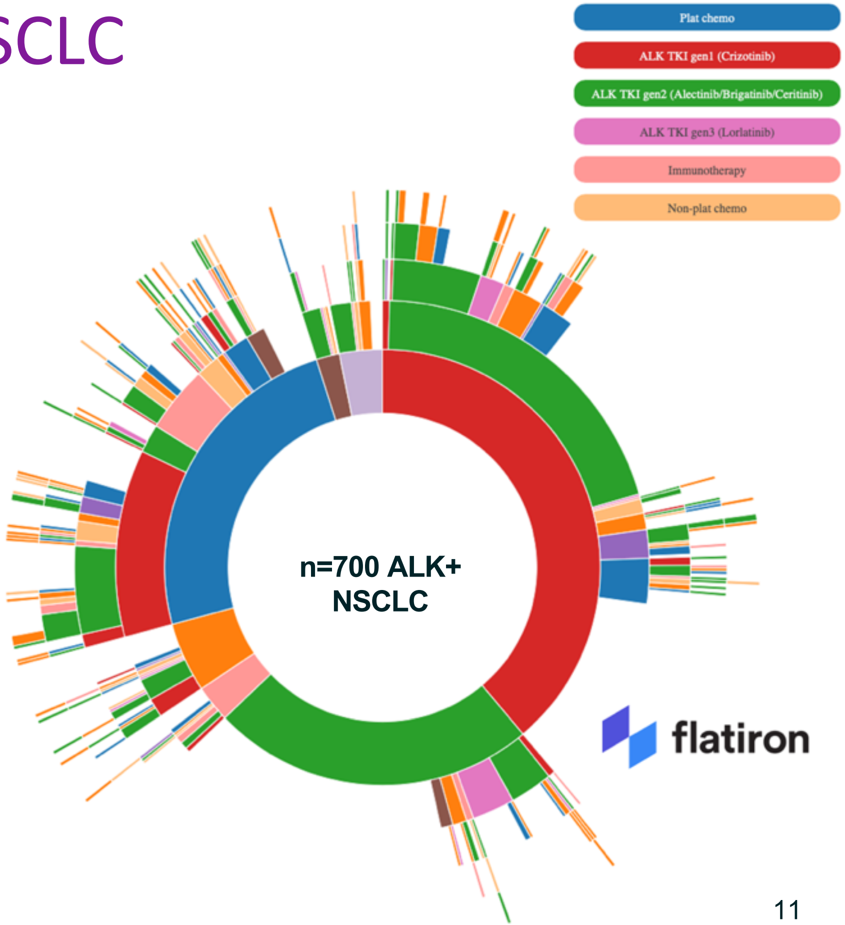


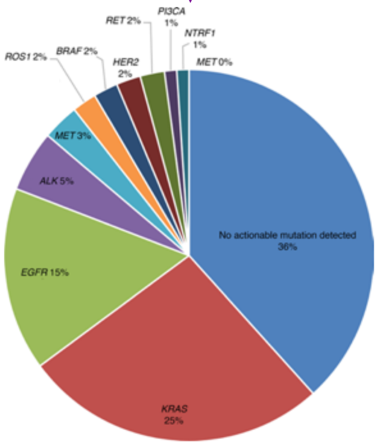
Chazan, Franchini, Alexander, John, Shah, IJzerman, Solomon; ***Lung Cancer*** (2022)

Population Health Economic Impact

PRIMCAT
PREDICTING THE IMPACT OF CANCER TREATMENT

NSCLC Incidence → T0 → 1st line → 2nd line → 3rd line → 4th line

T0	1st line	2nd line	3rd line	4th line
Biopsy	**Gefitinib**	**Erlotinib**	**Osimertinib**	**Carboplatin pemetrexed**



Population prevalence (NSCLC)

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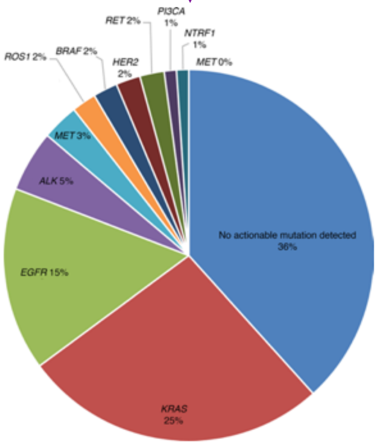
	Eligible 1st L (N)	Eligible 2nd L (N)	Eligible 1st L (N)	
	Received (%)	Received (%)	Received (%)	

Impact on PBS/MBS ($)



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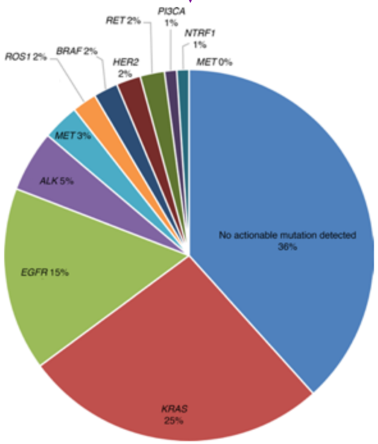

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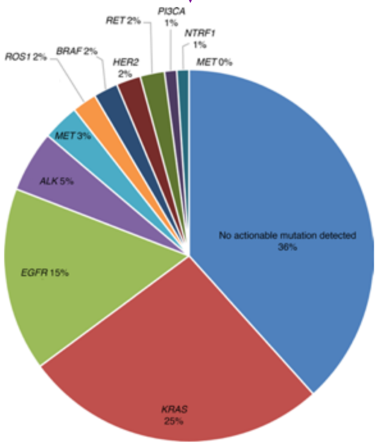

Population prevalence (NSCLC)

FDA approvals NSCLC (May, 2020)

- Ramucirumab/erlotinib
- Nivolumab/Ipilimumab
- Brigatinib
- Atezolizumab
- Capmatinib
- Selpercatinib

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Method – Defining treatment lines

- **Using a curated registry, building a treatment pathway: rules based**

Surgery + (neo)adj Tx

- Surgery +
  - Radiotherapy
  - Chemotherapy

→ Prior-After 3 months

Radiotherapy + chemo

- Radiotherapy (curative)
- Chemotherapy

→ Within 3 months

Maintenance chemotherapy

- Any chemotherapy
- Followed by pemetrexed

→ Within 3 months

Toxicity-related (1): swap from

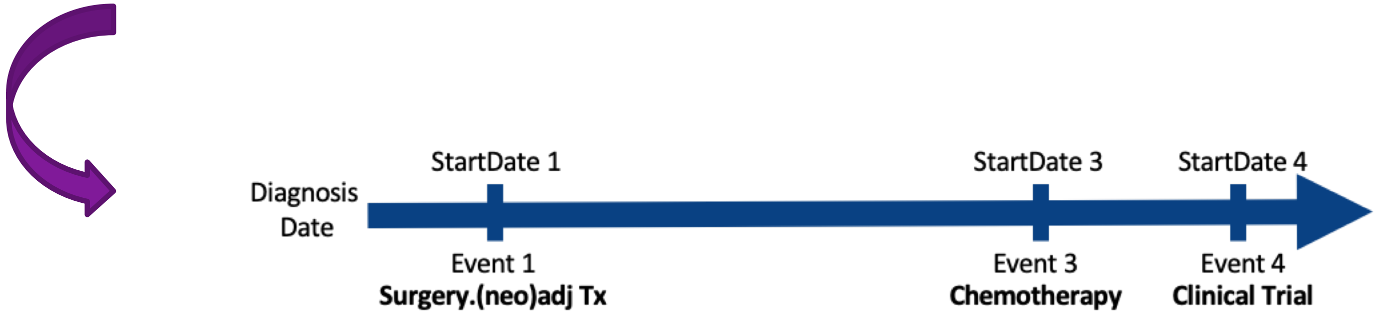
- Cisplatin-based chemo
- Carboplatin-based chemo

→ Within 3 months

Toxicity-related (2): swap from

- Biological agents
- Subset of agents

→ Within 3 months



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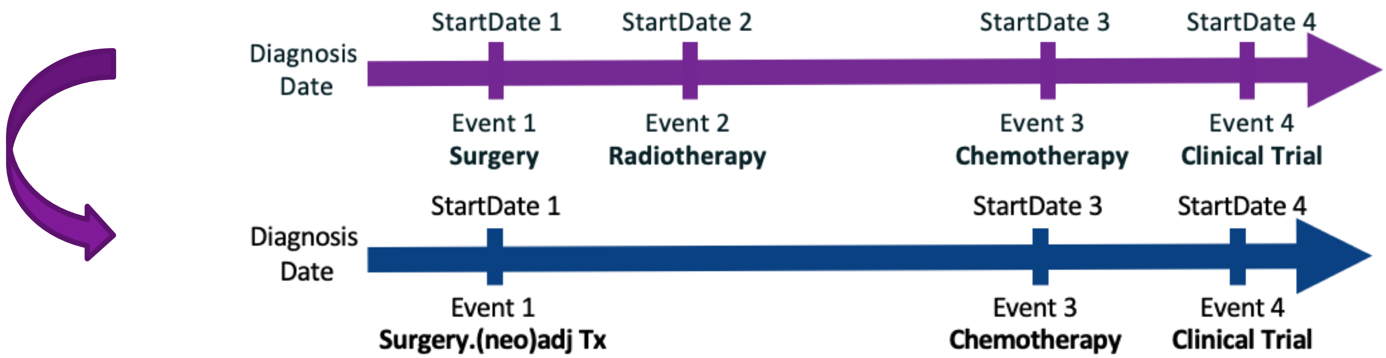

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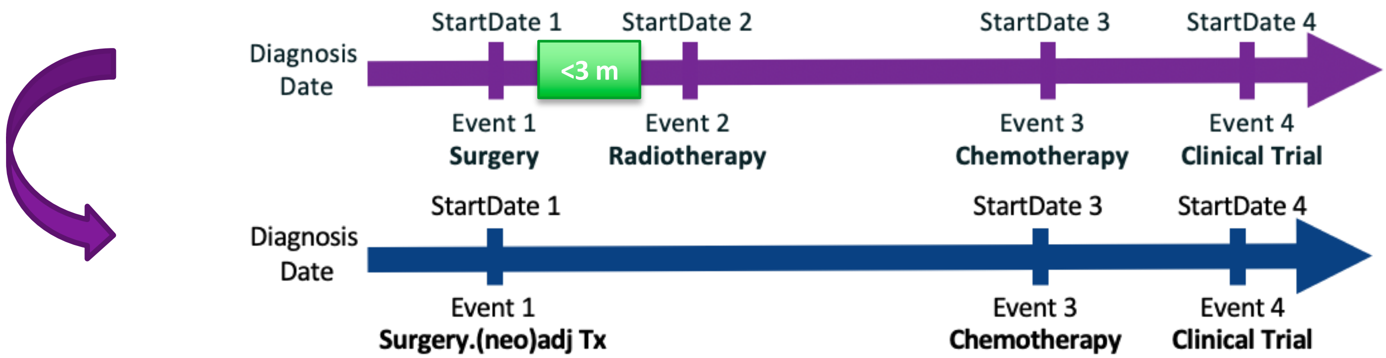


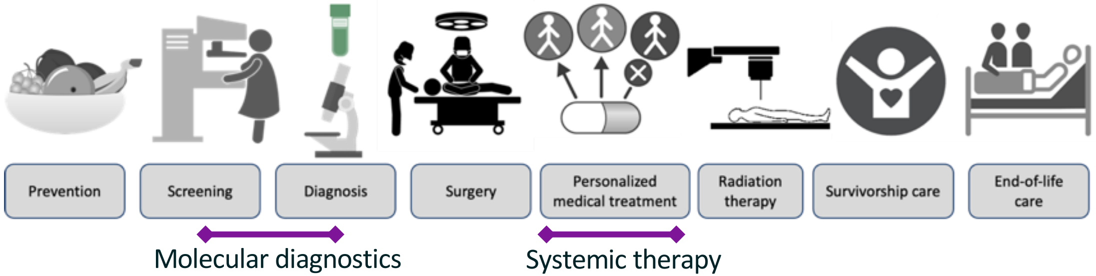
Analysis of the whole episodes of care: data driven

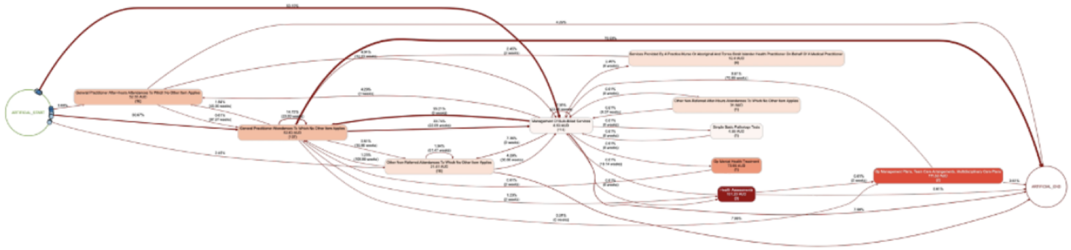
BioGrid

The Royal Melbourne Hospital

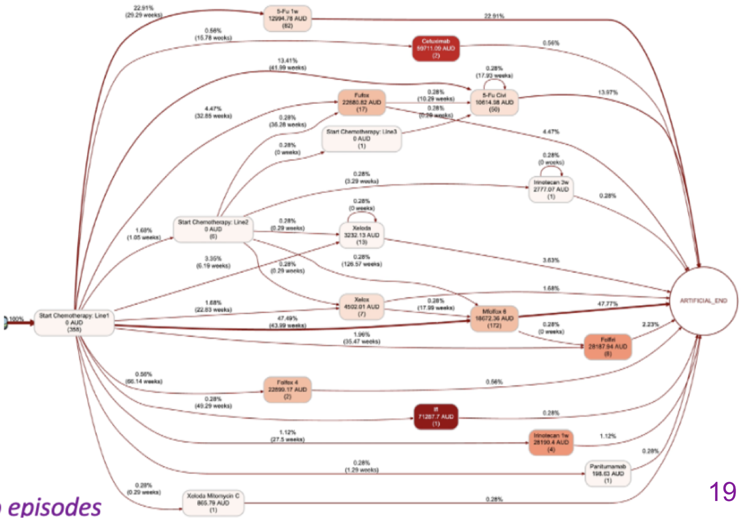
Western Health

NPS MEDICINEWISE



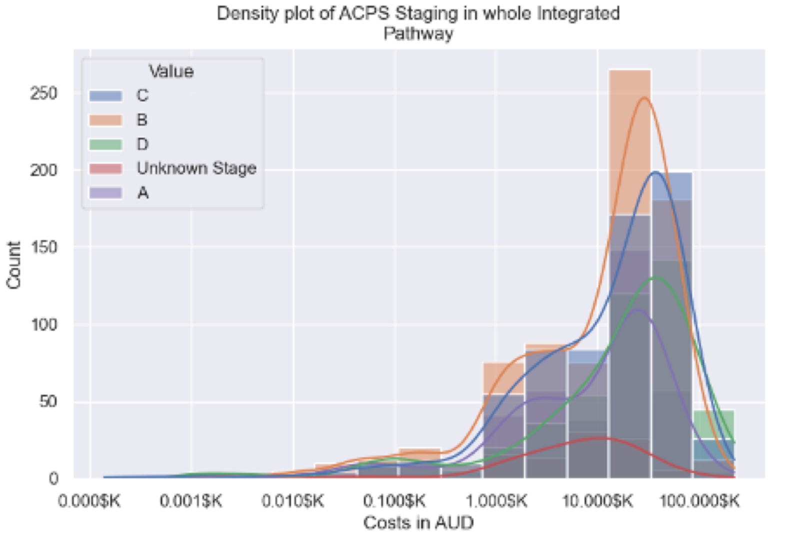


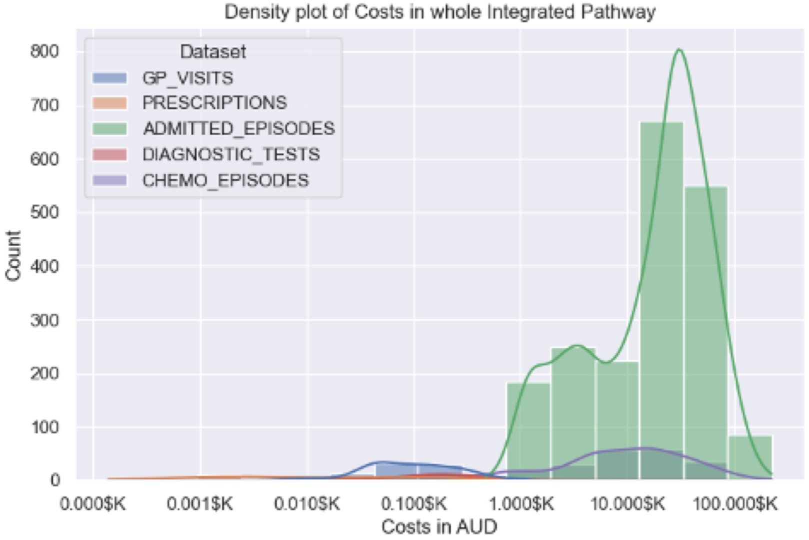
GP visits / tests ordered



Chemo episodes

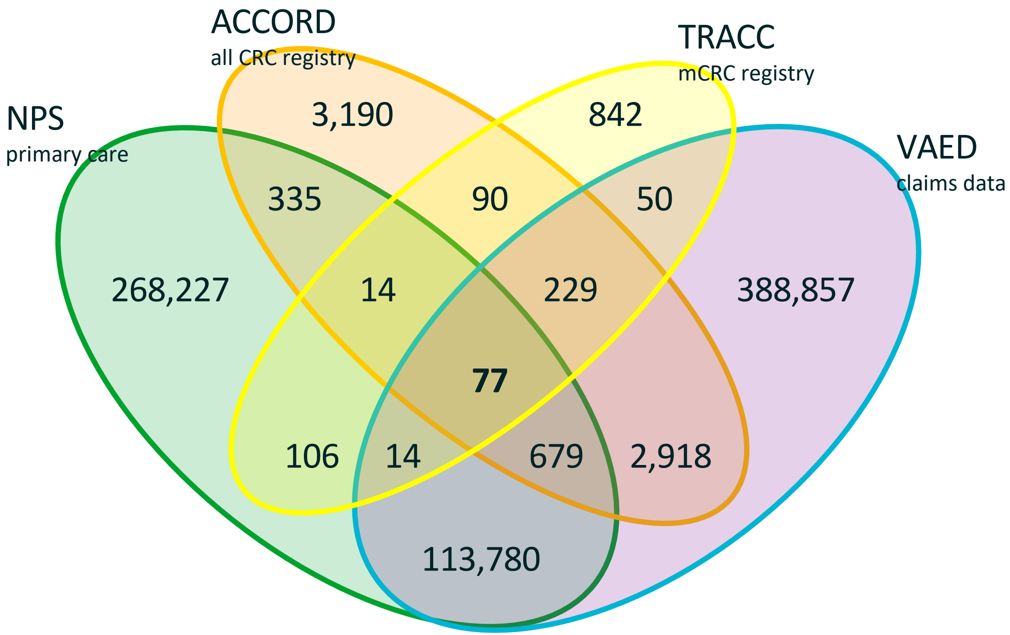
Cost analysis over entire care episodes





Sven Relyveld et al, Process model enhancement to establish the cost of entire episodes of colorectal cancer care using multi-centre linked data
Special Issue Mathematical Biosciences and Engineering, 2022

Challenges with Data Linkage I (missing patients)



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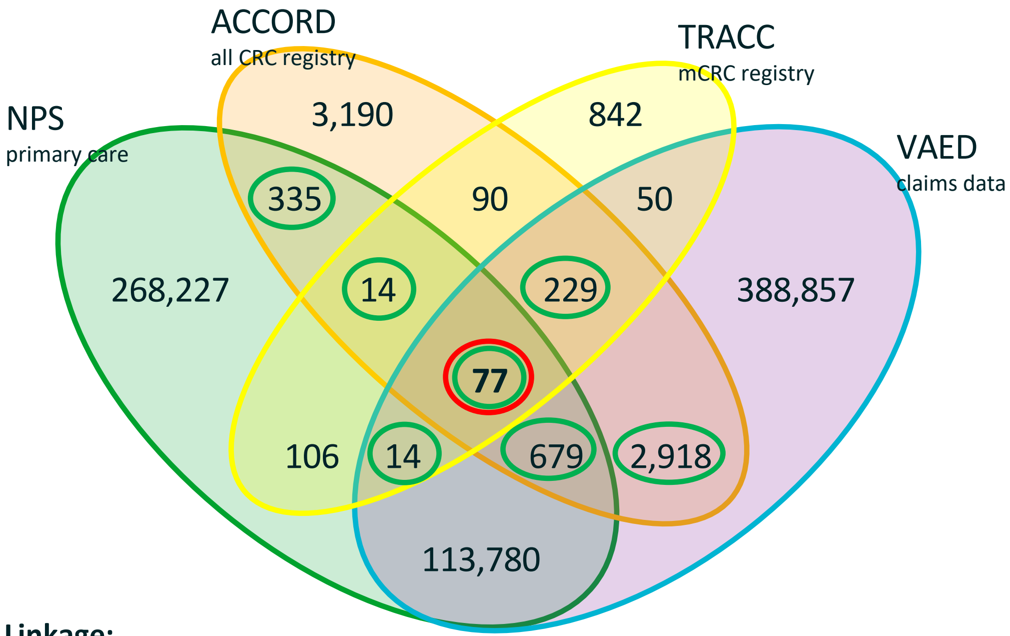

Linkage:

1. *VAED-ACCORD-NPS-TRACC (N=77)*
2. ACCORD-NPS (N=1,105)
3. VAED-ACCORD (n=3,903)
4. VAED-ACCORD-NPS (n=4,223)

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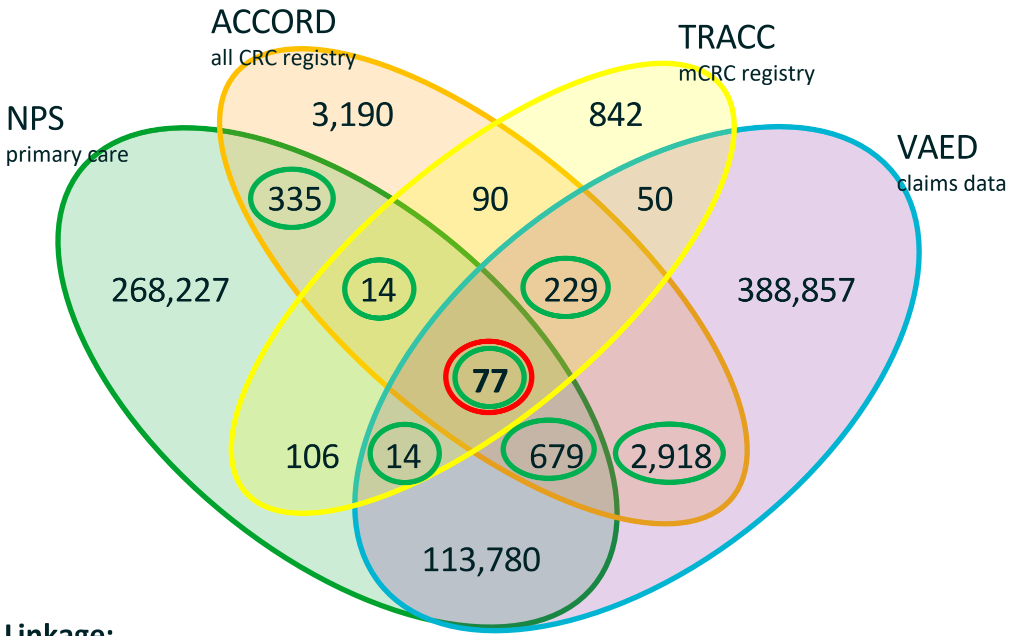

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The Royal Melbourne Hospital | Western Health

ACCORD Clinical registry	Royal Melbourne n=1,058	Western Health n=1,044
Coverage	June 2006-June 2017	June 2011-June 2018
% surgery <1 year	**90% (n=954)**	**83% (n=865)**
% chemo offered and accepted	30% (n=323) 90% (n=292)	28% (n=295) 90% (n=265)
% chemo received	**27.5% (n=292)**	**25.4% (n=265)**
Alive	64% (n=673)	75% (n=782)

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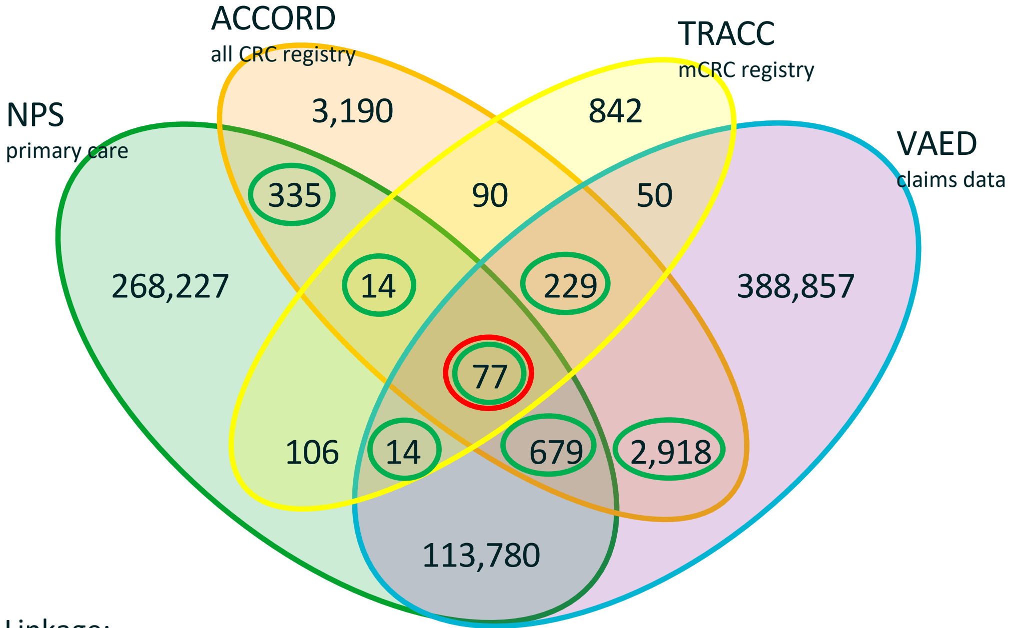

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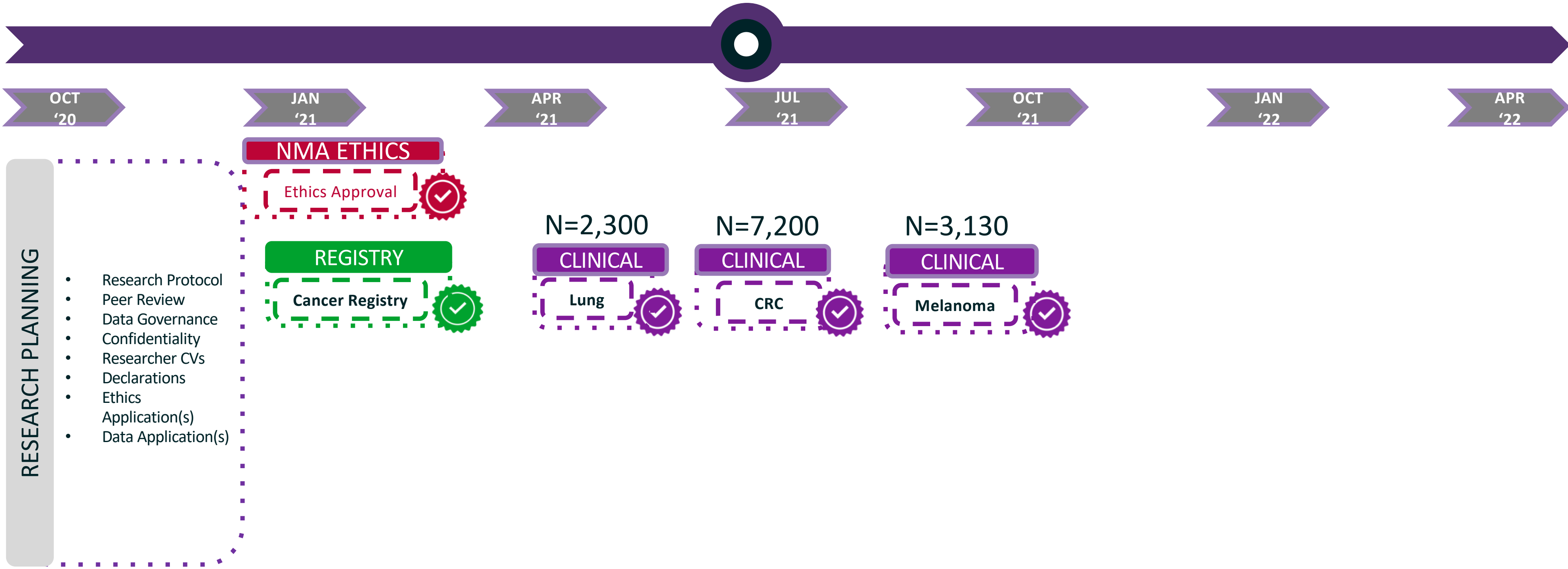
VAED Hospital episodes	Royal Melbourne n=1,058	Western Health n=1,044
Coverage	June 2006-June 2017	June 2011-June 2018
% surgery <1 year	42% (n=443)	65% (n=675)
% chemo received	**14% (n=150)**	**29% (n=302)**

An (enduring) linked population level dataset



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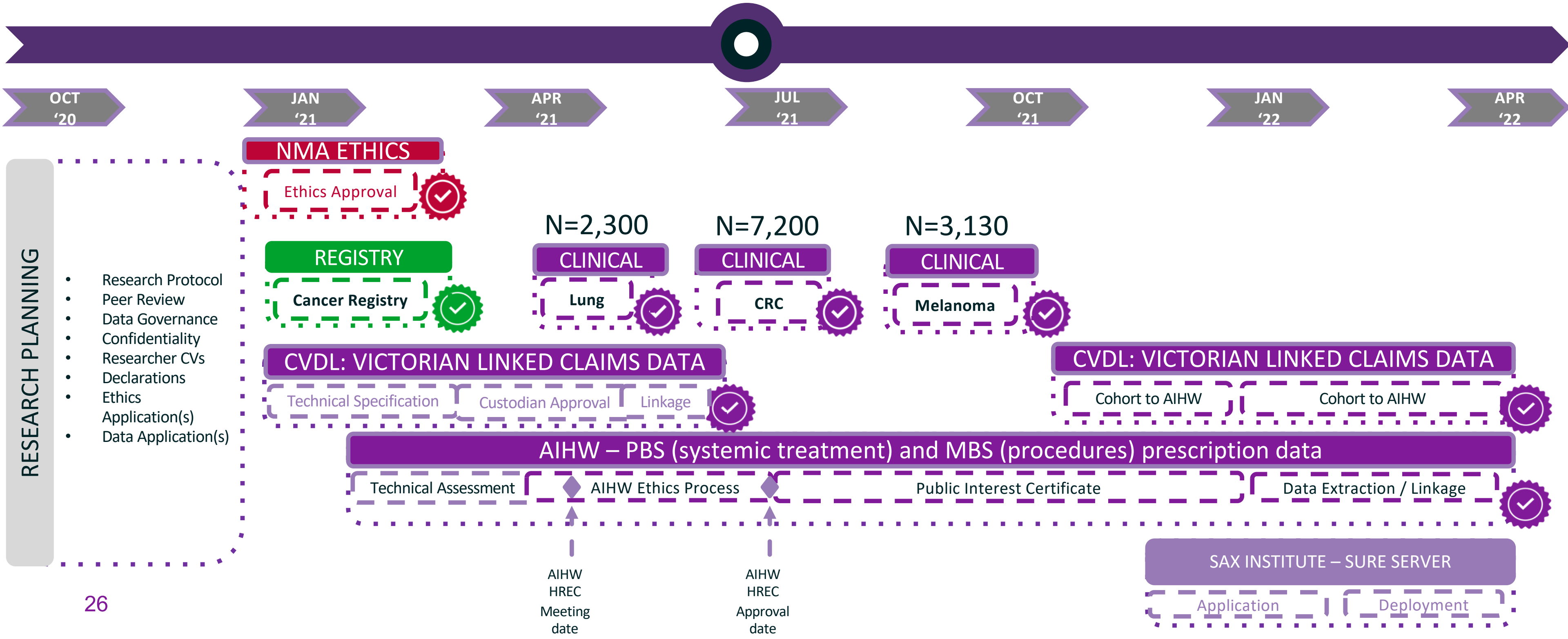
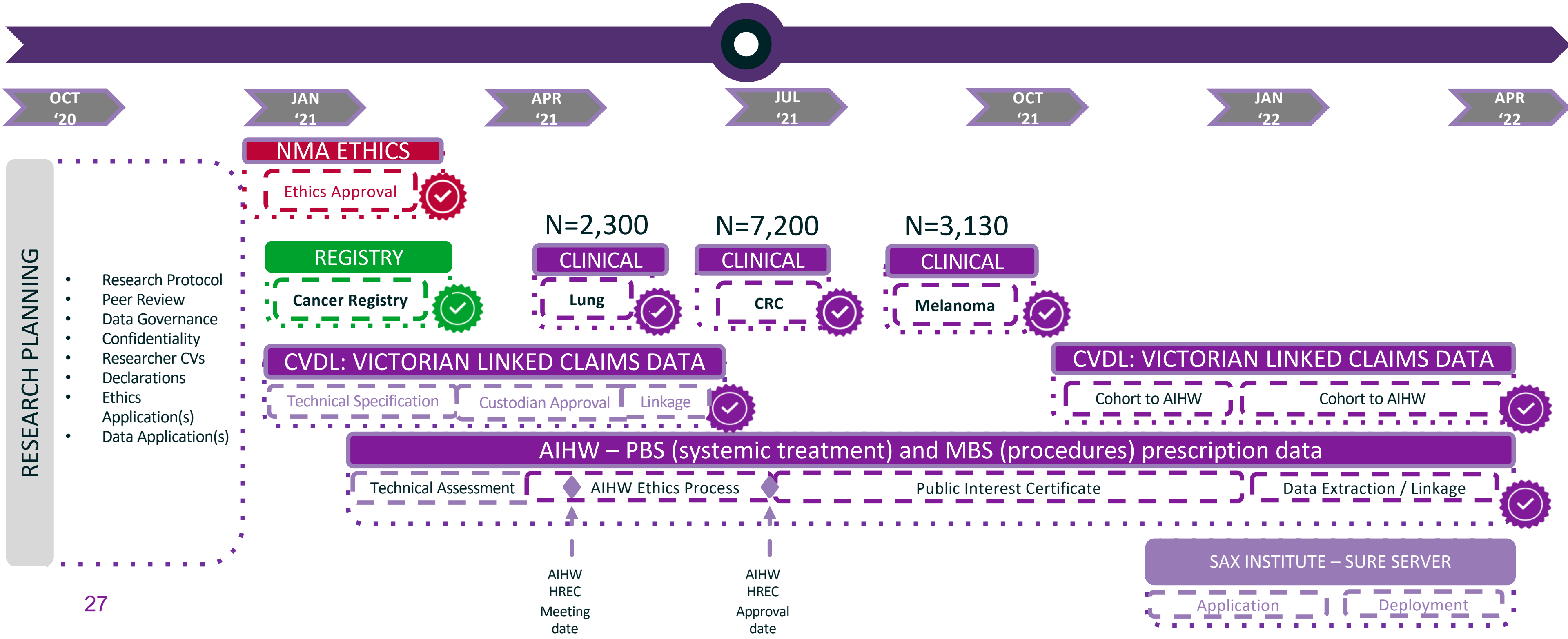
PRIMCAT
PREDICTING THE IMPACT OF CANCER TREATMENT



Challenges with data linkage II (data gaps)



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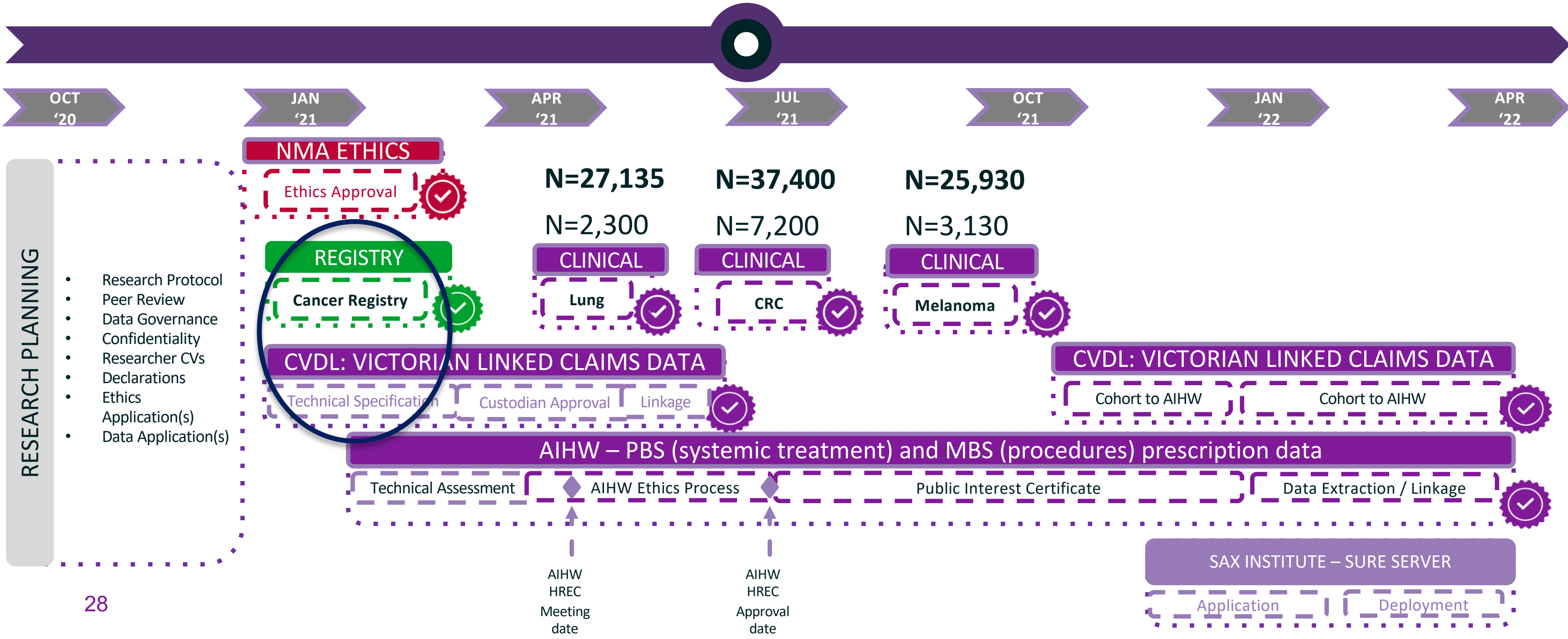

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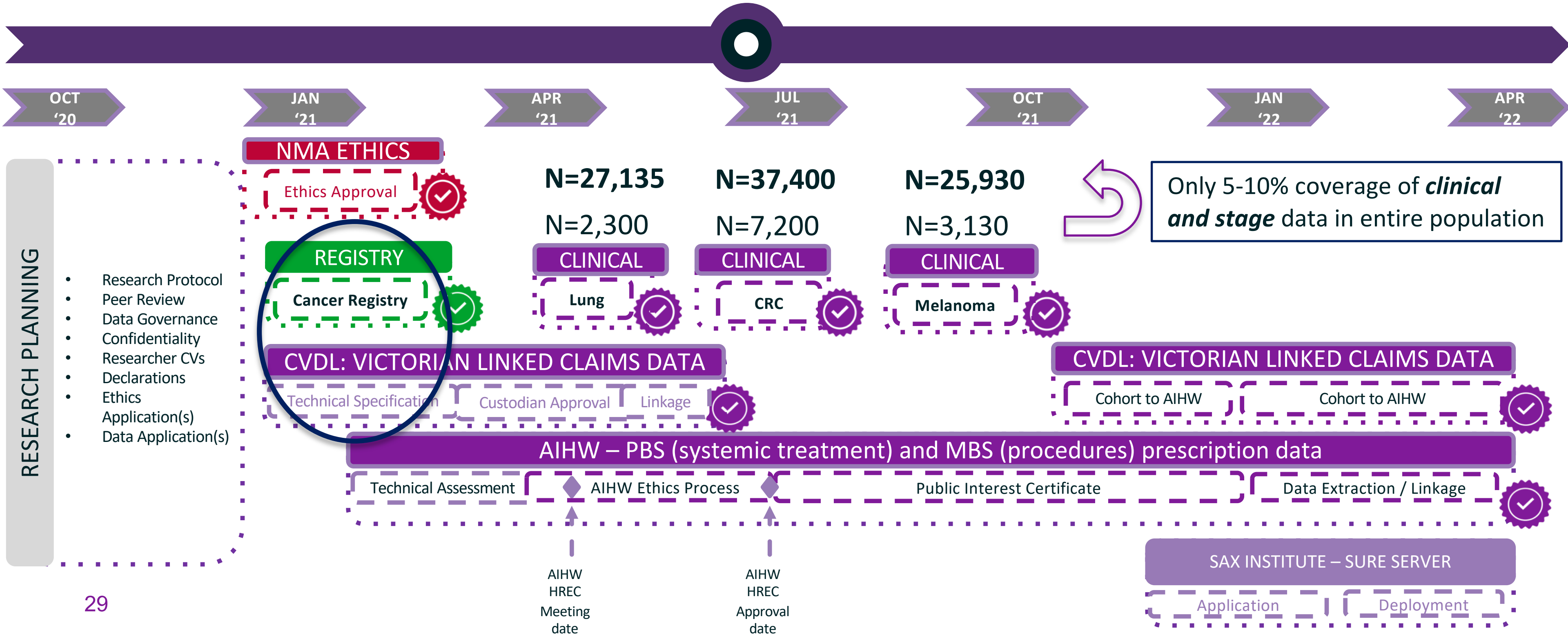


Machine learning for extracting and linking data

Mapping treatment episodes in relatively “clean” clinical datasets

Purpose: The analysis of specific treatments (sequences) and correlation with survival

Issue: Rule-based using clinical expertise is labor intensive

Use ML: Process mining is used to identify unique sequences of events

Combining various (clinical, claims, administrative) datasets through linkage

Purpose: The analysis of whole episodes of care, to investigate disparities in access to care and outcomes or health service utilisation across different settings

Issue: “Data gaps”, such as missing clinical information (stage, comorbidities) at population level

Use ML: ML methods can be used to infer clinical information from other data (e.g. pharmacy prescription data to infer toxicities)

Poll Question

How reliable is population level research if we only have complete data for a fraction of the patients? E.g. can we reliably estimate cost of care delivery from a subset of patients using process mining or ML methods?

Poll Question

If my dataset only has only 5% patients with complete clinical information (stage, comorbidities, ECOG, PROMs), there is insufficient statistical power to do any meaningful regression analyses

- Yes
- No

Poll Question

Inferring stage information or estimating immunotherapy related toxicities from drug dispensing data using machine learning will never be accepted by clinicians

- Yes
- No

Poll Question

We should not be using machine learning, instead we should solve data privacy and security issues to enable faster and better use of all existing data

- Yes
- No

Machine Learning Extraction and RWD Generation at Scale

Corey M. Benedum, PhD, MPH
Flatiron Health
@DrCoreyBenedum
coreybenedum

flatiron

Disclaimers

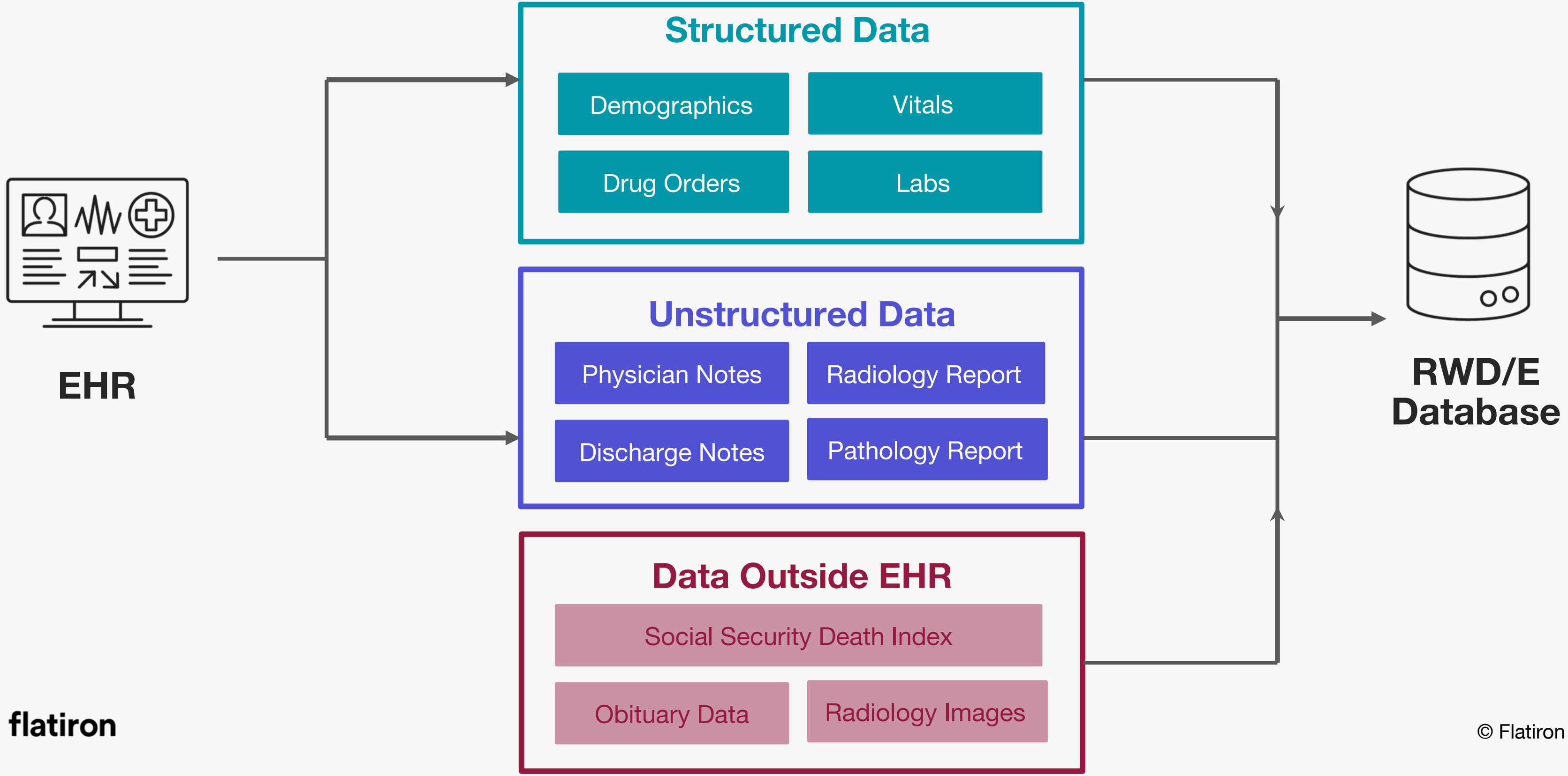
Corey Benedum is an employee of Flatiron Health, an independent subsidiary of Roche Group. He holds stock ownership in Roche.

The value of real-world evidence

- Compare Treatment Effectiveness
- Understand Treatment Effectiveness
- HTA decision making
- Measure safety and effectiveness of off-label treatments
- Identify disparity in care

And much more…

Real-world evidence generation

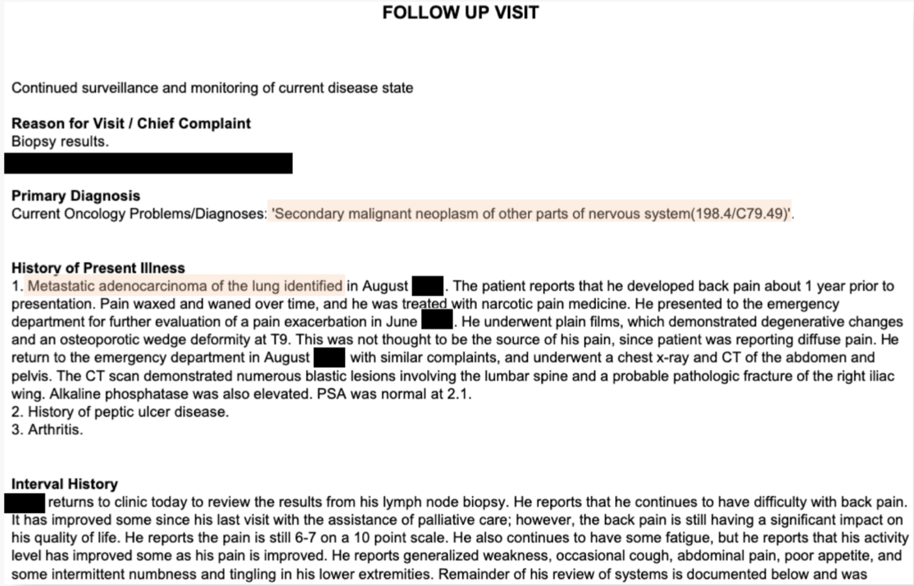


flatiron

Challenge:
Critical data elements come from unstructured data

Several data elements critical for outcomes research are stored in unstructured data sources.

Abstracting this information is a **costly** and **resource intensive** task.



FOLLOW UP VISIT

Continued surveillance and monitoring of current disease state

Reason for Visit / Chief Complaint
Biopsy results.
[redacted]

Primary Diagnosis
Current Oncology Problems/Diagnoses: 'Secondary malignant neoplasm of other parts of nervous system(198.4/C79.49)'.

History of Present Illness
1. Metastatic adenocarcinoma of the lung identified in August [redacted]. The patient reports that he developed back pain about 1 year prior to presentation. Pain waxed and waned over time, and he was treated with narcotic pain medicine. He presented to the emergency department for further evaluation of a pain exacerbation in June [redacted]. He underwent plain films, which demonstrated degenerative changes and an osteoporotic wedge deformity at T9. This was not thought to be the source of his pain, since patient was reporting diffuse pain. He return to the emergency department in August [redacted] with similar complaints, and underwent a chest x-ray and CT of the abdomen and pelvis. The CT scan demonstrated numerous blastic lesions involving the lumbar spine and a probable pathologic fracture of the right iliac wing. Alkaline phosphatase was also elevated. PSA was normal at 2.1.
2. History of peptic ulcer disease.
3. Arthritis.

Interval History
[redacted] returns to clinic today to review the results from his lymph node biopsy. He reports that he continues to have difficulty with back pain. It has improved some since his last visit with the assistance of palliative care; however, the back pain is still having a significant impact on his quality of life. He reports the pain is still 6-7 on a 10 point scale. He also continues to have some fatigue, but he reports that his activity level has improved some as his pain is improved. He reports generalized weakness, occasional cough, abdominal pain, poor appetite, and some intermittent numbness and tingling in his lower extremities. Remainder of his review of systems is documented below and was

The promise of clinical ML for RWE

Real-world data and analytics organizations are looking to machine learning (ML) to efficiently extract data found in unstructured data at scale.

REAL-WORLD EVIDENCE ALLIANCE

AETION ConcertAI flatiron.

Syapse. Syneos Health TEMPUS OM1.

Verana Health. verily IQVIA

flatiron

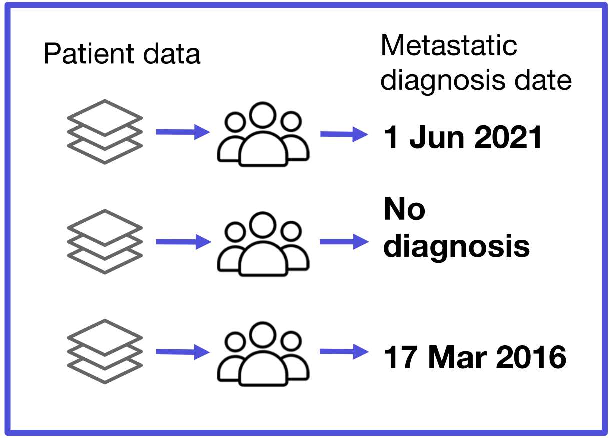
Keys to accurate information extraction with ML

1. **High quality** labels that are designed with clinical expertise and are consistently / accurately collected.

2. **Large volume** of labels obtained from trained clinical experts performing chart review (abstraction)

Approach for extracting metastatic diagnosis date with ML

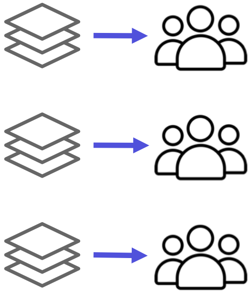
1. Abstractors label some of the patients



Approach for extracting metastatic diagnosis date with ML

1. Abstractors label some of the patients

Patient data	Metastatic diagnosis date
	1 Jun 2021
	No diagnosis
	17 Mar 2016

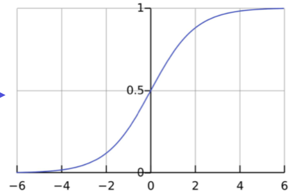


2. We train a model on this labeled data

Machine learning algorithm

Potential ML algorithms

1. Deep learning architectures
2. Logistic regression
3. RandomForest



The model learns the language patterns associated with metastatic disease

Approach for extracting metastatic diagnosis date with ML

1. Abstractors label some of the patients

Patient data	Metastatic diagnosis date
→ →	**1 Jun 2021**
→ →	**No diagnosis**
→ →	**17 Mar 2016**

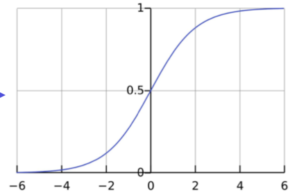
2. We train a model on this labeled data

Machine learning algorithm

Potential ML algorithms

1. Deep learning architectures
2. Logistic regression
3. RandomForest

Unlabeled patient data



3. We use a trained model to predict if and when the patient was diagnosed with metastatic disease

Is Metastatic:

TRUE

Metastatic Diagnosis Date:

15 Feb 2017

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Approach for extracting metastatic diagnosis date with ML

DETAILED LOOK INSIDE 2

1. Abstractors label some of the patients

Patient data	Metastatic diagnosis date
→ →	**1 Jun 2021**
→ →	**No diagnosis**
→ →	**17 Mar 2016**

2. We train a model on this labeled data

Machine learning algorithm

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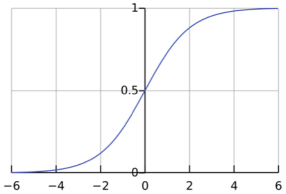

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15 Feb 2017

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Overview:
Building the model

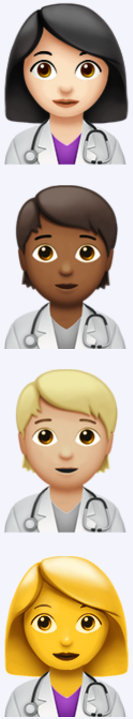
Model Building Process:

1. **construct list of relevant search terms**

2. filter to sentences with informative terms.

3. assign dates to sentences

4. create model input from sentence-date pairs



- Metastatic
- Mets
- Recurrent
- Stage
- relapsed

...

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Overview:
Building the model

Model Building Process:

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4. create model input from sentence-date pairs

- Metastatic
- Mets
- Recurrent
- Stage
- relapsed

...

Clinic note: 20 Mar 2018

Name: John Doe
DOB: 6/15/1952
History of Present Illness:
65 year old male w h/o Stage 4 lung adeno ca

(EGFR neg, ALK neg, ROS1 neg, BRAF neg, PDL1 high expression (60%) > cisplatin/alimta/pembro > 05/22/2017

Completed XRT L iliac bone, 01/26/2018 Completed XRT Anterior Subcutaneous Chest Nodule
...

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Overview:
Building the model

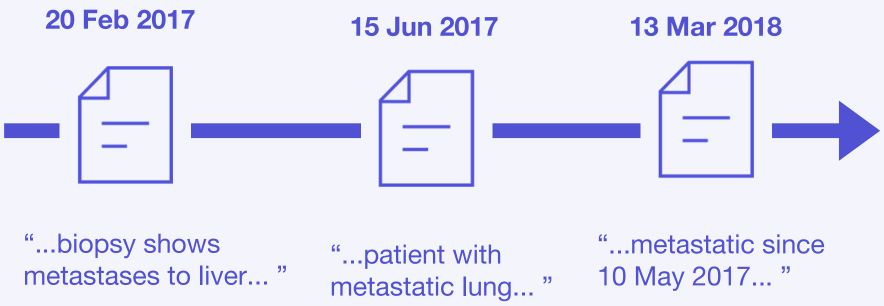
Model Building Process:

1. construct list of relevant search terms

2. filter to sentences with informative terms.

3. assign dates to sentences

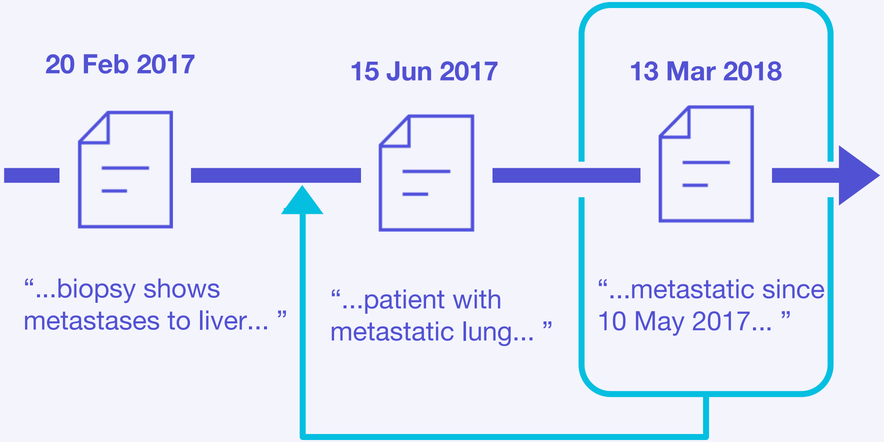
4. create model input from sentence-date pairs



Overview:
Building the model

Model Building Process:

1. construct list of relevant search terms
2. filter to sentences with informative terms.
3. **assign dates to sentences**
4. create model input from sentence-date pairs



Reassign the sentence to have a timestamp matching the date referred to in the sentence

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Overview: Building the model

Model Building Process:

1. construct list of relevant search terms
2. filter to sentences with informative terms.
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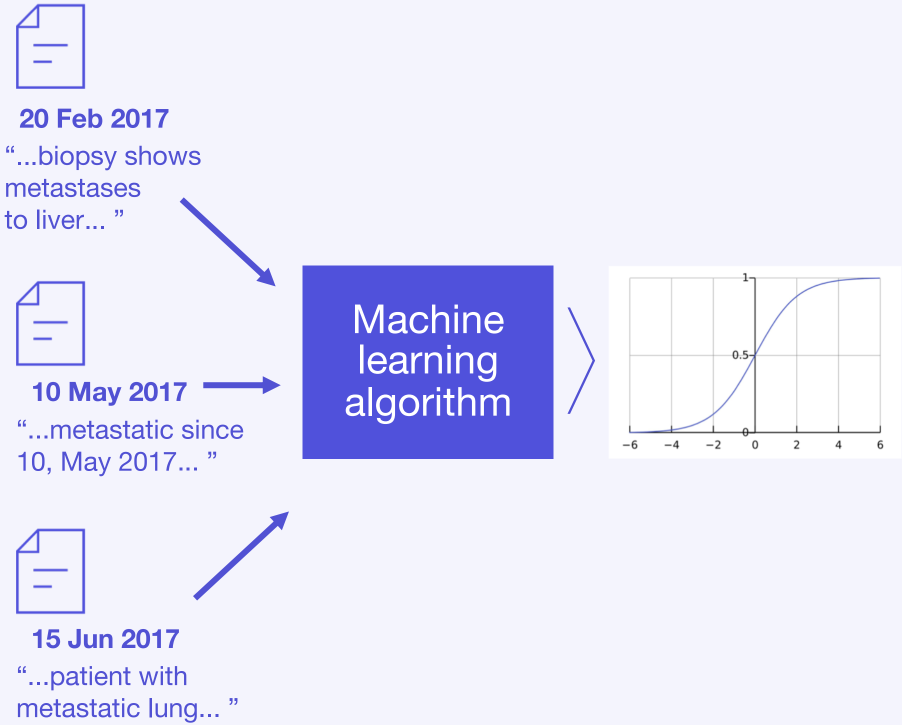

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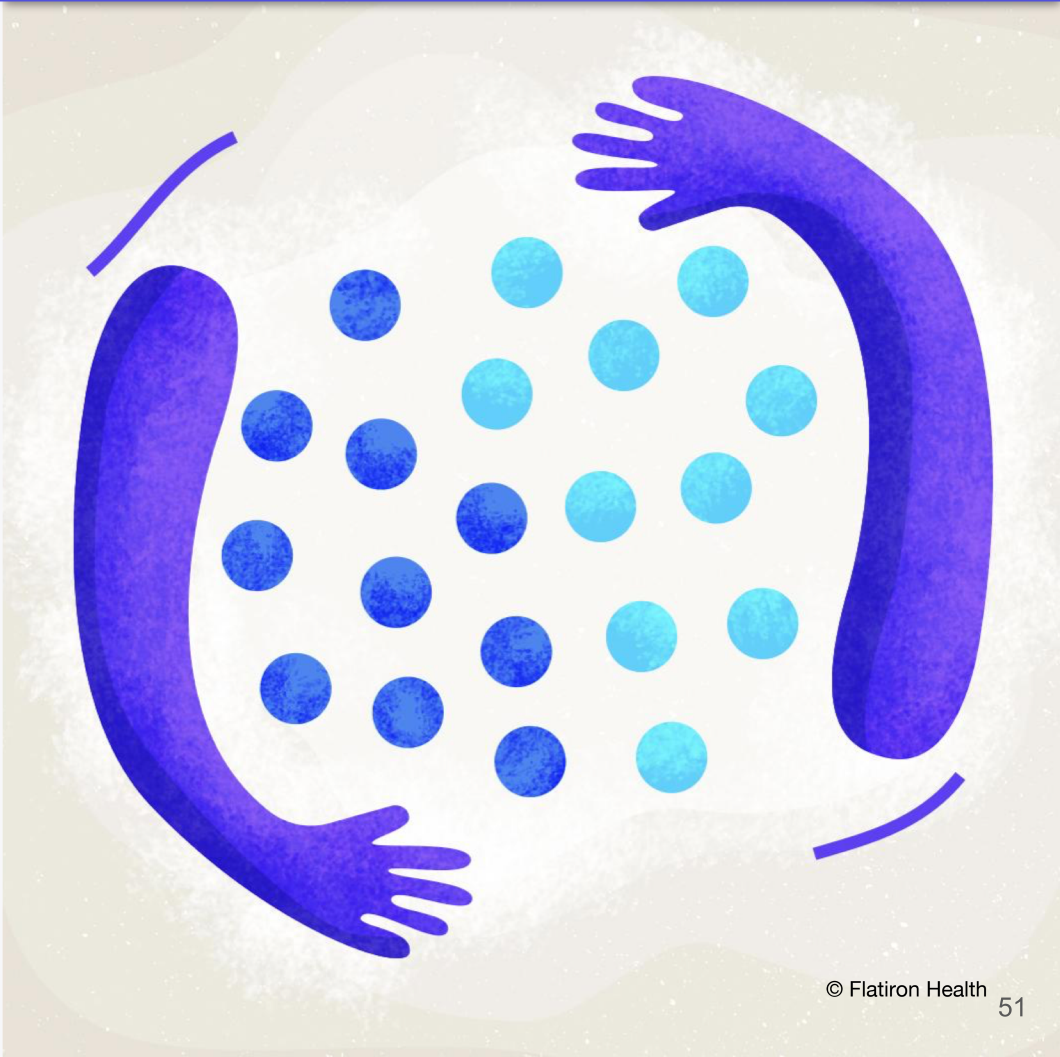
Models must be generalizable to the target population

Potential Negative Outcome

Model is not generalizable leading to low performance and bias

Solutions

- Clearly define the target population
- Understand how training data are derived from this population to ensure representativeness



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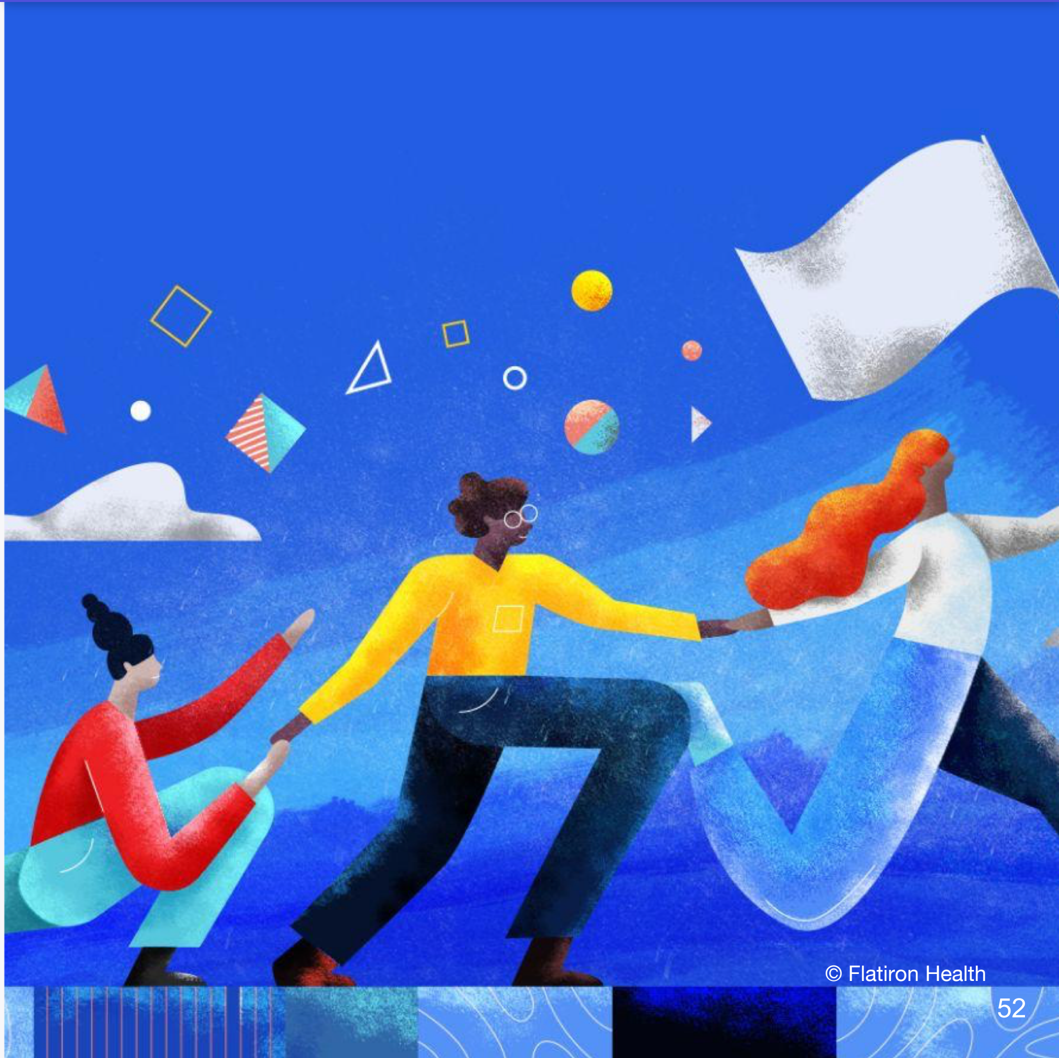
Models must be fair

Potential Negative Outcome

Model performs poorly among certain subpopulations resulting in inadvertent exclusion of historically marginalized populations

Solutions

- Training data should balance diversity and representativeness of target population
- Model training and testing data should include enough examples from select subgroups



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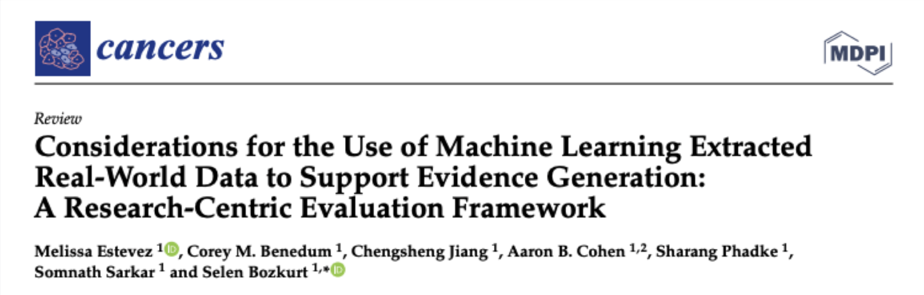
Models must be holistically and transparently evaluated


cancers

MDPI

Review

Considerations for the Use of Machine Learning Extracted Real-World Data to Support Evidence Generation: A Research-Centric Evaluation Framework

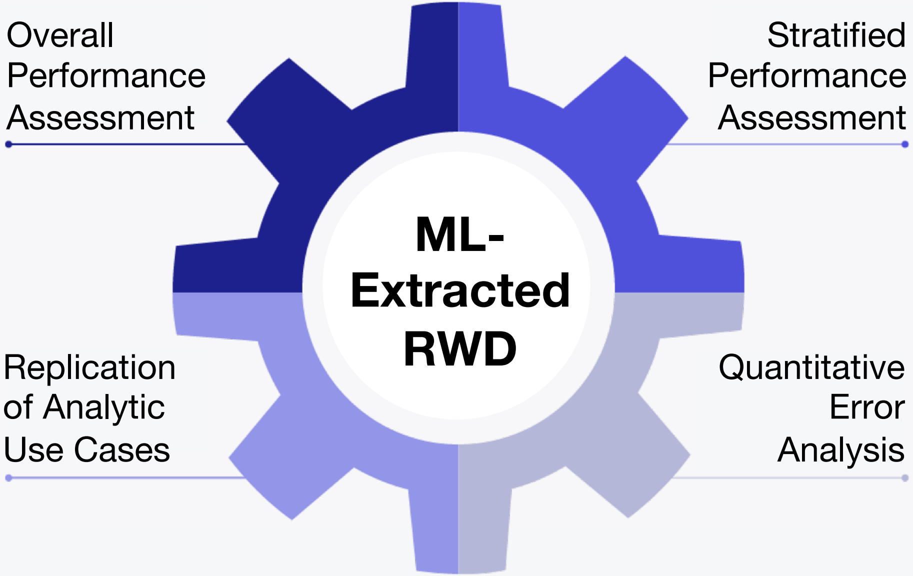
Melissa Estevez [1], Corey M. Benedum [1], Chengsheng Jiang [1], Aaron B. Cohen [1,2], Sharang Phadke [1], Somnath Sarkar [1] and Selen Bozkurt [1,*]

Potential Negative Outcome

Model errors may lead to biased study results and incorrect decisions / analytic conclusions.

Solutions

- Evaluate ML models and ML generated RWD
- Quantitative bias analyses and other bias correction methods



Presentation of Flatiron Health's replication of analytic use cases:

Nov 8, 15:00: Sondhi et al. Can ML-Extracted Variables Reproduce Real World Comparative Effectiveness Results From Expert-Abstracted Data? A Case Study in Metastatic Non-Small Cell Lung Cancer Treatment (**Poster RWD112**)

Nov 9, 10:00: Benedum et al. Machine Learning-Accelerated Outcomes Research: A Real-World Case Study of Biomarker-Associated Overall Survival in Oncology (**Session 314: Applications of Machine Learning and Artificial Intelligence in Real-World Studies**)

Poll Question

What would be the main barrier to adoption if you had access to ML-extracted data for HEOR?

1. Concerns of data quality
2. Explainability / interpretability of models
3. Lack of formal regulatory guidance
4. Other barriers
5. I am already an ML-extracted data user

Thank you

Additional Collaborators: Blythe Adamson, Aaron B. Cohen, Melissa Estevez, Erin Fidyk, Sheila Nemeth

Corey Benedum

Quantitative Scientist

Machine Learning

Flatiron Health

@DrCoreyBenedum

coreybenedum

IMPROVING MEDICAL DECISION MAKING: EVIDENCE AND UNCERTAINTY CONSIDERATIONS

Natalia Kunst, PhD

University of Oslo, Norway
Yale University Schools of Public Health and Medicine, USA
The Center for Healthcare Research in Pediatrics (CHeRP), Harvard Medical School, USA

Yale School of Public Health

COPPER

CHeRP | CENTER FOR HEALTHCARE RESEARCH IN PEDIATRICS

Natalia.kunst@medisin.uio.no
@NataliaKunst

MEDICAL DECISION MAKING

Medical decision making

Li M and Chapman GB (2020). Medical Decision Making. In The Wiley Encyclopedia of Health Psychology (eds K Sweeny, ML Robbins and LM Cohen).

MEDICAL DECISION MAKING

Trade-offs

Medical decision making

Li M and Chapman GB (2020). Medical Decision Making. In The Wiley Encyclopedia of Health Psychology (eds K Sweeny, ML Robbins and LM Cohen).

MEDICAL DECISION MAKING

Prognoses about future outcomes

Trade-offs

Medical decision making

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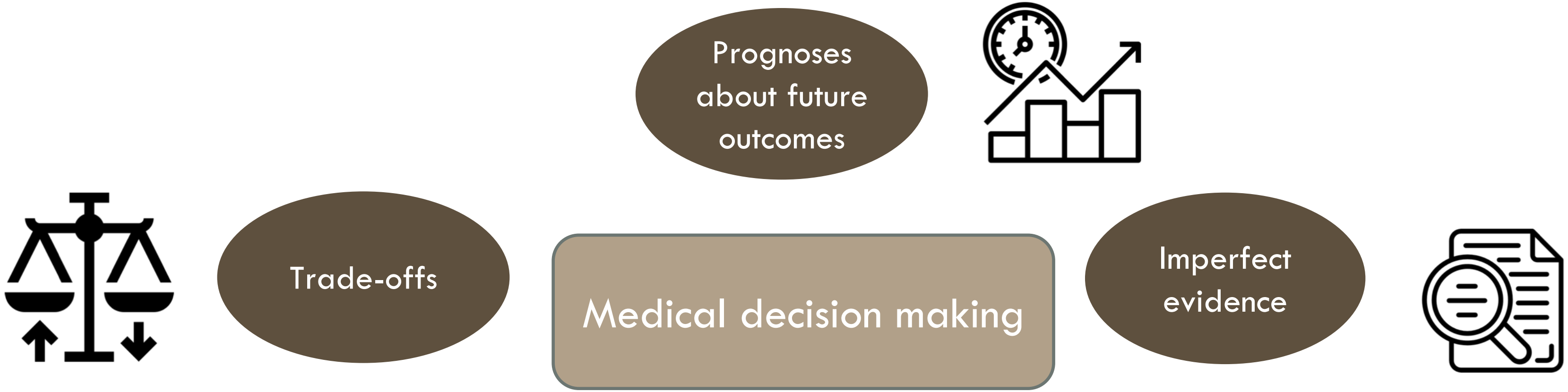
MEDICAL DECISION MAKING



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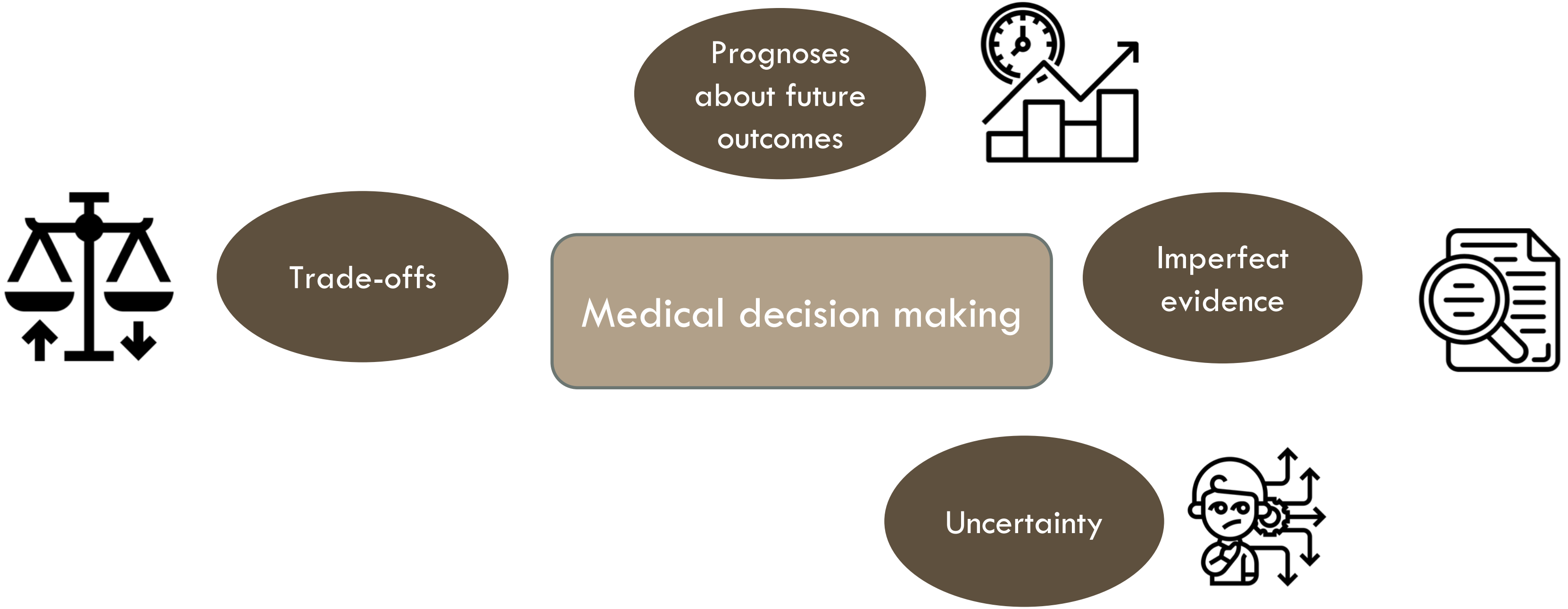
MEDICAL DECISION MAKING



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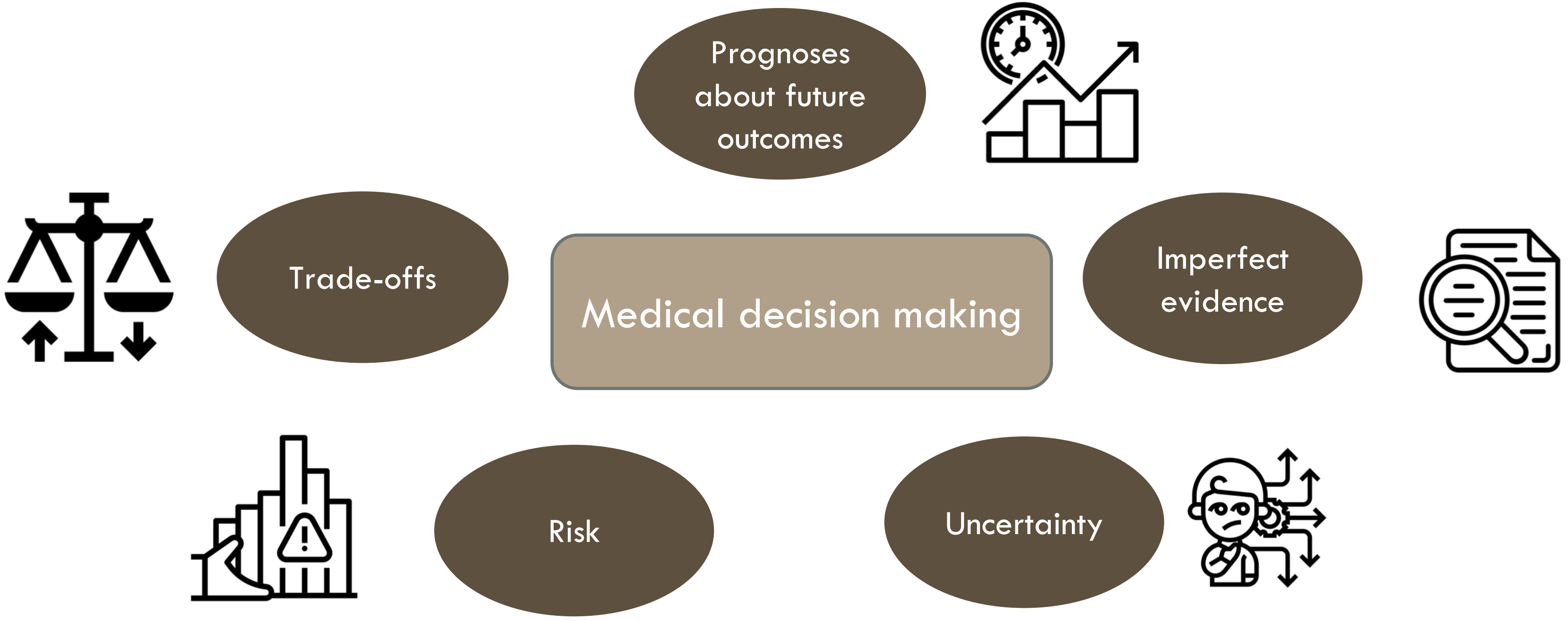
MEDICAL DECISION MAKING



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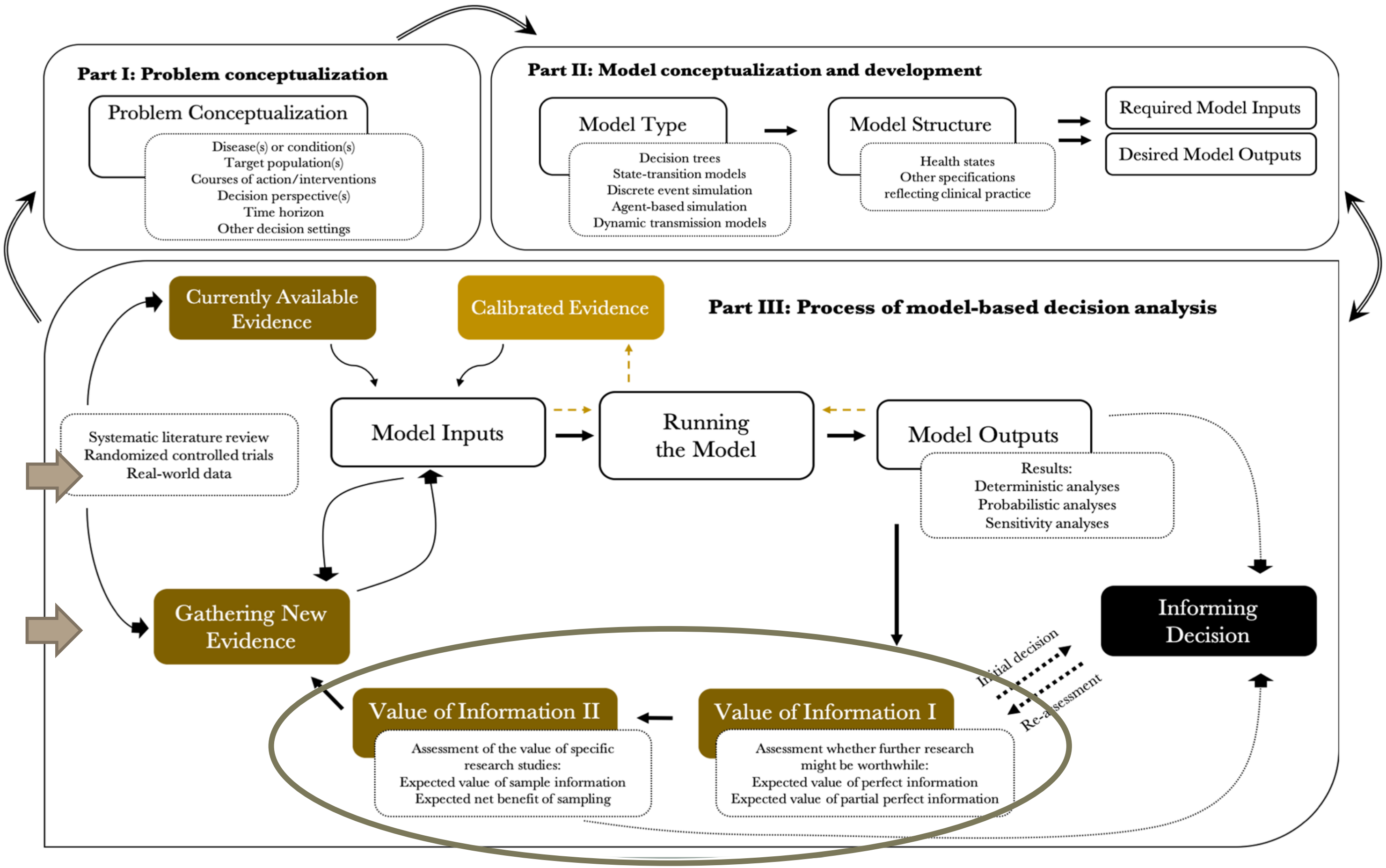
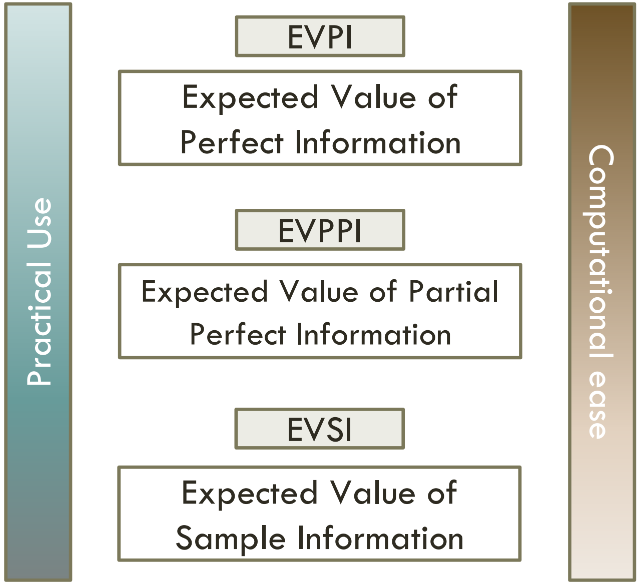

Part I: Problem conceptualization
Problem Conceptualization
Disease(s) or condition(s)
Target population(s)
Courses of action/interventions
Decision perspective(s)
Time horizon
Other decision settings
Part II: Model conceptualization and development
Model Type
Decision trees
State-transition models
Discrete event simulation
Agent-based simulation
Dynamic transmission models
Model Structure
Health states
Other specifications reflecting clinical practice
Required Model Inputs
Desired Model Outputs
Part III: Process of model-based decision analysis
Currently Available Evidence
Calibrated Evidence
Systematic literature review
Randomized controlled trials
Real-world data
Model Inputs
Running the Model
Model Outputs
Results:
Deterministic analyses
Probabilistic analyses
Sensitivity analyses
Gathering New Evidence
Informing Decision
Initial decision
Re-assessment
Value of Information II
Assessment of the value of specific research studies:
Expected value of sample information
Expected net benefit of sampling
Value of Information I
Assessment whether further research might be worthwhile:
Expected value of perfect information
Expected value of partial perfect information

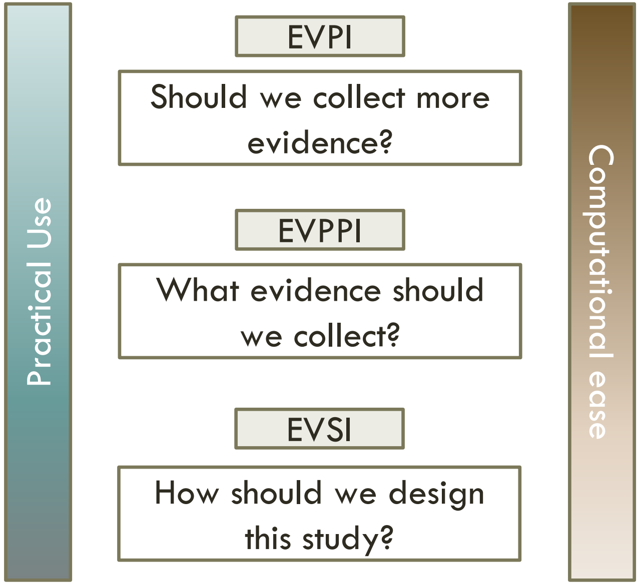
VALUE OF INFORMATION

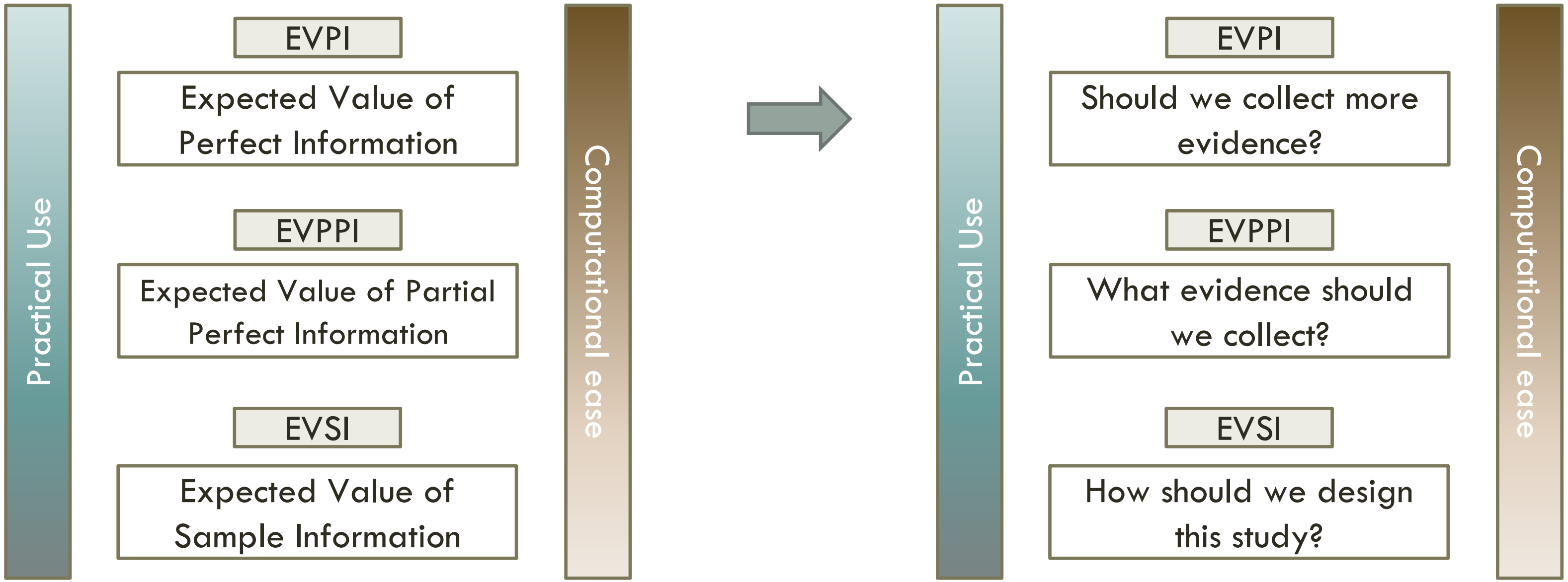
- Uncertainty in every decision
- There's a probability of making the wrong decision
- What are the consequences of making the wrong decision?
  - Costs?
  - Forgone benefits?
- Size of population being affected by the decision

VALUE OF INFORMATION

- **How likely** we are making the wrong decision and **how bad** it is to make the wrong decision
  - Uncertainty regarding our model parameters driven by the limited amount of information
- **Cost** of uncertainty (i.e., expected loss based on current information)
  - There is an opportunity cost in the sense that we expect to have made a better decision had we had additional information/greater certainty
- **Expected benefit** of research
  - How valuable it is to collect additional evidence that enables us to reduce our uncertainty about the parameters


Practical Use
EVPI
Expected Value of Perfect Information
EVPPI
Expected Value of Partial Perfect Information
EVSI
Expected Value of Sample Information
Computational ease


Practical Use
EVPI
Should we collect more evidence?
EVPPI
What evidence should we collect?
EVSI
How should we design this study?
Computational ease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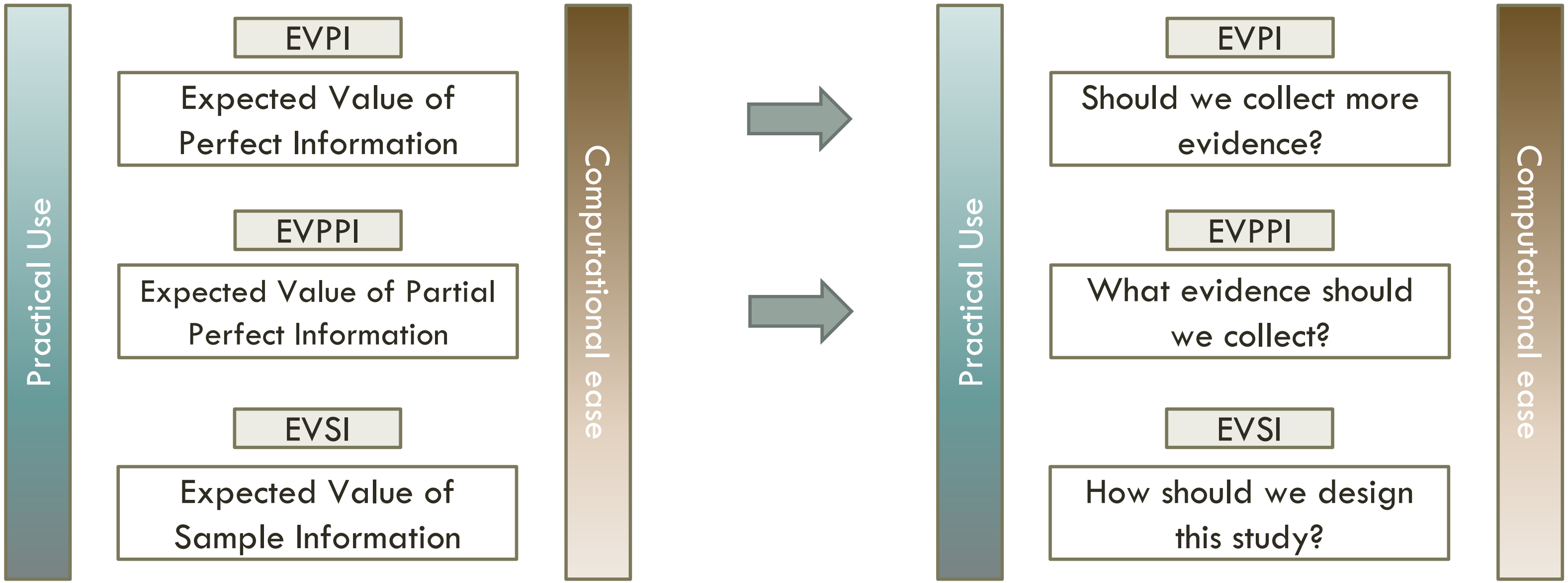
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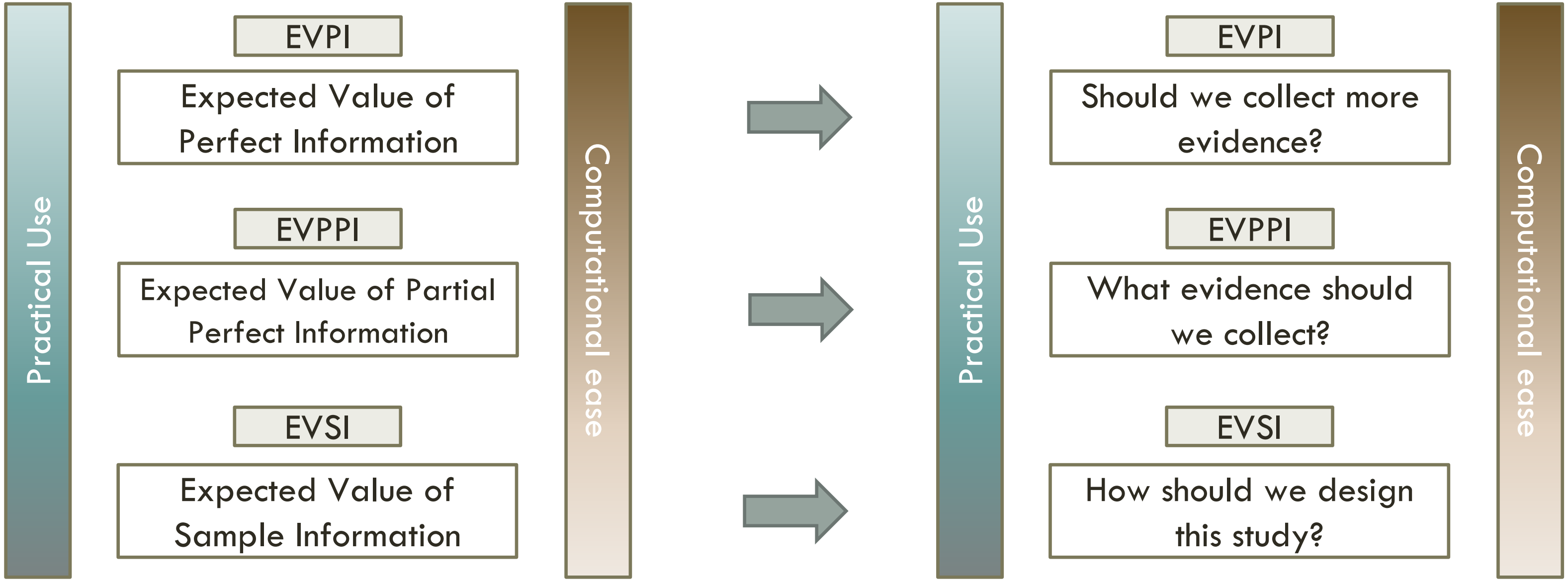
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PARAMETER UNCERTAINTY AND POTENTIAL BIAS

- Populating the model inputs with **appropriate** and **relevant evidence** is necessary to ensure **model credibility**
- Sometimes the **existing evidence** may be **insufficient** to inform some of the relevant model inputs, thereby reducing or inhibiting the model's usefulness
- As indicated by the ISPOR VOI Task Force, when the **risk of bias** or **appropriate technique** for data analysis is **unclear**, the **existing guidelines** to aid characterization of uncertainty about **methodological choice** should be followed. These include:
  - Bilcke J. et al. Accounting for Methodological, Structural, and Parameter Uncertainty in Decision-Analytic Models: A Practical Guide. Med Decis Making. 2011; 31: 675-692
  - Jackson C.H. et al. Structural and parameter uncertainty in Bayesian cost-effectiveness models. J R Stat Soc Ser C Appl Stat. 2010; 59: 233-253

GATHERING NEW EVIDENCE TO POPULATE THE MODEL

CANCER EPIDEMIOLOGY, BIOMARKERS & PREVENTION | RESEARCH ARTICLE

Estimating Population-Based Recurrence Rates of Colorectal Cancer over Time in the United States

Natalia Kunst[1,2,3,4], Fernando Alarid-Escudero[5], Eline Aas[1], Veerle M.H. Coupé[3], Deborah Schrag[6], and Karen M. Kuntz[7]

ABSTRACT

Background: Population-based metastatic recurrence rates for patients diagnosed with nonmetastatic colorectal cancer cannot be estimated directly from population-based cancer registries because recurrence information is not reported. We derived population-based colorectal cancer recurrence rates using disease-specific survival data based on our understanding of the colorectal cancer recurrence-death process.

Methods: We used a statistical continuous-time multistate survival model to derive population-based annual colorectal cancer recurrence rates from 6 months to 10 years after colorectal cancer diagnosis using relative survival data from the Surveillance, Epidemiology, and End Results Program. The model was based on the assumption that, after 6 months of diagnosis, all colorectal cancer–related deaths occur only in patients who experience a metastatic recurrence first, and that the annual colorectal cancer–specific death rate among patients with recurrence was the same as in those diagnosed with *de novo* metastatic disease. We allowed recurrence rates to vary by post-diagnosis time, age, stage, and location for two diagnostic time periods.

Results: In patients diagnosed in 1975–1984, annual recurrence rates 6 months to 5 years after diagnosis ranged from 0.054 to 0.060 in stage II colon cancer, 0.094 to 0.105 in stage II rectal cancer, and 0.146 to 0.177 in stage III colorectal cancer, depending on age. We found a statistically significant decrease in colorectal cancer recurrence among patients diagnosed in 1994–2003 compared with those diagnosed in 1975–1984 for 6 months to 5 years after diagnosis (hazard ratios between 0.43 and 0.70).

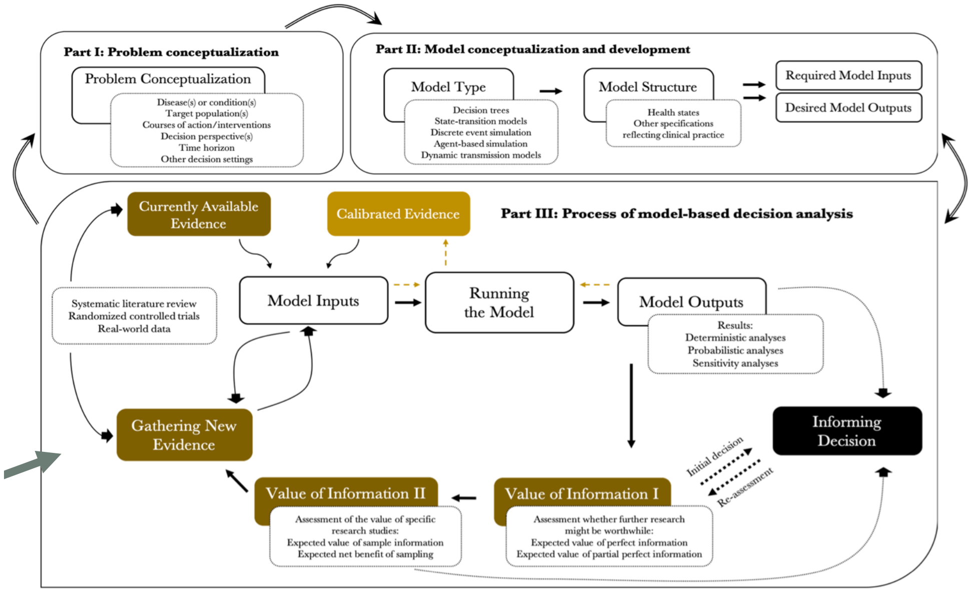
Conclusions: We derived population-based annual recurrence rates for up to 10 years after diagnosis using relative survival data.

Impact: Our estimates can be used in decision-analytic models to facilitate analyses of colorectal cancer interventions that are more generalizable.

Introduction

Improvements in colorectal cancer care have prolonged patient survival since 1975 (1, 2), but many patients still develop (metastatic) recurrence (3–5), from which patients can die from their disease. second cancer in that the former has the same type of cancer cells as the primary cancer, as opposed to the latter, which is unrelated to the primary cancer. The focus of our study was on distant recurrences.

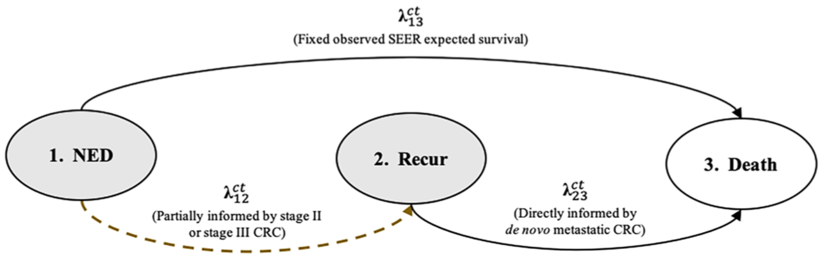
Current evidence on recurrence rates comes from randomized controlled trials (RCT) in which disease-free survival is a common



GATHERING NEW EVIDENCE TO POPULATE THE MODEL

Objective: To estimate of **population-based** annual recurrence rates of colorectal cancer considering two diagnosis periods: 1975-1984 and 1994-2003

Methods: Statistical **multistate survival modeling** techniques using data from the Surveillance, Epidemiology, and End Results (SEER) Program



NED: No evidence of disease

Recur: Symptomatic distant recurrence

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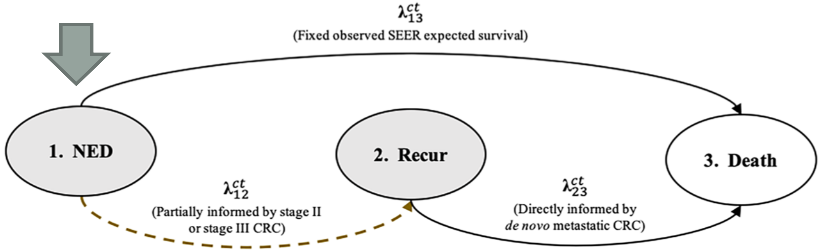

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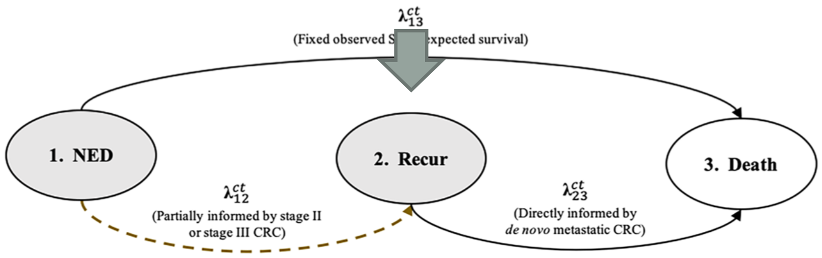

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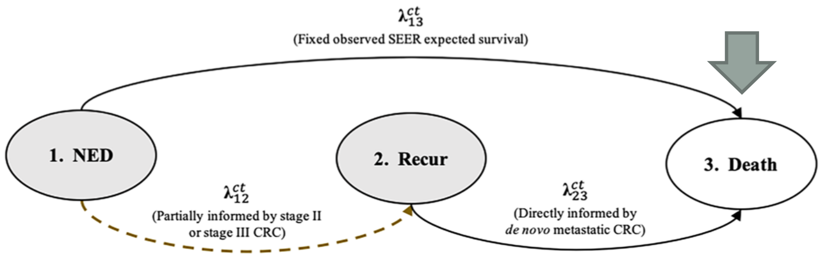

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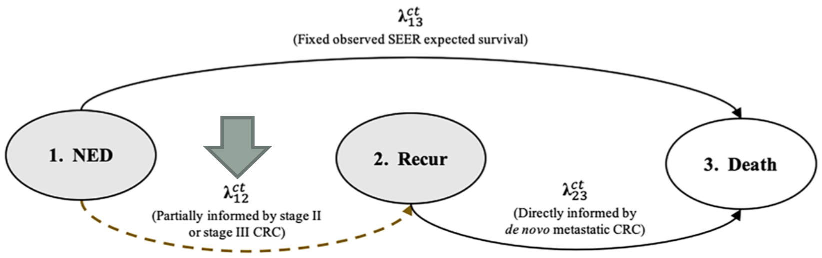

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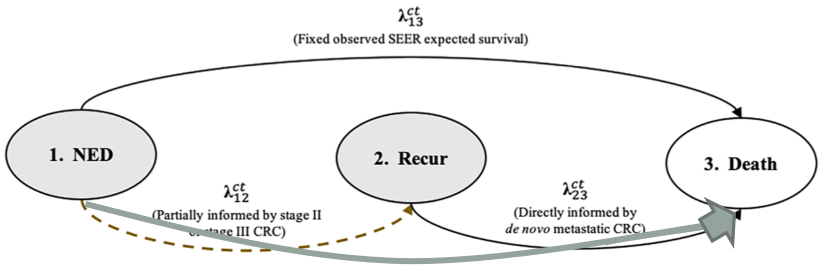

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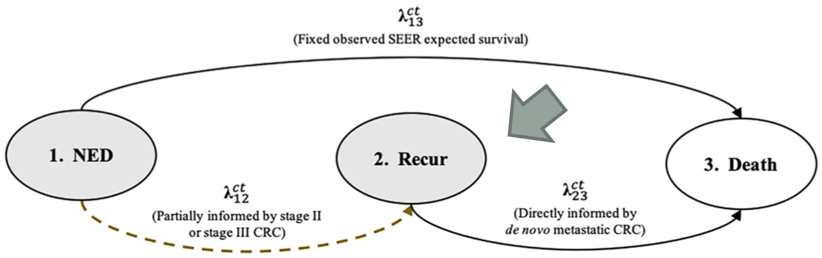

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GATHERING NEW EVIDENCE TO POPULATE THE MODEL

Results:

- The estimated **population-based** colorectal cancer recurrence rates were **higher** than the previously available trial-based estimates.
- The 10-year cumulative risk from **population-based** data vs. from trial-based estimates was:
  - Stage II colorectal cancer: **8.8-22.4% higher**
  - Stage III colorectal cancer: **3.9-18.4% higher**
- Potential **bias** in the **effectiveness and cost-effectiveness evaluation**

(FDA) REGULATORY DECISIONS

Accelerated approval decisions made with limited, preliminary data have:

- High uncertainty, and
- Significant downstream societal costs, if these decisions are made in error