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Treatment and outcomes in metastatic colorectal cancer (mCRC): A causal study design framework

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Disclosures

- Dixon R, Guzman M, Hopkins K, Lanes S, and Grabner M are employees of Carelon Research, a wholly owned subsidiary of Elevance Health.
- Grabner M is a shareholder of Elevance Health.
- Hill N and Dixon M are employees and shareholders of Bristol-Myers Squibb Company.
- Carelon Research received funding from Bristol-Myers Squibb (BMS) for the conduct of this study.

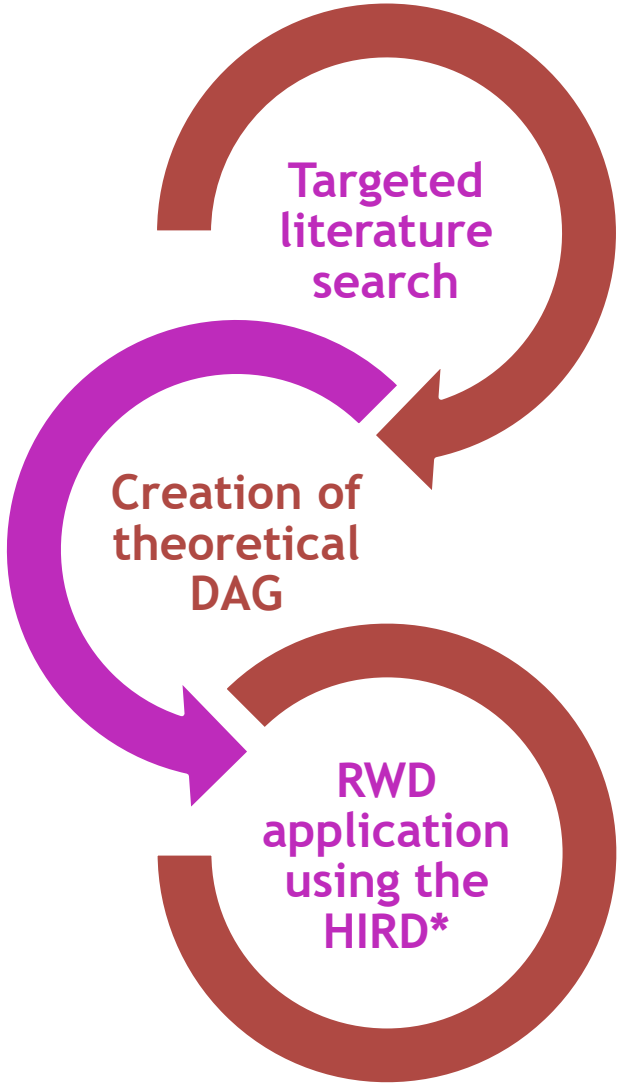
Overview

Study objective
To systematically develop a directed acyclic graph (DAG) to determine causal drivers and support comparative effectiveness research

Therapeutic area
1L metastatic colorectal cancer (mCRC)

Comparators
Immuno-oncology (IO) vs. historical standard of care chemotherapy

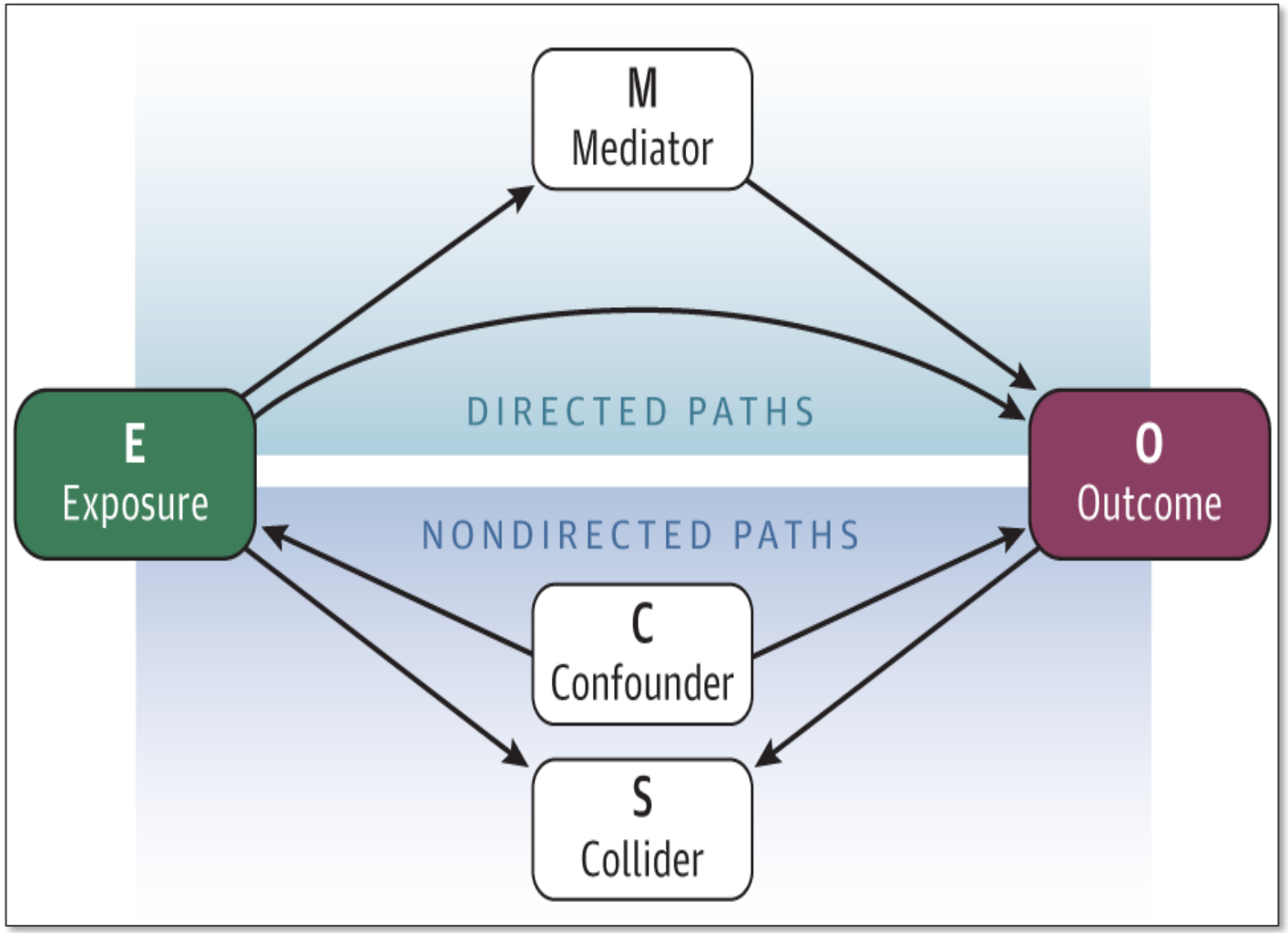
Outcome
Progression-free and overall survival



*Carelon Research's Healthcare Integrated Research Database (HIRD®)

What are DAGs?

- DAGs are graphical models used to encode assumptions about the data-generating process
- DAGs depict relationships between variables and are used to study causal relationships between exposures and outcomes
- The nodes/vertices correspond to variables of potential interest in a study
- Edges/arrows depict hypothesized direct causal effects



Lipsky AM, et al. JAMA. 2022;327(11):1083-1084

How DAGs are used and why we need them

- How:
  - Identifying appropriate adjustment strategies for causal analysis
  - Understanding confounding variables and their impact
  - Direct primary data analysis and DAG-based sensitivity analysis
- Why:
  - Systematic and transparent creation of DAGs improves evidence for regulatory submissions
    - FDA guidance on RWE analyses
    - EMA guidance on RWE analyses
    - Local HTA guidance
- So what:
  - Increased patient access to life-saving therapies

US FDA RWD/RWE Draft Guidance 2024; https://www.fda.gov/media/177128/download
Institute for Quality and Efficiency in Health Care (IQWiG); https://www.iqwig.de/en/projects/a19-43.html

DAGs creation process

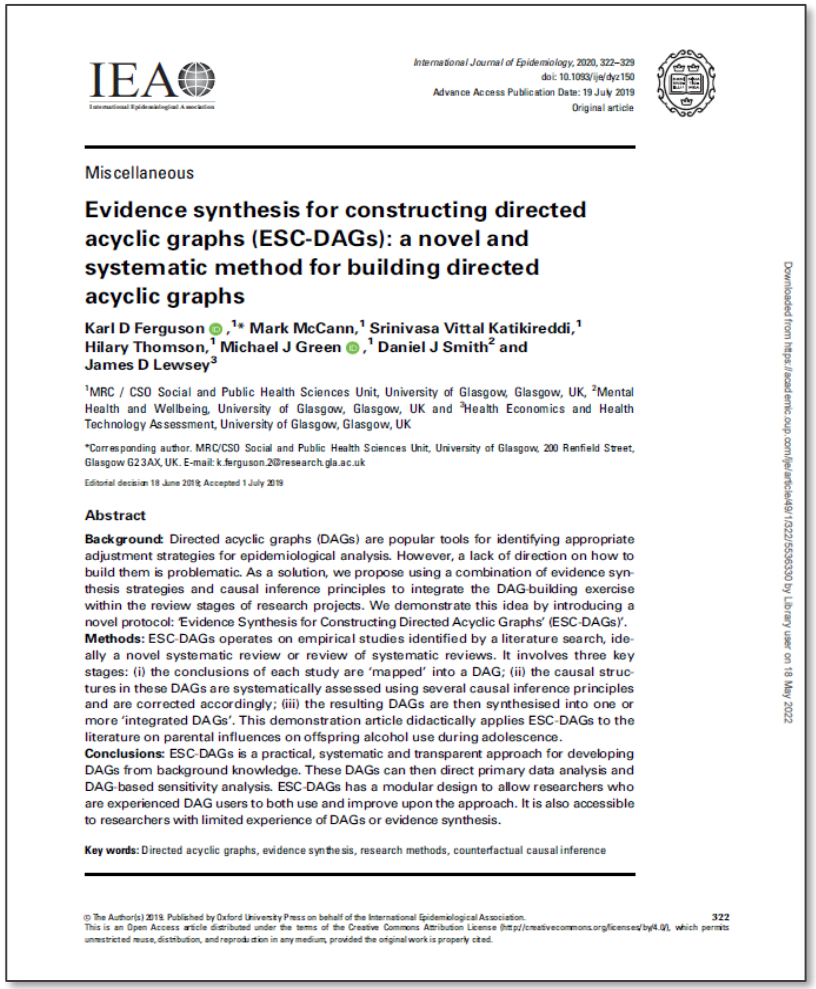
- DAGs were developed using evidence synthesis from three separate literature searches, causal inference principles, and expert opinion.
- We implemented 4 causal judgements to the potential arrows in our DAG:

    1) Temporality

    2) Face-validity

    3) Recourse to theory

    4) Counterfactual thought experiment



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Original article

Miscellaneous

Evidence synthesis for constructing directed acyclic graphs (ESC-DAGs): a novel and systematic method for building directed acyclic graphs

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Abstract

Background: Directed acyclic graphs (DAGs) are popular tools for identifying appropriate adjustment strategies for epidemiological analysis. However, a lack of direction on how to build them is problematic. As a solution, we propose using a combination of evidence synthesis strategies and causal inference principles to integrate the DAG-building exercise within the review stages of research projects. We demonstrate this idea by introducing a novel protocol: 'Evidence Synthesis for Constructing Directed Acyclic Graphs' (ESC-DAGs)'.
Methods: ESC-DAGs operates on empirical studies identified by a literature search, ideally a novel systematic review or review of systematic reviews. It involves three key stages: (i) the conclusions of each study are 'mapped' into a DAG; (ii) the causal structures in these DAGs are systematically assessed using several causal inference principles and are corrected accordingly; (iii) the resulting DAGs are then synthesised into one or more 'integrated DAGs'. This demonstration article didactically applies ESC-DAGs to the literature on parental influences on offspring alcohol use during adolescence.
Conclusions: ESC-DAGs is a practical, systematic and transparent approach for developing DAGs from background knowledge. These DAGs can then direct primary data analysis and DAG-based sensitivity analysis. ESC-DAGs has a modular design to allow researchers who are experienced DAG users to both use and improve upon the approach. It is also accessible to researchers with limited experience of DAGs or evidence synthesis.

Key words: Directed acyclic graphs, evidence synthesis, research methods, counterfactual causal inference

Ferguson KD, et al. Int J Epidemiol. 2020;49(1):322-329

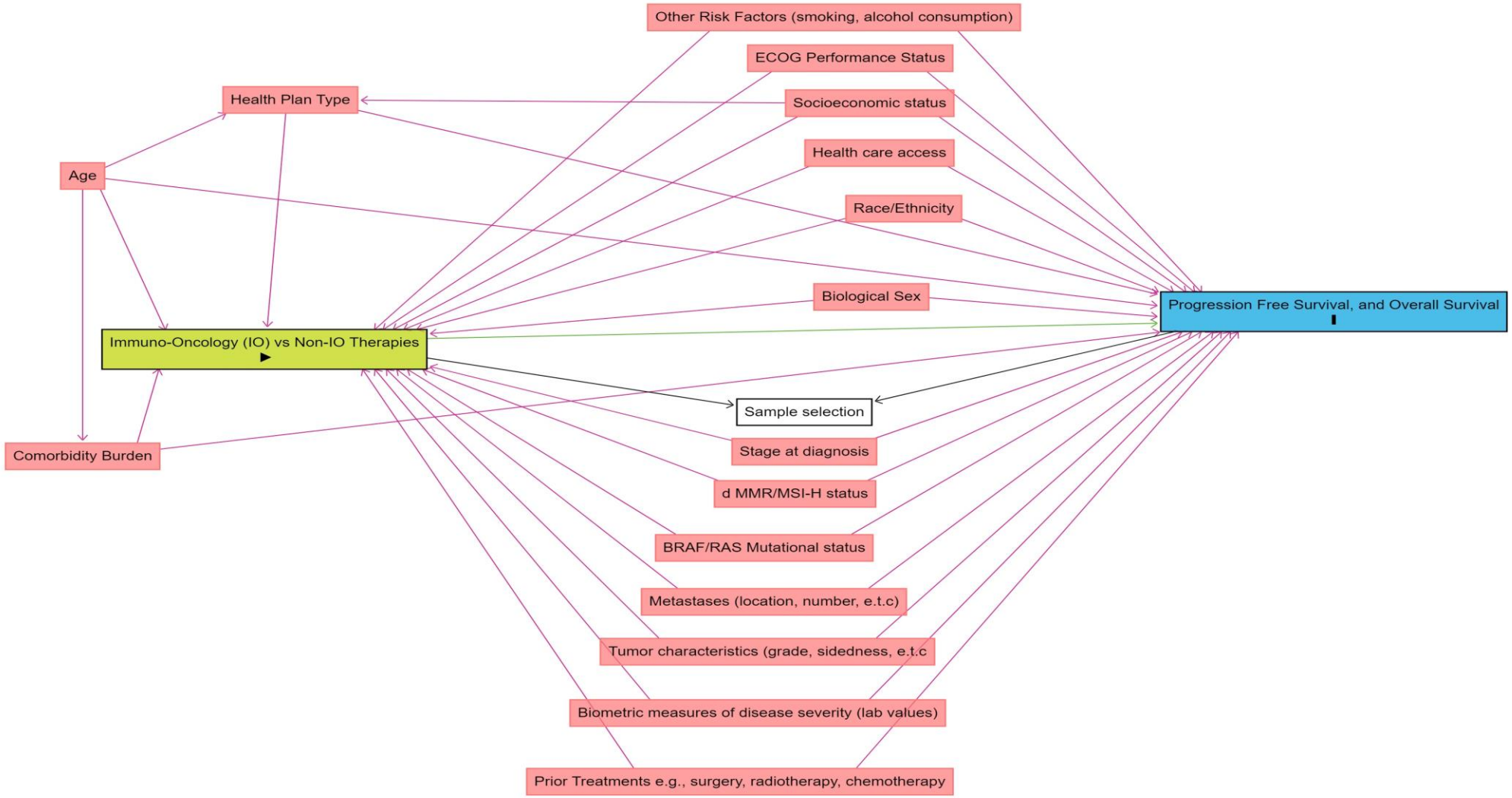
Causal judgements for creating theoretical DAG

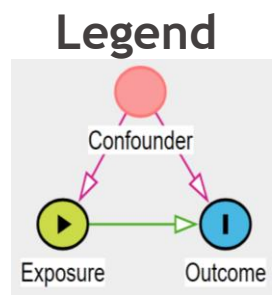
Potential confounders	Directed arrows	Temporality: *Does the posited cause precede effect?*	Face-validity: *Is the posited relationship plausible?*	Recourse to theory: *Is the posited relationship supported by theory?*	Counterfactual: *Is the posited relationship informed by a POF thought experiment?*
Age *(<65 years vs ≥65 years)*	Exposure (IO vs. non-IO therapies)	Yes	Yes	Yes	Yes
	Overall survival	Yes	Yes	Yes	Yes
ECOG performance status *(0 vs 1+)*	Exposure (IO vs. non-IO therapies)				
	Overall survival				
Prior chemotherapy *(Yes, vs No)*	Exposure (IO vs. non-IO therapies)				
	Overall survival				

ECOG, Eastern Cooperative Oncology Group; IO, immuno-oncology; POF, potential outcomes framework

Aparicio T, et al. Ann Oncol. 2016;27(1):121-127, Cremolini C, et al. Ann Oncol. 2018;29(7):1528-1534, Datta SS, et al. ecancer. 2019; (13). 913, Goey KKH, et al. Eur J Cancer. 2018;100:35-45

The theoretical DAG





Two targeted literature searches identified 94 RCTs and 22 RWD studies, from which 28 variables were extracted. These potential confounders (e.g., tumor characteristics, performance status, health care access) or colliders (e.g., sample selection) relative to the treatment-outcome relationship were built into the DAG. The theoretical DAG was created using the free online tool DAGitty (https://www.dagitty.net/); Textor J, et al. Int J Epidemiol. 2016;45(6):1887-1894

Using real-world data to refine the DAG

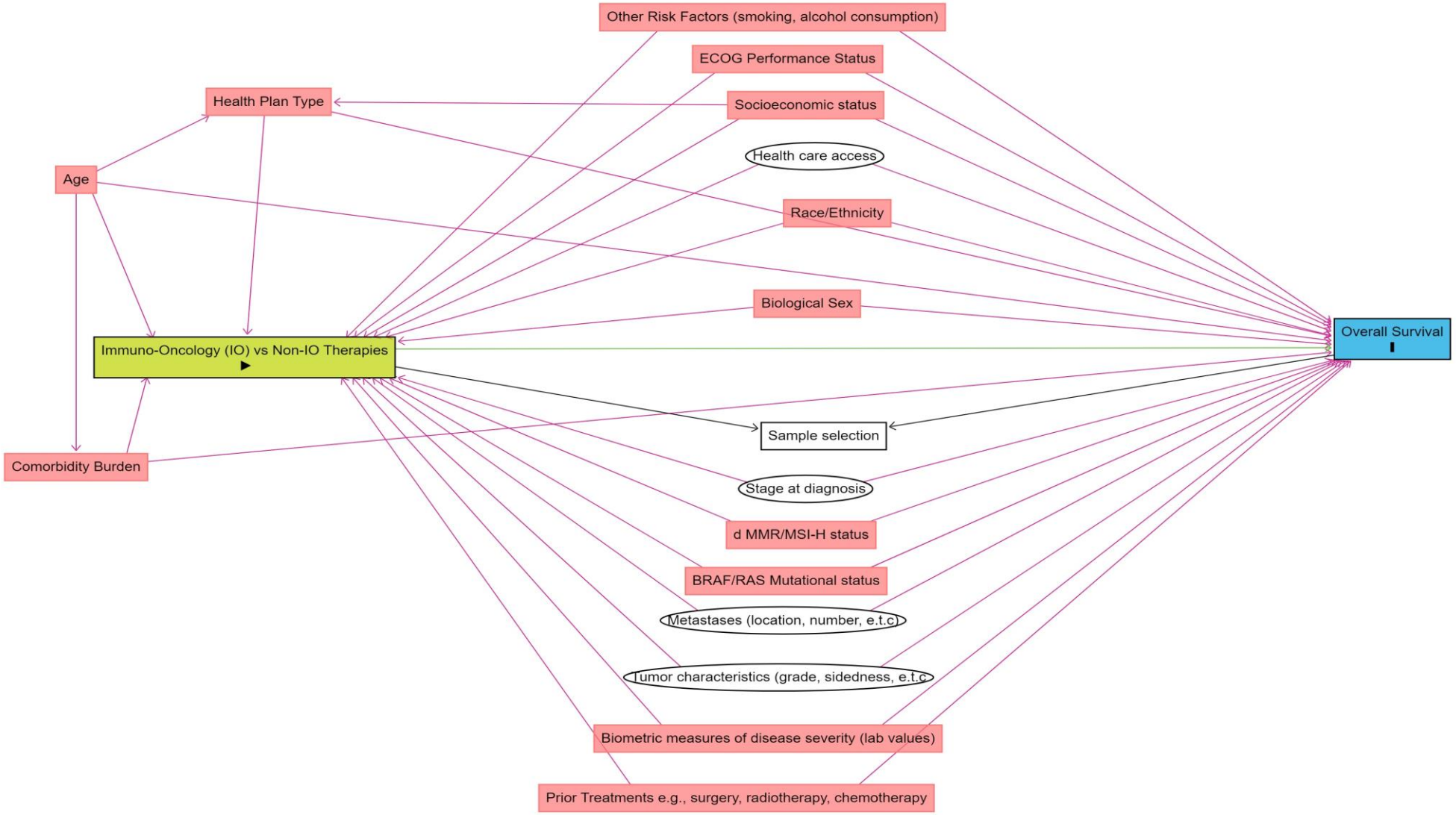
We applied our DAG to a real-world database to:

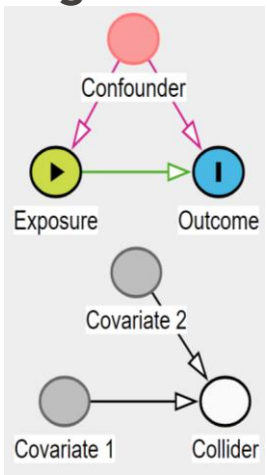
- **Distinguish** measured from unmeasured confounders (feasibility assessment)
- Calculate **bivariate associations** between exposure, outcome, and each confounder to assess the relative strength of the relationships: a weak relationship, combined with other supporting information, may allow researchers to remove arrows
- Calculate **DAG-implied unconditional independencies** between confounders: a strong relationship may indicate that arrows must be added

Source of real-world data

- The Healthcare Integrated Research Database (HIRD®) is a proprietary database curated and maintained by Carelon Research.
  - It is one of the largest, most comprehensive healthcare databases in the US, and contains health-related information for individuals currently and formerly enrolled in commercial, Medicare, and Medicaid health plans.
  - Contains integrated enrollment files, medical and Rx claims, social determinants of health, mortality, and clinical data updated monthly, with historical data available from January 2006.
- The HIRD has been used in >1,700 peer-reviewed publications since 2006.
- For more information, please refer to the HIRD Technical White Paper available via email to rwe@carelon.com.

Unmeasured variables in RWD (example)





Created using the free online tool DAGitty (https://www.dagitty.net/)

Textor J, et al. Int J Epidemiol. 2016;45(6):1887-1894

HIRD patient characteristics

Demographics and clinical characteristics of mCRC patients in the HIRD from 2014-01-01 to 2023-05-31			
	All patients	IO	Non-IO*
Sample size	9,046	213	8,866
Age (years), median (IQR)	57 (50-63)	60 (50-71)	57 (50-63)
Age ≥ 65 years, n (%)	1,795 (19.8%)	71 (33.3%)	1,730 (19.5%)
ECOG performance status grouping, n (%)			
0	2,890 (46.0%)	58 (32.6%)	2,842 (46.3%)
1	3,021 (48.1%)	104 (58.4%)	2,932 (47.8%)
2	330 (5.3%)	15 (8.4%)	317 (5.2%)
3	41 (0.65%)	<5	41 (0.67%)
4	<5	0	<5
Prior chemotherapy, n (%)	2,391 (26.4%)	55 (25.8%)	2,362 (26.6%)

ECOG, Eastern Cooperative Oncology Group; IO, immuno-oncology ; *IO and non-IO populations are not mutually exclusive. There are 33 patients in the non-IO cohort that also had a claim for an IO therapy in the 30 days pre/post mCRC case start.

Bivariate associations

Edge originates from	Edge terminates at	Sample size	Measure of association (odds ratio)	95% CI	p-value	Notes and interpretation
Age *(≥65 years vs. <65 years*)	Exposure (IO therapy vs non-IO therapies)	9046	2.35	1.74 – 3.16	<0.01	Strong evidence for relationship
	Overall Survival	9046	1.61	1.43 – 1.81	<0.01	Strong evidence for relationship
ECOG performance status *(0 vs 1+)*	Exposure (IO vs non-IO therapies)	6283	1.87	1.33 – 2.61	<0.01	30% Data Missing; Strong evidence for relationship
	Overall survival	6283	1.67	1.47 – 1.9	<0.01	30% Data Missing; Strong evidence for relationship
Prior chemotherapy *(Yes, vs No)*	Exposure (IO vs non-IO therapies)	9046	0.60	0.41 – 0.87	<0.05	Strong evidence for relationship
	Overall survival	9046	1.63	1.47 – 1.82	<0.01	Strong evidence for relationship

ECOG, Eastern Cooperative Oncology Group; IO, immuno-oncology

DAG-implied independencies

Variable	DAG-implied independency	Sample size	Measure of association (odds ratio)	95% CI	p-value	Notes and interpretation
ECOG performance status *(0 vs 1+)*	ECOG ⊥ Age*	6283	1.84	1.62 - 2.09	<0.01	strong evidence for relationship; older members much more likely to have worse ECOG. Causal directionality can go both ways
Prior chemotherapy (*Yes, vs No*)	Prior chemotherapy ⊥ Age	9046	0.94	0.83 – 1.05	0.27	Weak evidence for relationship

ECOG, Eastern Cooperative Oncology Group; *Age defined as binary variable (≥65 years vs. <65 years)

Study limitations

- The DAG does not address time-varying elements such as treatment changes and mediators (e.g., characteristics of the tumor and metastases after exposure).
- Age at treatment initiation was used to examine DAG-implied independencies; this exercise could be repeated for all covariates.
- We did not make changes to the DAG based on findings from the bivariate associations or the DAG-implied independency analysis for age.
- DAGs do not provide guidance on the appropriate functional form of the exposure-outcome relationship, how to deal with missing or misclassified data, how to quantify biases, or how to identify effect measure modifiers.

Conclusions

- Targeted literature searches and causal judgments identified 28 variables that could bias the IO/survival relationship in mCRC.
- The DAG distinguishes potential confounders that *should be controlled* from colliders that *should not be controlled*.
- The resulting DAG can assist in future comparative effectiveness research by providing a transparent framework for the hypothesized underlying causal relationships and choice of adjustment variables (e.g., using propensity score methods).
- Testing bivariate relationships and DAG-implied independencies using a real-world dataset such as the HIRD allows further refinements for a particular analysis in a specific data source.

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Questions & Answers

Please reach out with any questions and comments to: rwe@carelon.com