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Target Trials: A Gentle Introduction to Causal Inference Concepts for Clinicians

Core Center for Clinical Research
Clinical and Translational Research Incubator Seminar (CCCR-CTRIS)
Northwestern University
March 9, 2021
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Brief Overview

1. Introduction to **causal inference concepts**

2. **Target trials** to answer causal questions in observational data

3. An example: using **SEER-Medicare** for comparative effectiveness

Causal Inference

- **Goal:** To estimate the **causal effect** of an action (A) on an outcome (Y)

- **Everyone wants to do it.**
  - "Hard" sciences (biology, chemistry, physics, engineering) primarily use *experimentation*
  - "Soft" sciences (epidemiology, public health, economics, sociology) often turn to *observation*

Causal Inference

Not all questions are causal, but many are.

- Examples of **causal** questions
  - Does liver transplant surgery increase the life expectancy of individuals with cirrhosis?
  - Does receiving the MMR vaccine reduce the incidence of measles, mumps, and rubella in children under age 18?

- Examples of **non-causal** questions
  - How many people in the U.S. have early-onset dementia?
  - Does obesity in adulthood cause mental health problems in teenage years?

Causal Inference

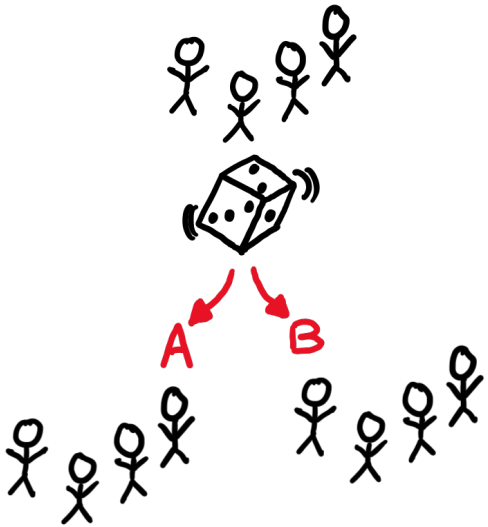
- **Our motivation: making decisions in medicine**
  - "Should I prescribe drug A or drug B as first-line chemotherapy to extend my patient's expected life?"
  - "If I implement this policy, will I reduce the disease burden on a population?"

- **Many of these questions can be answered using a well-designed randomized controlled trial (RCT)**
  - The RCT is considered the gold standard for **evidence generation** in medical decision making

Why are RCTs so great?

- **An imaginary perfect (vaccine) RCT**
  - Recruit n participants; randomize 1:1 to vaccine or placebo
  - Follow for a set period of time (e.g. 1 year); record outcome

- **Analyze according to the *Intention-to-Treat Principle***
  - Participants are analyzed according to the treatment they were assigned to



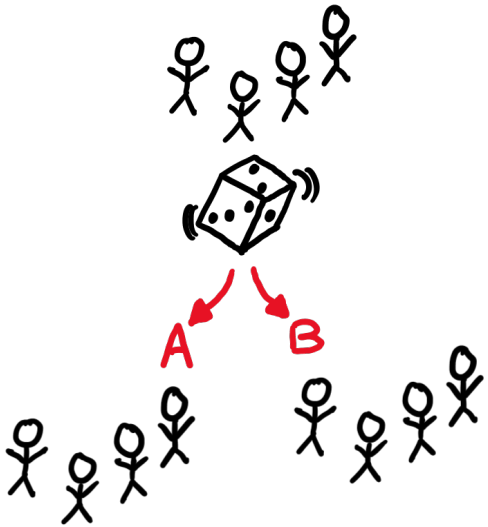
@EpiEllie

Why are RCTs so great?

- **An imaginary less-perfect (drug) RCT**
  - Recruit n participants; randomize 1:1 to taking drug A for 3 months or placebo
  - Follow for a set period of time (e.g. 1 year); record outcome

- **Can analyze according to the *Intention-to-Treat Principle***
  - Participants are analyzed according to the treatment they were assigned to

- What about adherence? **Consider *per-protocol* effects too**



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  - Consistency

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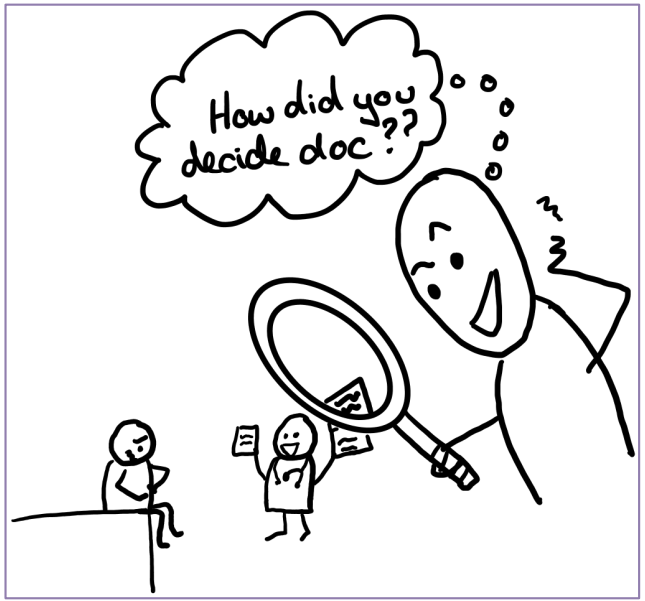
- What is **Exchangeability**?
  - No **unmeasured confounding**
    - All common causes of the treatment and outcome are known and measured in the data
  - No **selection bias**
    - We have not conditioned or restricted on a variable that is a common effect of the exposure and outcome (or outcome cause)



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- What is **positivity?**
  - There is non-zero probability of all levels of treatment for all types of individuals in our population

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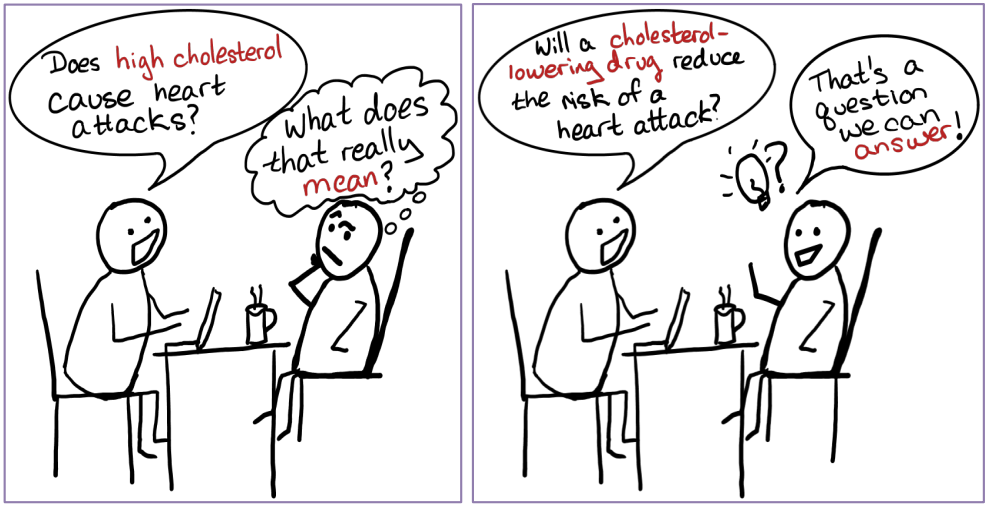

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- What is **consistency**?
  - Clear specification of treatment levels – can think of as:
    - Well-defined interventions
    - Well-defined causal questions

Why are RCTs so great for causal inference?

- **Causal inference relies on three main assumptions:**
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- **When we estimate intention-to-treat effects in RCTs, randomization becomes our "exposure"**
  - Randomization ensures no confounding at baseline for **treatment assignment**
  - Randomization also ensures positivity for **treatment assignment**
  - Randomization is a well-defined intervention
  - **Intention-to-treat analyses often give unbiased estimates of intention-to-treat effects!**

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- **Intention-to-treat analyses often give unbiased estimates of intention-to-treat effects**
  - Hypothetical vaccine trial

  - Hypothetical drug trial – we can't move quite so quickly
    - Treatment and loss to follow-up happen after randomization
    - Post-randomization events are not guaranteed to be unconfounded!

That said, there are barriers to conducting RCTs

- **$$$** - on average, conducting an RCT costs $12 million USD
- **Untimely** – studying long-term outcomes takes a long time (e.g. strategies for timing of colorectal cancer screening)
- **Unethical** – you probability believe smoking causes lung cancer, but where did that evidence come from?

So, what can you do instead?

Use observational data to answer our questions

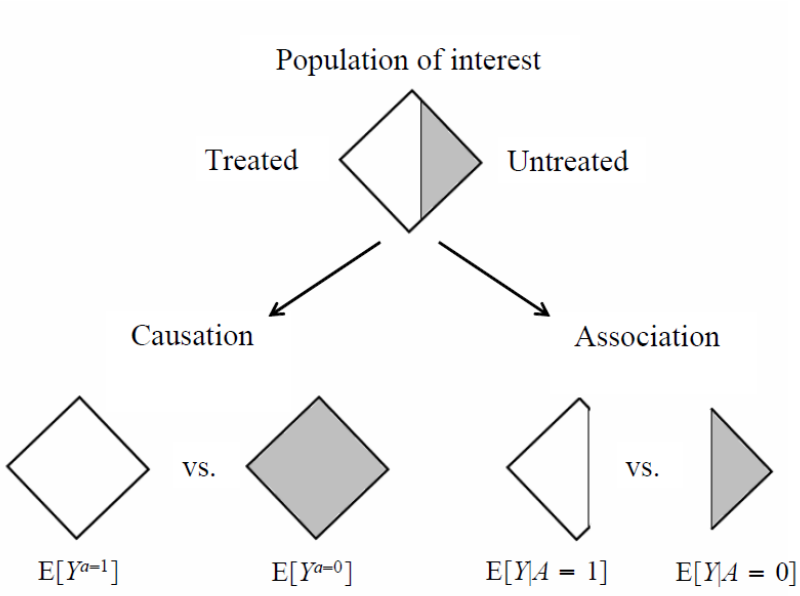
- Two categories:
  - Classic epidemiologic studies: cohort studies, case-control studies
  - **"Found"** data: electronic medical records, administrative claims databases, national registers

- Big picture: We want to conceptualize observational studies designed in found data as **conditionally randomized experiments**

- **Caveat:** <u>These secondary data analyses are not our preferred choice.</u>

When do associational measures equal causal measures?

To fully answer this, we must combine causal knowledge with statistical modeling!



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- **Selection bias**. This can occur:
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- **Selection bias**. This can occur:
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- **Measurement error**. This may occur in the:
  - Outcome variable
  - Treatment/exposure variable
  - Confounders

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- Confounding is everywhere
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    - Cause and effect? Teen moms do not raise kids as well as older moms
    - Confounding? Teen moms tend to live in more disadvantaged environments than older moms
  - "Educated people earn more money."
    - Cause and effect? Formal education teaches skills and provides a contact network to access better jobs
    - Confounding? Highly motivated, well connected, privileged people are more likely to seek education

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- **Negative controls** can provide some reassurance that you aren't missing something monumental
  - Note: the treatment - negative control outcome relationship should have similar confounders as the treatment – outcome relationship
- **Instrumental variable analysis**
  - Local average treatment effect doesn't always approximate average treatment effect
  - Most instruments are imperfect; best example is randomization

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- **Instrumental variable analysis**
  - Local average treatment effect doesn't always approximate average treatment effect
  - Most instruments are imperfect; best example is randomization
- That said, **unmeasured confounding is often not the biggest issue with observational studies**
  - Selection bias; Assignment of baseline time for analysis

Other issues for causal inference

- Even if we manage to avoid bias due to confounding, selection bias, and measurement error, we may encounter other issues.
- Estimates may not be **transportable** to other populations
  - No external validity
- Even if the estimate is unbiased and transportable, it may be too **unstable**
  - Because the effective sample size is too small
  - Use statistical methods to quantify the role of chance
- The model may be **misspecified**.
  - The choice of parametric model to represent the confounding may impact study results
  - Curse of dimensionality!

Why do we need to be so careful?

Classic example: hormone replacement therapy in post-menopausal women and coronary heart disease (CHD)

- Women's Health Initiative (WHI): randomized experiment, found **20% increased risk** of CHD in initiators compared with non-initiators (Manson et al., *NEJM* 2003)

- Observational study: **>30% lower risk** in current users compared with never users in Nurses' Health Study (Grodstein et al., *J Women's Health* 2006)

Why do we need to be so careful?

Classic example: hormone replacement therapy in post-menopausal women and coronary heart disease (CHD)

- What went wrong?
  - Unable to control for confounding?
  - **Asked different questions**

- When re-analyzed Nurses' Health Study to compare *incident* users vs. nonusers, found similar estimates to initial WHI findings (Hernán et al., *Epidemiology* 2008)

Dr. Miguel Hernán's 2-step Algorithm for Causal Inference

Hernán & Robins. (2016) *American Journal of Epidemiology* doi:10.1093/aje/kwv254

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Step 1. **Ask** a causal question.

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Thought experiment: Imagine a *hypothetical* randomized trial that we would prefer to conduct and analyze: the **target trial**

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Then we have a choice:

1. Go into the world and secure funding to conduct the target trial
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Caveat: We can never hope to emulate a tightly monitored, placebo-controlled RCT using observational data – emulate *pragmatic* trials instead

Components of the Target Trial

Target trial (hypothetical)	
Eligibility criteria	
Treatment strategies	
Assignment procedures	
Follow-up Period	
Outcome	
Causal contrast(s) of interest	
Analysis plan	

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Example: Comparative Effectiveness in SEER-Medicare

- The Surveillance, Epidemiology, and End Results (SEER) database was linked with Medicare beginning in the early 1990s

SEER Contains:	Medicare Contains:
• Demographics • Tumor characteristics • Some genetic factors	• Treatment history from diagnosis to present • Comorbities • Alternate therapies

- Still have unmeasured confounding – cannot capture physician's judgment or patient preferences towards treatment

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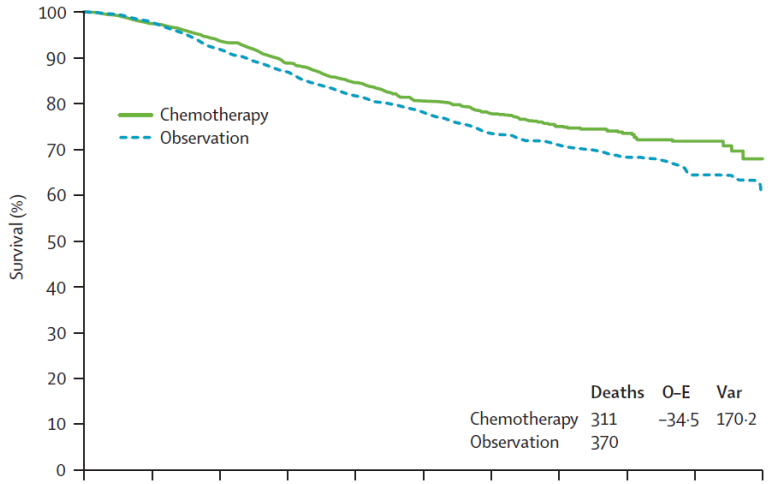
- Still have unmeasured confounding – cannot capture physician's judgment or patient preferences towards treatment
- How can we know whether SEER-Medicare can be used to answer comparative effectiveness questions? **Benchmark to an existing pragmatic RCT**

Treating Stage II Colorectal Cancer

- Surgery with curative intent is first line treatment for stage I, II, and III colorectal cancer
- Physicians disagree about using adjuvant fluorouracil-based chemotherapy for individuals with stage II colorectal cancer
- QUASAR Collaborative group ran a **pragmatic RCT** to test this hypothesis

Overall HR	Ages 70+ HR
0.82 (0.70 to 0.95)	1.02 (0.70 to 1.48)



QUASAR Collaborative group. (2007) *The Lancet* doi:10.1016/S0140-6736(07)61866-2

Target Trial: *Who/When?*

	Target trial (hypothetical)	Emulation in SEER-Medicare ("found" data)
Eligibility criteria	• Histologic diagnosis of stage II colorectal cancer (node negative) between January 2008 and December 2012 • Evidence of complete resection of colon or rectal cancer with "uncertain indication for chemotherapy" • No history of prior cancer (except non-melanoma skin cancer) • No prior chemotherapy • Medicare beneficiaries ages 66 years or older who aged into Medicare and were continuously enrolled in Medicare Parts A & B and not an HMO for 12 months prior to diagnosis	

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Petito et al. (2020) *JAMA Network Open* doi:10.1001/jamanetworkopen.2020.0452

Target Trial: *Who/When?*

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Target Trial: *What?*

	Target trial (hypothetical)	Emulation in SEER-Medicare ("found" data)
Treatment Strategies	• **Strategy A**: Initiate any dose of fluorouracil as first-line treatment within the grace period: up to 3 months after post-surgery hospital discharge • **Strategy B**: Do not initiate any chemotherapy within the grace period Under both strategies, leave decision to discontinue fluorouracil to physician and patient. Patients can receive any additional therapies to supplement fluororuracil	
Outcome	Death from any cause certified by a physician, reported to Medicare and confirmed by the National Death Index within 5 years of beginning of follow-up	

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Target Trial: *What?*

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Outcome	Death from any cause certified by a physician, reported to Medicare and confirmed by the National Death Index within 5 years of beginning of follow-up	Same

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Target Trial: *What?*

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Treatment Assignment	Patients are randomized to either treatment strategy at baseline and *are aware of the strategy they are assigned to.*	

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Target Trial: *What?*

	Target trial (hypothetical)	Emulation in SEER-Medicare ("found" data)
Treatment Assignment	Patients are randomized to either treatment strategy at baseline and *are aware of the strategy they are assigned to.*	Emulate randomization by adjusting our estimates for baseline confounders: • Demographics • Tumor/surgery characteristics: time between diagnosis and surgery, hospitalization >14 days after surgery, preoperative radiotherapy, rectal/colon cancer, tumor grade, colonoscopy, abdominal or pelvic CT scan • Comorbidities: Anemia, abdominal distention, abnormal weight loss, asthenia, change in bowel movements, constipation, diarrhea, irritable bowel syndrome, # emergency department visits, Charlson comorbidity index

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Target Trial: *When?*

	Target trial (hypothetical)	Emulation in SEER-Medicare ("found" data)

Follow-up Period	• Follow-up begins at **time zero**, when an individual meets all eligibility criteria
	  • When an individual is randomly assigned to one of the treatment strategies
	  • Occurs on date patient is discharged from the hospital after their surgery
	• Follow-up ends at the earliest of
	  • Death
	  • Loss to follow-up (loss of enrollment in Medicare Parts A or B; enrollment in an HMO)
	  • Administrative end of follow-up (5 years after time zero or 12/31/2013)	

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		Same

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Target Trial: How?

	Target trial (hypothetical)	Emulation in SEER-Medicare ("found" data)
Causal Contrast	• **Intention-to-treat effect**: effect of being randomized to the strategies at baseline, regardless of whether the individuals adhere to them during follow-up • **Per-protocol effect**: effect of adhering to the strategies (as defined in the protocol) during follow-up	

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Target Trial: How?

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Causal Contrast	• **Intention-to-treat effect**: effect of being randomized to the strategies at baseline, regardless of whether the individuals adhere to them during follow-up • **Per-protocol effect**: effect of adhering to the strategies (as defined in the protocol) during follow-up	Per-protocol effect only

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Target Trial: How?

	Target trial (hypothetical)	Emulation in SEER-Medicare ("found" data)
Statistical Analysis	Per-protocol effect: use randomization as IV • **Censor** individuals when they deviate from their assigned protocol • Use a discrete hazards (pooled logistic) model in the censored data to estimate **absolute risks** • Standardize the above model to calculate an average **hazard ratio** • To adjust for potential selection bias, **inverse probability weight** the discrete hazards model to adjust for post-baseline prognostic factors associated with adherence to treatment strategy • **Non-parametric bootstrap** for 95% CIs	

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Target Trial: How?

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Statistical Analysis	Per-protocol effect: **use randomization as IV** • **Censor** individuals when they deviate from their assigned protocol • Use a discrete hazards (pooled logistic) model in the censored data to estimate **absolute risks** • Standardize the above model to calculate an average **hazard ratio** • To adjust for potential selection bias, **inverse probability weight** the discrete hazards model to adjust for post-baseline prognostic factors associated with adherence to treatment strategy • **Non-parametric bootstrap** for 95% CIs	Two choice for analyses that respect the definition of time zero: • Randomly assign individuals who die or are censored in the grace period before fluorouracil initiation to treatment strategy • Clone all individuals, assign one clone to each strategy Then conduct analysis as for hypothetical target trial

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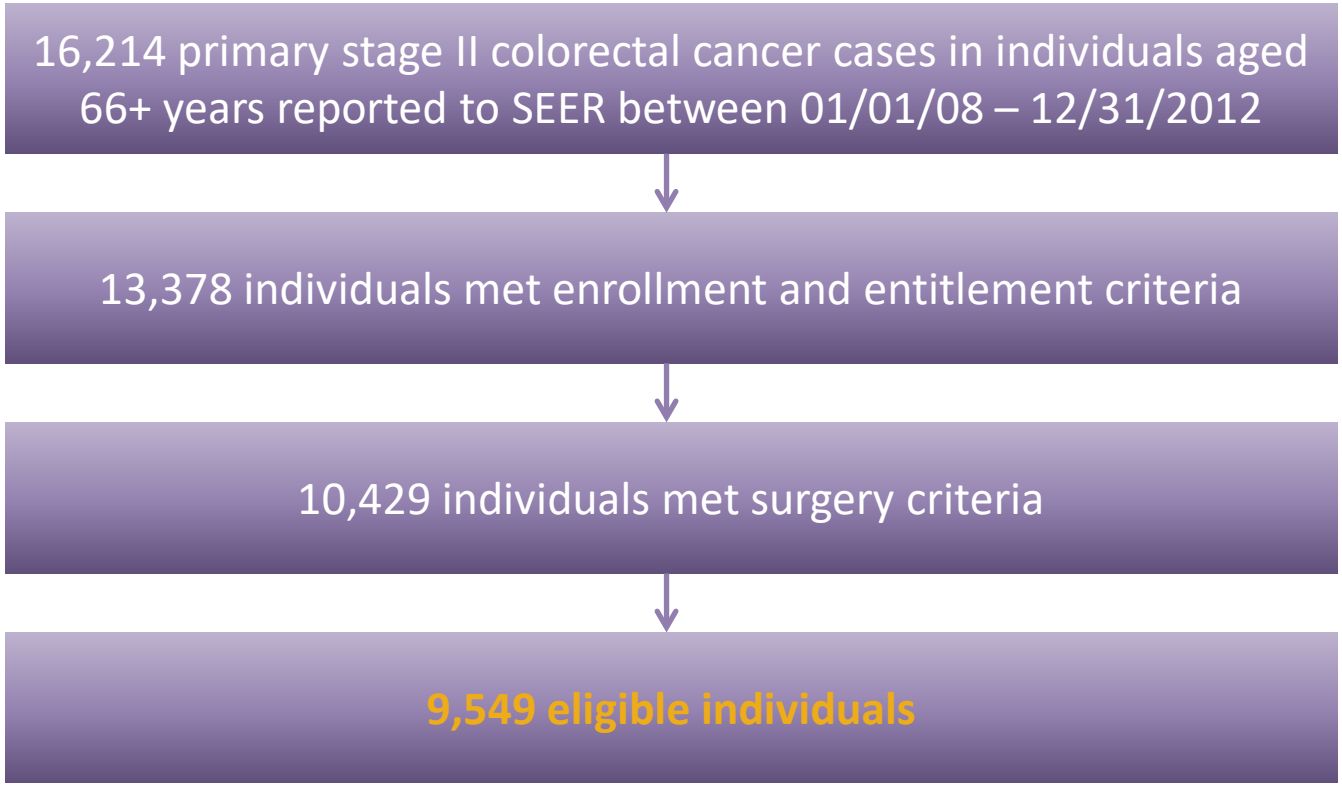
Petito et al. (2020) *JAMA Network Open* doi:10.1001/jamanetworkopen.2020.0452

Eligible Sample from SEER-Medicare



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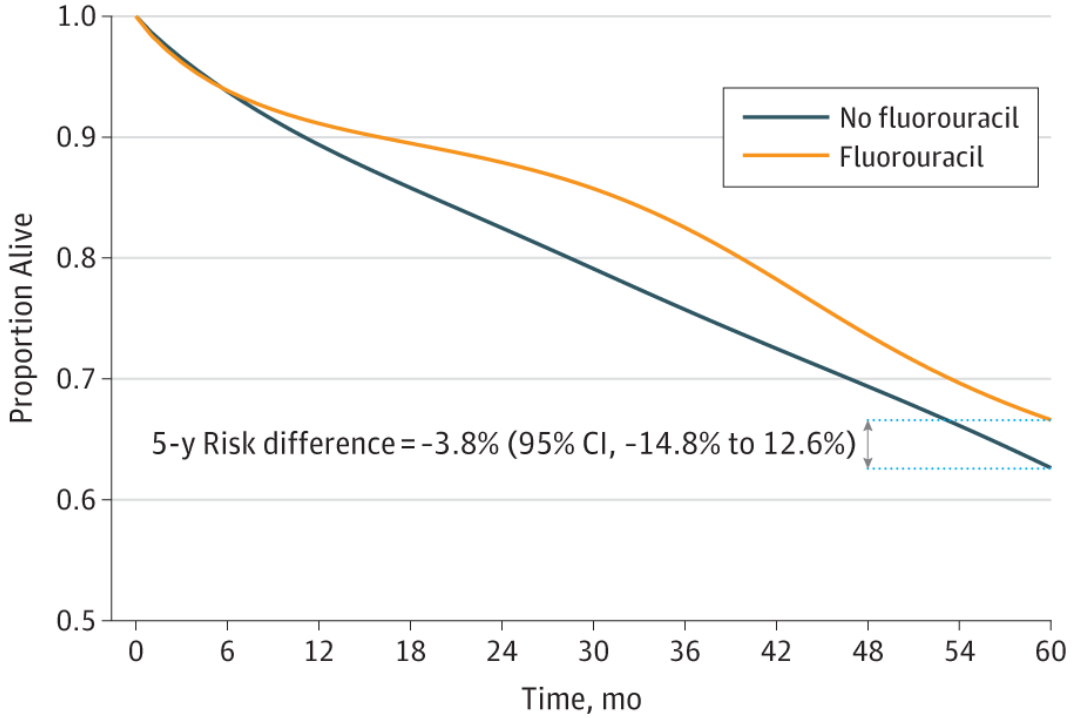
Petito et al. (2020) *JAMA Network Open* doi:10.1001/jamanetworkopen.2020.0452

Brief Sample Description

- 204 individuals initiated fluorouracil within 3 months of their hospital discharge after surgery
  - By the end of the grace period, 195 individuals remained in the fluorouracil arm; 6,150 in observation arm
- Fluorouracil initiation was **more likely** in:
  - Younger, married individuals
  - Diagnosis of rectum or both rectum and colon cancer
  - T4 tumor stage
- Fluorouracil initiation was **less likely** in:
  - Prolonged hospitalization after surgery (>14 days)
  - Anemia or asthenia in year prior to diagnosis
  - Pre-operative radiotherapy

Petito et al. (2020) *JAMA Network Open* doi:10.1001/jamanetworkopen.2020.0452

Survival estimates for effect of fluorouracil on overall survival in elderly stage II colorectal cancer patients



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Comparison to QUASAR (2007)

	QUASAR (2007)	SEER-Medicare
HR (95% CI)	1.02 (0.70 to 1.48)	0.95 (0.86 to 1.05)
5-year survival		
Fluorouracil	82%	66.6%
Observation	78%	62.7%
5-year risk difference (95% CI)	-4%	-3.8% (-14.8 to 12.6%)

- HR: Change in direction probably not meaningful
- Absolute risks being roughly 10% lower may reflect the older sample

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Petito et al. (2020) *JAMA Network Open* doi:10.1001/jamanetworkopen.2020.0452
QUASAR Collaborative group. (2007) *The Lancet* doi:10.1016/S0140-6736(07)61866-2

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Collaborators

- Miguel Hernán, MD, ScD
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- Roger Logan, PhD
- Issa Dahabreh, MD PhD
- Nadia Howlader, PhD, MS
- Angela Mariotto, PhD

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Take-Away Messages

- The target trial framework is a useful tool to ensure that your observational analysis is appropriate to answer your scientific question
- Confounding, selection bias, and measurement error are all concepts to consider when designing causal studies in observational data
- DAGs can be a useful tool to visualize data generating processes http://www.dagitty.net/
- Benchmarking analyses to published RCTs can help establish ability to adequately control for confounding before using real-world data to generate novel hypotheses
- **Big data is not always as big as we think it is!**

Questions?

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