UNIVERSITY of MARYLAND SCHOOL OF PHARMACY

Lilly

HealthCore

Workshop

Approaches to Algorithm Development for the Estimation of Lines of Therapy in Oncology Using Real-World Data

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Disclosures

- No funding was received for the research on which this workshop is based
- Chi Nguyen and Bal Nepal are employees of HealthCore, Inc. (a wholly owned subsidiary of Elevance Health, Inc.), which conducts health services research with both internal and external funding, including a variety of private and public entities
- Lisa Hess is an employee of Eli Lilly and Company
- Julia Slejko has no conflicts to disclose
- The comments stated herein are the opinions of the authors. The University of Maryland School of Pharmacy, Eli Lilly and Company, and HealthCore, Inc. make no representations or warranties, express or implied, with respect to the use or reliance on the opinions stated herein

It’s a Team Effort

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Agenda

Background
Dr. Nguyen ~10 mins

Best Practices to Develop and Validate Line of Therapy Algorithms
Dr. Hess ~12 mins

A Case Study –Biliary cancer
Dr. Nepal ~12 mins

Additional Considerations & Conclusions
Dr. Slejko~12 mins

Background

Chi Nguyen

Learning Objectives

Participants will be able to…

- ✓ Understand the importance of accurately defining lines of therapy (LOTs) for cancer treatment
- ✓ Identify the necessary components of a LOT algorithm
- ✓ Assess the differences in algorithms by tumor type
- ✓ Critically evaluate research using LOT algorithms

Audience Poll Question #1

How much experience do you have with cancer treatment patterns or LOTs using real-world data?

A. Very experienced

B. Somewhat experienced

C. Not experienced

Audience Poll Question #2

For those who indicated having experience with cancer treatment patterns or LOT algorithms, what database(s) do you use? (Check all that apply)

A. Administrative claims data

B. Registries

C. Electronic health/medical records (EHR/EMR)

D. Chart review

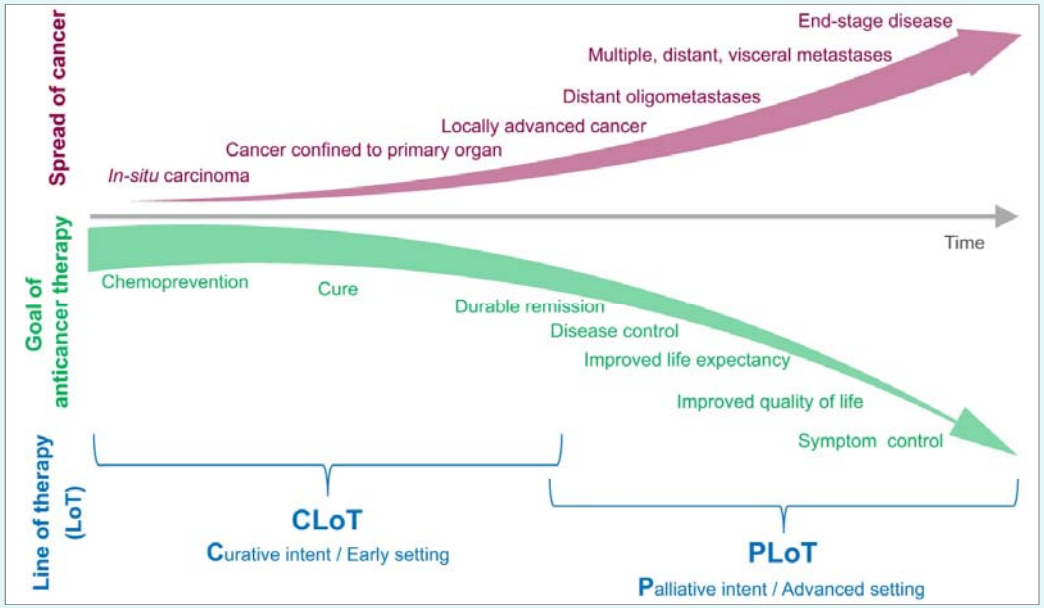
E. Survey/report data

F. Other

Background

Cancer treatment is complex, involving the sequential use of different treatment regimens as disease progresses

- Surgery
- Radiation therapy
- Systemic anti-cancer therapy (chemotherapy, endocrine therapy, targeted therapy, immunotherapy)
- Stem cell transplant
- Palliative care



Source: Saini et al, 2021

Saini KS, Twelves C. Determining lines of therapy in patients with solid cancers: a proposed new systematic and comprehensive framework. *British Journal of Cancer*, volume 125, pages155–163 (2021).

Background

- LOT is defined as self-contained treatment episode
- The definition varies depending on type of cancer, treatment intent, and treatment guidelines. No consistent definition exists of what to include and how to count a LOT
- Considerations include:
  - Include/exclude surgery, radiation, systemic anti-cancer therapy?
  - Monotherapy or in combination?
  - Neoadjuvant, adjuvant, locally advanced, metastatic, palliative care?
  - Planned and unplanned treatment gaps

Why Do We Care About LOT(s)?

HealthCare Professionals

- How patients respond to treatment at various LOTs
- How to decide on next best treatment
- Conduct medication audits
- Determine eligibility for enrollment in clinical trials

Healthcare Payers

- Perform accurate reimbursement
- Support decision-making/ Health Technology Assessment

Outcomes Research

- Describe real-world status and trends in treatment patterns/sequencing
- Evaluate unmet need (e.g., as a proxy for disease progression; to estimate treatment-free intervals, time to the next treatment, costs)
- When comparing treatments: Reduce confounding from differences in disease severity and treatment pathways

Best Practices to Develop and Validate Line of Therapy Algorithms

Lisa Hess

Components of a LOT algorithm

Regimen

- The set of drugs that are used together for treatment

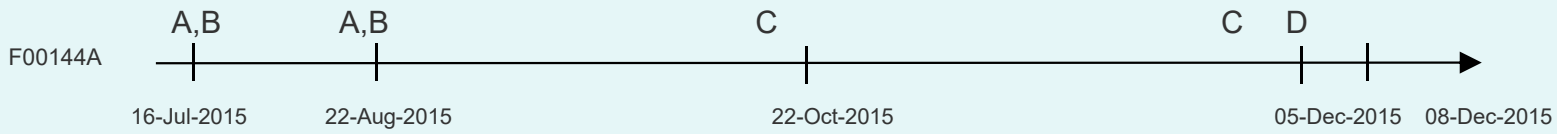
Advancement of Lines

- When a drug is discontinued
- When a new drug is added
- When drugs are exchanged
- When treatment stops
- Gaps in therapy

Hess et al. Defining treatment regimens and lines of therapy using real-world data in oncology. https://www.futuremedicine.com/doi/pdf/10.2217/fon-2020-1041 (SAS code provided in the supplementary materials)

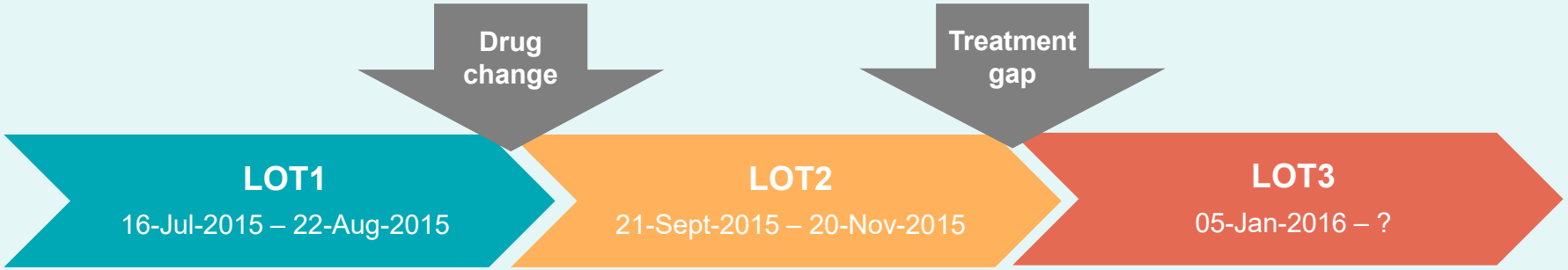
Regimen Rules

PATIENT ID	DATE	DRUGNAME
F00144A	16-Jul-2015	DRUGA
F00144A	16-Jul-2015	DRUGB
F00144A	22-Aug-2015	DRUGA
F00144A	22-Aug-2015	DRUGB
F00144A	22-Oct-2015	DRUGC
F00144A	05-Dec-2015	DRUGC
F00144A	08-Dec-2015	DRUGD
F00EA089	23-May-2017	DRUGC
F00EA089	23-May-2017	DRUGD
F00EA089	23-May-2017	DRUGE
F00EA089	03-Jul-2017	DRUGA
F00EA089	03-Jul-2017	DRUGB
F00EA089	21-Sept-2017	DRUGA
F00EA089	21-Sept-2017	DRUGB



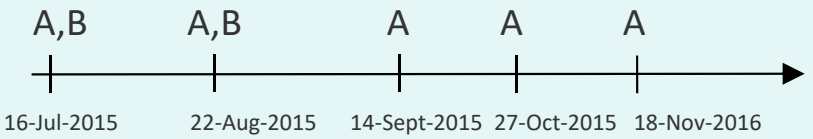
Key Components to Define When a LOT Advances

PATIENT ID	REGIMEN	LINE OF TX (LOT)	START DATE	STOP DATE
AF317A	DRUGA + DRUGB	1	16-Jul-2015	22-Aug-2015
AF317A	DRUGC	2	21-Sept-2015	20-Nov-2015
AF317A	DRUGC + DRUGD	3	05-Jan-2016	--

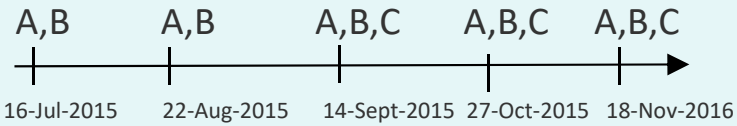


Drug Changes

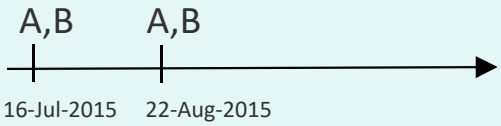
Discontinuation of a single drug



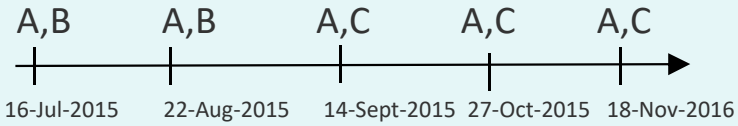
Addition of new drug



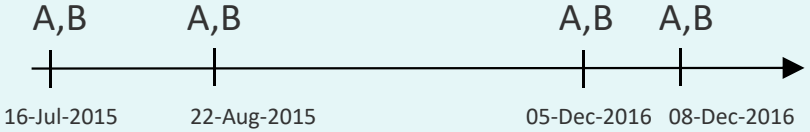
Discontinuation of all drugs



Exchanging drugs



Gaps in therapy



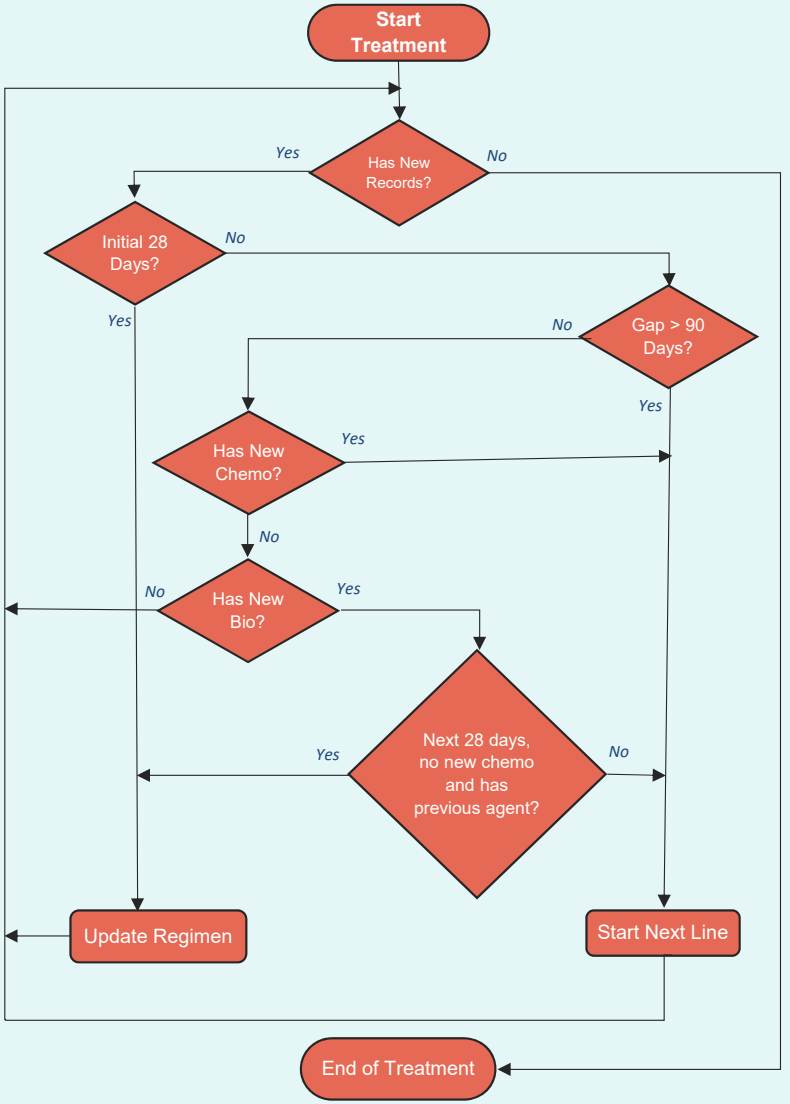
Example Rules (Gastric Cancer)

Line of therapy changes when:
Patient has had no treatment for a gap of greater than 90 days and then restarts the same treatment
Patient adds one or more chemotherapy drugs
Patient drops all drugs and starts a new treatment

Line of therapy DOES NOT change when:
Any biologic/targeted drug is added to a regimen
Exchange of 5-fluorouracil or capecitabine (these agents are considered equivalent)
Exchange of cisplatin or carboplatin (these agents are considered equivalent)

Therapy ends when:
The last observation occurs of all systemic therapy drugs

Rules → Algorithm



Summary

Know Your Disease

- When developing rules for lines of therapy, include practicing clinicians
- Understand the guideline-based treatment and what is expected in usual care settings
- Which drugs are active systemic therapies versus supportive care agents?

Develop Some Rules with Key Components

- REGIMEN: What is the time period to define a ‘regimen’?
- DRUG CHANGES:
  - What happens if a new drug appears?
  - What happens if a drug is discontinued?
  - What happens if a period of time without treatment is observed?

Know Your Data

- Does each drug have a singular date or is there just a start/stop period?
- Are oral drugs recorded differently than infused drugs?
- Draw an image to visualize the flow of patients before coding

Review. Apply. Repeat.

A Case Study – Biliary Cancer

Bal Nepal

Biliary Cancer

- **Biliary Tract Cancer (BTC)** - malignancies of gall bladder, intrahepatic cholangiocarcinoma, and extrahepatic cholangiocarcinoma. Also called bile duct cancer, originates mostly in the bile ducts
- **American Cancer Society** estimates 12,130 new cases of BTC to occur in the US in 2022 (American Cancer Society, 2022)
- **Poor prognosis and limited treatment choices.** Gemcitabine (GEM) plus platinum chemotherapy is the standard of care (Sasaki, 2021)

American Cancer Society, Key statistics for Gallbladder cancer, last revised: January 12, 2021, https://www.cancer.org/cancer/gallbladder-cancer/about/key-statistics.html
Sasaki, Takashi, et al. "Chemotherapy for Biliary Tract Cancer in 2021." *Journal of clinical medicine* 10.14 (2021): 3108.

Methods

Study Design

- Retrospective observational study
- Time period
  - Study period: 07/01/2014 - 03/31/2021
  - Intake period: 01/01/2015 - 09/30/2020
- Patients included if:
  - Biliary cancer or bile duct cancer or cholangiocarcinoma or gall bladder cancer in Cancer Care Quality Program (CCQP)
  - Any stages (I, II, III, IV) per the CCQP data on index date
- **Index date**: the first claim of systemic treatment identified using claims data around ±30 days of first reported line of therapy in CCQP during the intake period
- Start of 1L is identified using CCQP

Methods

Data Sources

- HealthCore Integrated Research Database (HIRD®)
  - Health insurance database containing medical and pharmacy claims from a large US national commercial payer
  - 2006 to present
  - Geographically diverse data representing members in each of the 50 US states
- CCQP
  - Offers evidence-based cancer treatment information allowing physicians to compare planned cancer treatment regimens against evidence-based clinical criteria
  - Identifies treatment pathways based upon current clinical evidence, published literature, and national guideline recommendations, which have shown to be efficacious, less toxic, and cost effective
  - 2014 to present
  - Variables: cancer type, staging, biomarkers, pathology/histology, line of treatment, weight/height, performance status

Methods

Eligible Therapies for Inclusion in Lines of Therapy

- Systemic treatment (e.g., antineoplastic therapies) but not radiotherapy and surgery

Gap in Therapy

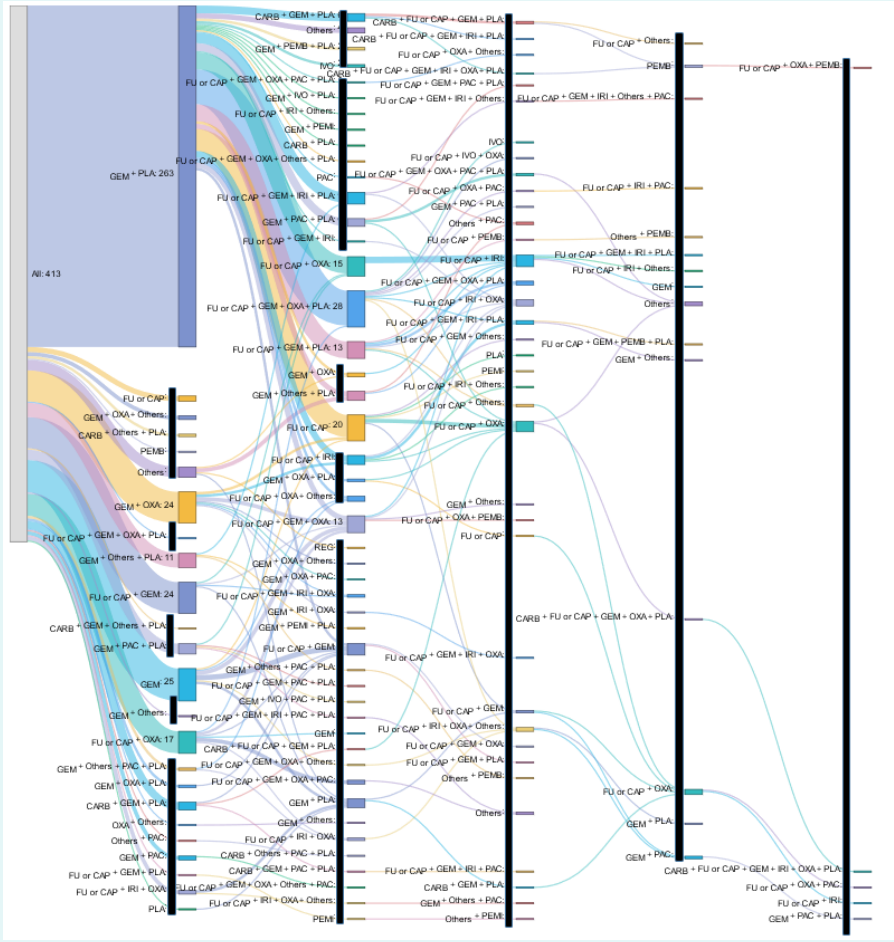
- When a gap in drug episodes of more than 120 days occurs, the LOT number is advanced

Line of Therapy Rules

- Substitution of cisplatin for carboplatin or vice-versa does not advance the LOT
- Substitution of fluorouracil for capecitabine or vice-versa does not advance the LOT
- "Drug component suppression" of one or more drugs within a combination regimen that is subsequently reintroduced does not advance the LOT
- If there is a complete change in the set of drugs being used, with or without a gap period, this is a new LOT
- If there is a gap between cycles of a pre-determined number of days (120 days), the next cycle is a new LOT

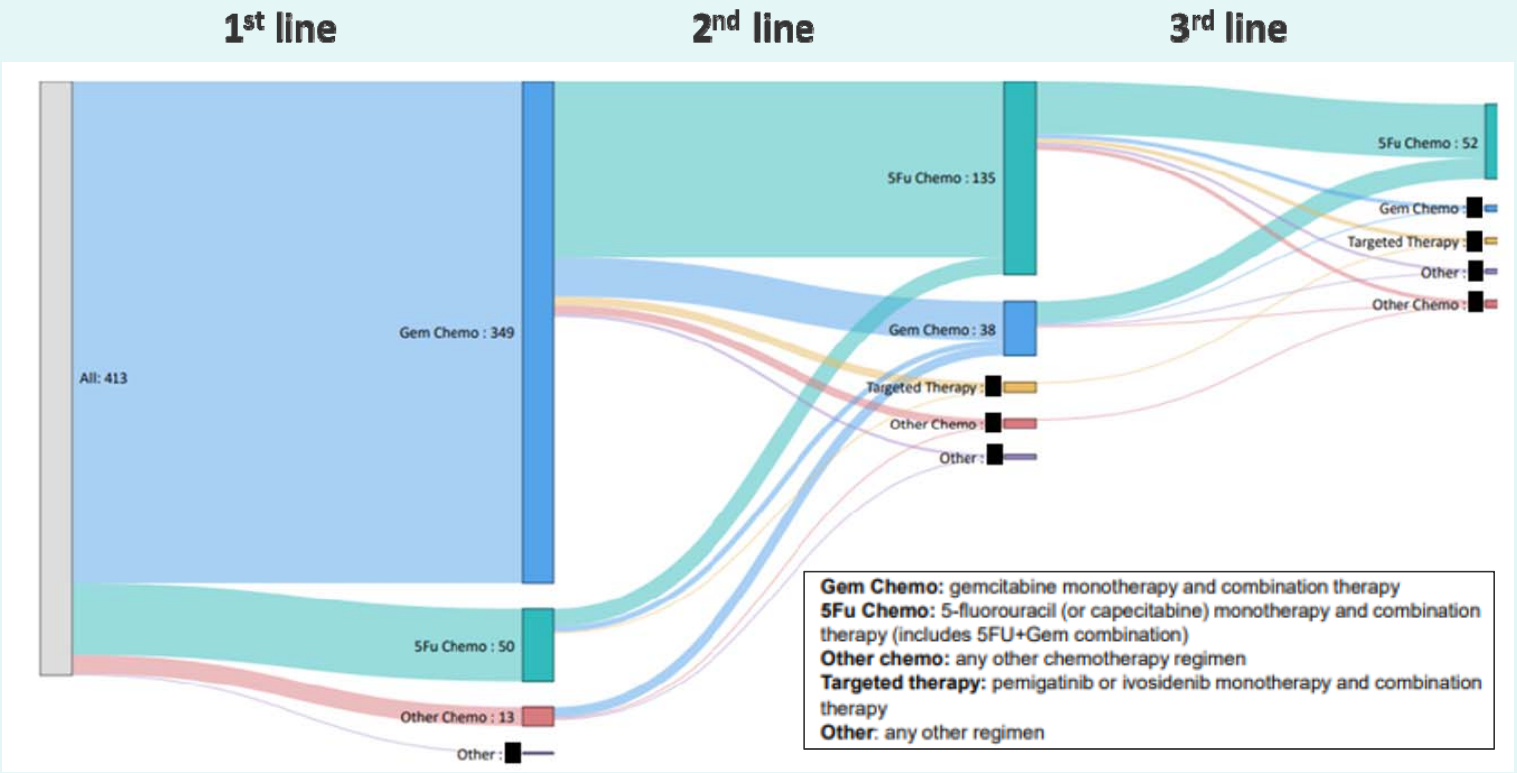
Sankey Chart with all Possible Rx Combinations

(full graphical representation of treatment change)



Median FU: 219 days

Sankey Chart with Monotherapy or Combination Therapy



Note: Results with values of any monotherapy or combination therapy ≤10 are masked due to Elevance Health, Inc. patient privacy policy.

Valderrama A, et. al. Treatment patterns and clinical outcomes among patients with biliary tract cancers in a large commercially insured US population. Virtual poster presented at the ASCO Gastrointestinal Cancers Symposium, San Francisco, CA, January 2022.

Recommended Steps When Developing LOT Algorithm

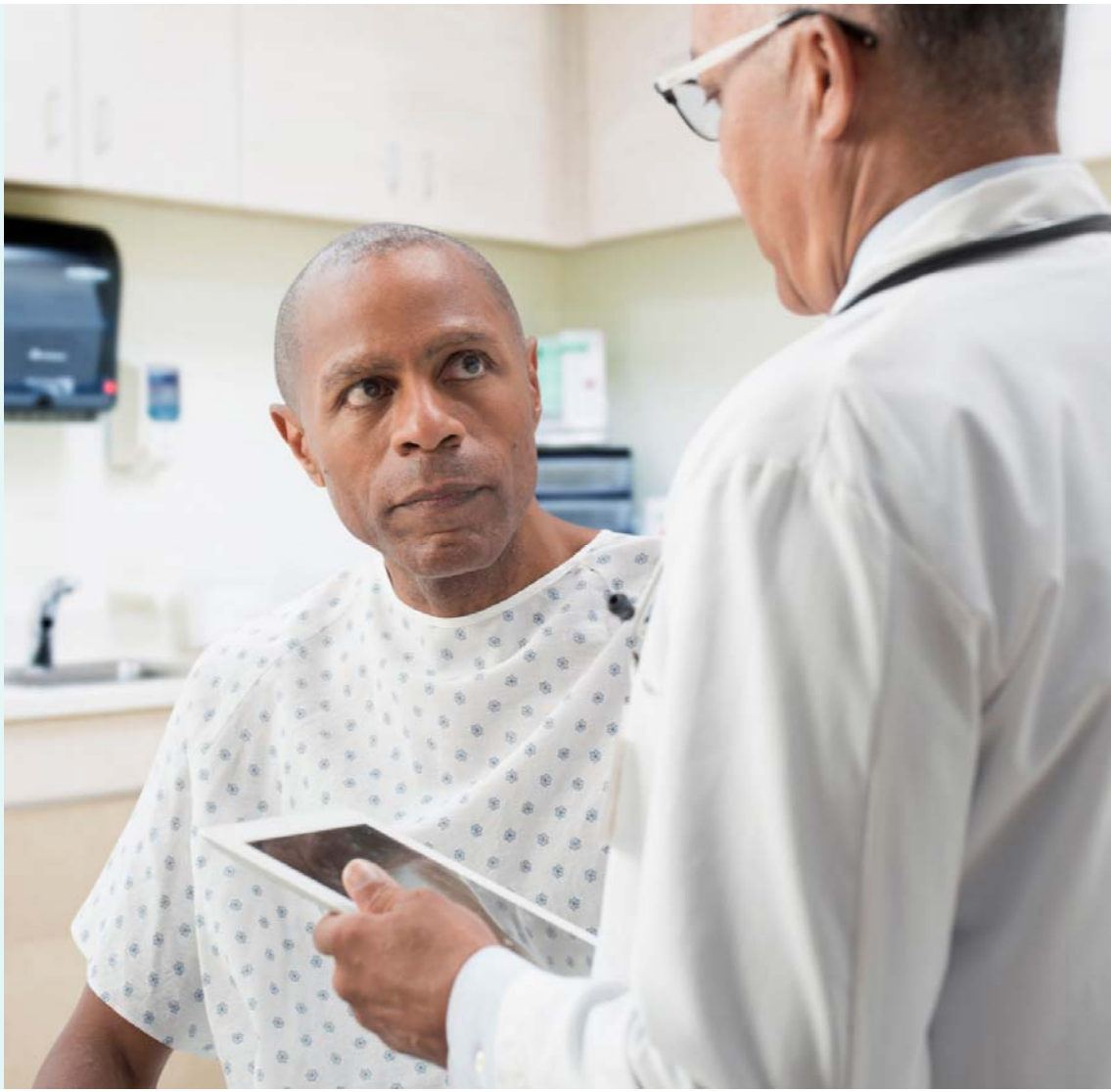
Step 1	Determine cancer type, stage, pathology of interest.
Step 2	Decide how to handle baseline therapies (e.g., exclude if looking for patients starting first-line therapy) and loss of follow-up enrollment (censoring) and death.
Step 3	Define what treatments are part of LOT algorithm (systemic only, or also surgery, radiation, stem cells, supportive drugs).
Step 4	Define the (expected) treatment regimens and cycle lengths, and if maintenance therapy is possible.
Step 5	Define permissible gaps to determine LOT discontinuation vs. interruption & restart/drug holiday.
Step 6	Determine what medication substitutions or additions will and will not advance LOT.
Step 7	Examine results in aggregate and for individual patients to check plausibility; review with clinical experts; conduct sensitivity analysis (e.g., different permissible gap).

Additional Considerations and Conclusions

Julia Slejko

Potential Challenges and Scenarios

- Cancer/Tumor Type
- Oral Oncolytics
- Biomarker Testing



Cancer/Tumor Type: Hematologic vs. Solid Tumor

Utilization Categories

Solid Tumor

- Surgery
- Radiation
- Systemic therapy

Hematologic

- Stem-cell therapy/transplant
  - Consolidation therapy
- Palliative radiation
- Systemic therapy
  - Maintenance therapy
- Chimeric antigen receptor (CAR)-T and other cell therapy
  - Emerging real-world studies

Keating SJ, Gu T, Jun MP, McBride A. Health Care Resource Utilization and Total Costs of Care Among Patients with Diffuse Large B Cell Lymphoma Treated with Chimeric Antigen Receptor T Cell Therapy in the United States. *Transplant Cell Ther*. 2022 Jul;28(7):404.e1-404.e6.

Cancer/Tumor Type: Hematologic vs. Solid Tumor

Data Considerations

SEER-Medicare (Registry and Claims) Linked Data

- Detailed utilization data, but staging information may be scarce for non-solid tumors
  - Proxy measures may be possible
- Pharmacy- and outpatient-administered located in different data sets
  - Eligibility for pharmacy benefit not consistent among beneficiaries
  - Has implication for sample size available to study pharmacy-dispensed drugs

Goto D, Khairnar R, Yared JA, Yong C, Romanus D, Onukwugha E, Slejko JF. Utilization of novel systemic therapies for multiple myeloma: A retrospective study of front-line regimens using the SEER-Medicare data. *Cancer Med*. 2020 Jan;9(2):626-639.

Oral Oncolytics

Utilization Patterns

Real-world studies of medication adherence use prescription refill data: medication possession ratio (MPR) or proportion of days covered (PDC)

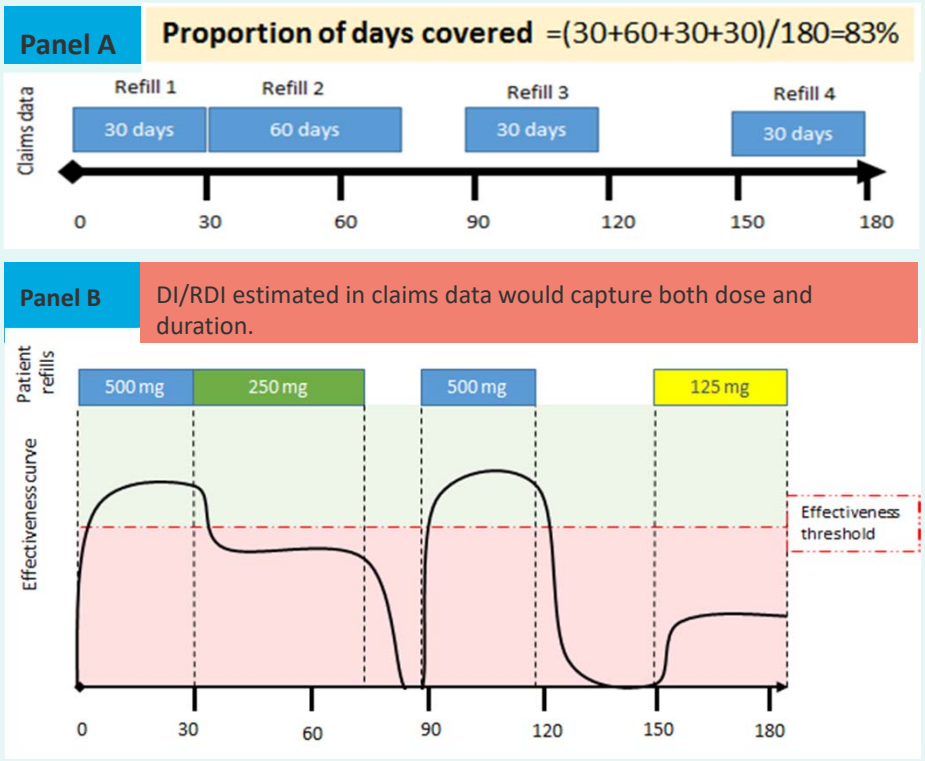
- Measures the number of doses dispensed over the entire refill
- Does not capture dose or dose adjustments over time
- Dosing may be more individualized in the oncology setting

Slejko JF, Rueda JD, Trovato JA, Gorman EF, Betz G, Arcona S, Zacker C, Stuart B. A Comprehensive Review of Methods to Measure Oral Oncolytic Dose Intensity Using Retrospective Data. *J Manag Care Spec Pharm*. 2019 Oct;25(10):1125-1132.

Oral Oncolytics

Measures of Interest

- Dose intensity is a measure that has been used to capture the amount of a particular chemotherapeutic agent administered per unit of time and is associated with patient outcomes, including survival.
- Relative dose intensity (RDI) expresses dose intensity as the fraction of the amount recommended, relative to the standard dose indicated in a protocol or in evidence-based guidelines



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Cytogenetics or Genomic Biomarker Testing

Data Source Considerations

- Test receipt is identifiable, results may not be

Do the Test Results Impact your LOT Calculation?

- Delay from test until result
- Days until next line
- Does the treatment switch?

Workshop Conclusions

- All research in oncology needs line of therapy data
- Accept the imperfect
  - Misclassification tolerance depends on your research question
- No data source is the gold standard
  - Exploit synergies and potential linkages
- Recommend refresh of algorithms on a regular basis
  - Guidelines and data sources change

Audience Poll Question #3

As a result of this workshop, are you more confident in describing the essence of a LOT algorithm, and/or trying the methods presented here?

A. Much more confident

B. Somewhat more confident

C. Same as before

D. Somewhat less confident

E. Much less confident

Thank You!