VANDERBILT UNIVERSITY

The HemOnc Chemotherapy Regimen Ontology

Background and Applications

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Monday, February 8th, 2021
National Childhood Cancer Registry Data Summit

Disclosures

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- Equity: HemOnc.org LLC (no monetary value)
- Funding: NIH, AACR, Vanderbilt University

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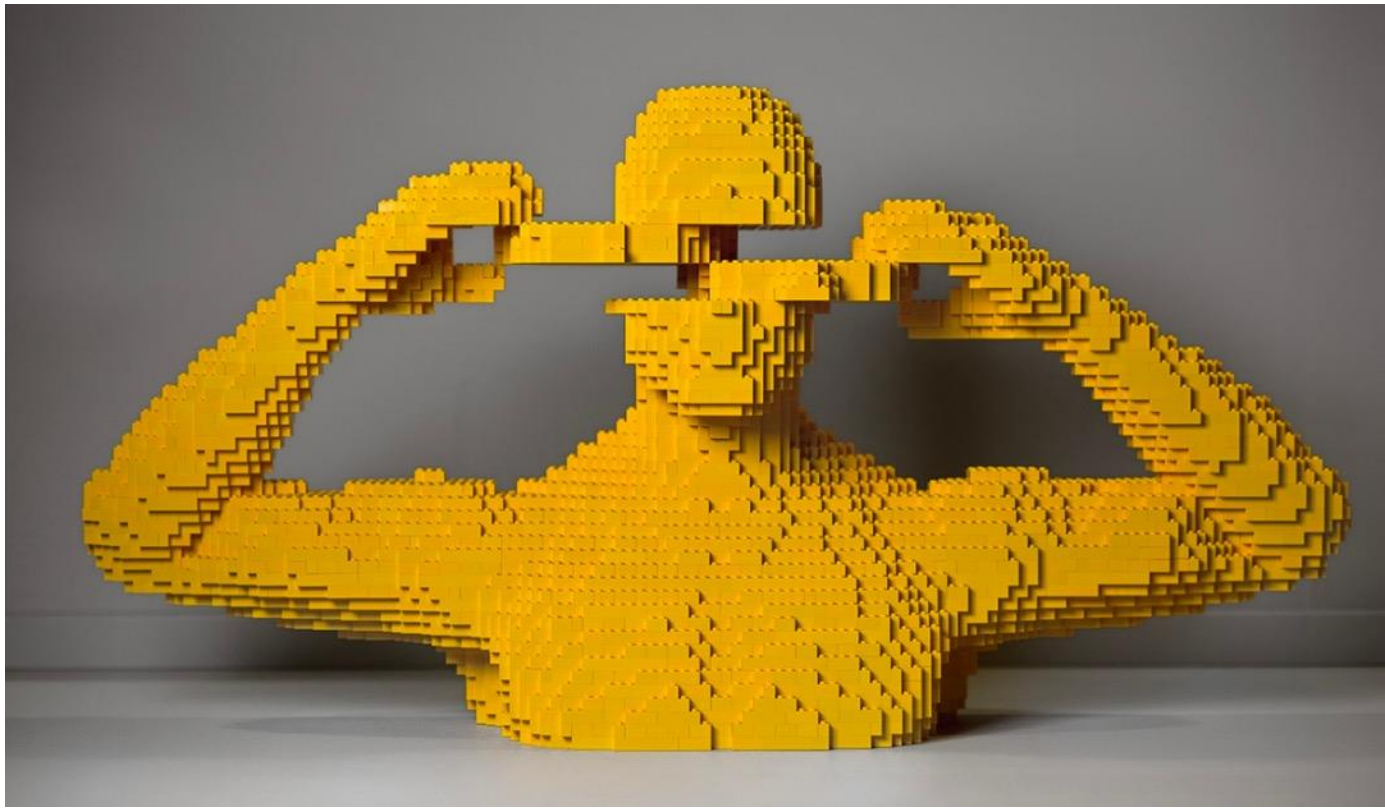
Current: AACR GENIE BPC; NCI U01 CA194215; U01 CA231840; U24 CA248010; UG3 CA243120

Former: NCI P30 CA068485; U24 CA184407



Chemotherapeutics are usually given in complex combination regimens and protocols

Efficacy and toxicity are dependent on combinations, dosing, cycle lengths, cycle numbers, etc.

Regimens are not well-represented in current systems, leading to an unmet need in data representation

Motivation

HemOnc.org – a growing resource

By the numbers

876 primary content pages

>700k lines of content

235 disease-specific pages

>6300 primary references

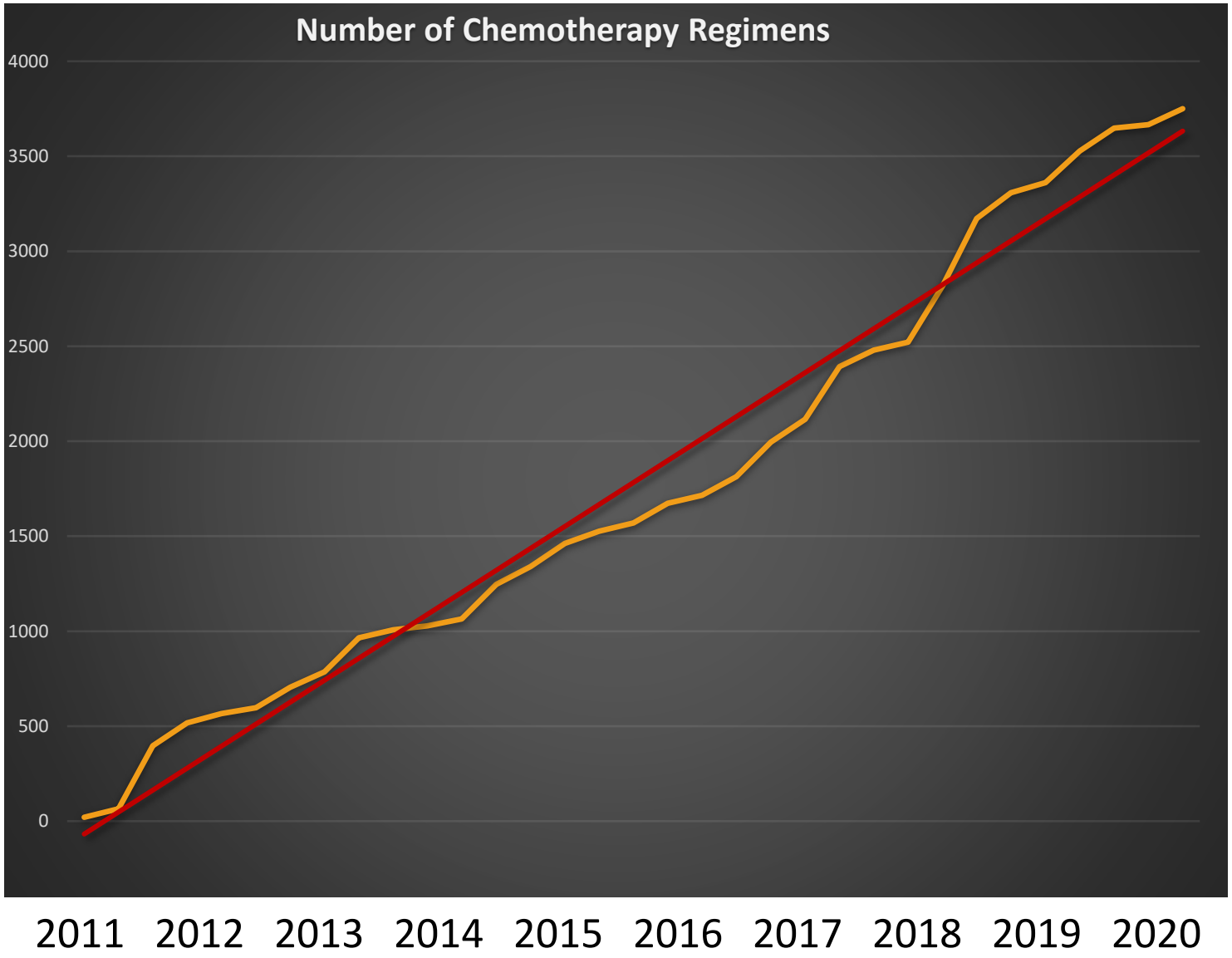
>3500 context-specific regimens

~1500 registered users

36 members of editorial board

2020 page views

1,252,575



CY20 Stats

2019

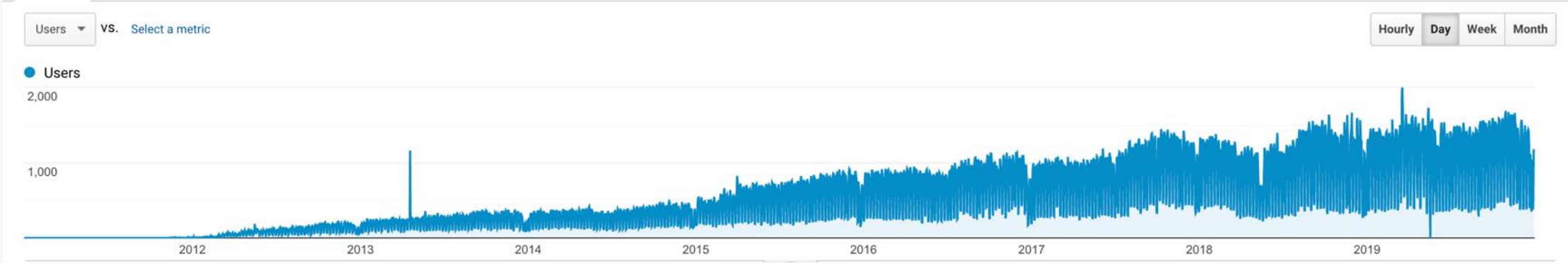
Users: 213,527

Pageviews: 1,165,947

2020

Users: 259,039

Pageviews: 1,252,575



2020 vs 2019

21% user growth

7% pageview growth


Global Reach
181 countries/territories

https://hemonc.org/wiki/Editorial Board

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Guidelines

Osteosarcoma

Guidelines [edit | edit source]

ESMO [edit | edit source]

- **2014:** Bone sarcomas: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. PubMed

ESMO/PaedCan/EURACAN [edit | edit source]

- **2018:** Casali et al. Bone sarcomas: ESMO–PaedCan–EURACAN Clinical Practice Guidelines for diagnosis, treatment and follow-up

NCCN [edit | edit source]

- NCCN Guidelines - Bone Cancer

Dactinomycin (Cosmegen)

Semi-structured Drug Information

Share

Contents [hide]

General information [edit | edit source]

Class/mechanism: Antibiotic oncologic, intercalates between guanine and cytosine DNA base pairs, inhibiting DNA and RNA synthesis.[1][2]
Route: IV
Extravasation: vesicant

For conciseness and simplicity, HemOnc.org currently will focus on treatment regimens and not list information such as: renal/hepatic dose adjustments, metabolism (including CYP450), excretion, monitoring parameters (although this will be considered for checklists), or manufacturer. Instead, for the most current information, please refer to your preferred pharmacopeias such as Micromedex, Lexicomp, UpToDate (courtesy of Lexicomp), or the prescribing information.[1]

Diseases for which it is used [edit | edit source]

- Endometrial cancer
- Ewing sarcoma
- Gestational trophoblastic neoplasia
- Osteosarcoma
- Rhabdomyosarcoma
- Wilms tumor

Patient drug information [edit | edit source]

- Dactinomycin (Cosmegen) patient drug information (Chemocare)[3]
- Dactinomycin (Cosmegen) patient drug information (UpToDate)[4]

History of changes in FDA indication [edit | edit source]

- 12/10/1964: Initial FDA approval
- 3/13/2009: (earliest label available on Drugs@FDA) Approved as part of a combination chemotherapy and/or multi-modality treatment regimen for the treatment of Wilms tumor, childhood rhabdomyosarcoma, Ewing sarcoma and metastatic, nonseminomatous testicular cancer.
- 3/13/2009: (earliest label available on Drugs@FDA) Approved as a single agent, or as part of a combination chemotherapy regimen, for the treatment of gestational trophoblastic neoplasia.
- 3/13/2009: (earliest label available on Drugs@FDA) Approved as a component of regional perfusion for the palliative and/or adjunctive treatment of locally recurrent or locoregional solid malignancies.

Also known as [edit | edit source]

- **Generic names:** AC-DE, actinomycin D
- **Brand names:** Cosmegen, Dacmozen, Lyovac

Dactinomycin (Cosmegen)

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Semi-structured Regimens

GM-CSF, IL-2, Isotretinoin, Dinutuximab [edit | edit source]

Regimen [edit | edit source]

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Study	Years of enrollment	Evidence	Comparator	Comparative Efficacy
Yu et al. 2010 (COG ANBL0032)	2001-2009	Phase III (E-RT-esc)	Isotretinoin	Seems to have superior OS

Note: in distinction from most chemotherapy regimens, the first day of a cycle is day 0 and the last day of a 28-day cycle is day 27.

Immunotherapy [edit | edit source]

- Dinutuximab (Unituxin) as follows:
  - Cycles 1, 3, 5: 25 mg/m^2 IV once per day on days 3 to 6
  - Cycles 2 & 4: 25 mg/m^2 IV once per day on days 7 to 10
- Sargramostim (Leukine) as follows:
  - Cycles 1, 3, 5: 250 mcg/m^2 SC once per day on days 0 to 13
- Aldesleukin (Proleukin) as follows:
  - Cycles 2 & 4: 3,000,000 IU/m^2/day IV continuous infusion over 96 hours, started on day 0, then 4,500,000 IU/m^2/day IV continuous infusion over 96 hours, started on day 7 (total dose per cycle: 30,000,000 IU/m^2)

Chemotherapy [edit | edit source]

- Isotretinoin (Accutane) 160 mg/m^2/day PO on days 14 to 27

28-day cycle for 6 cycles

References [edit | edit source]

1. **COG ANBL0032:** Yu AL, Gilman AL, Ozkaynak MF, London WB, Kreissman SG, Chen HX, Smith M, Anderson B, Villablanca JG, Matthay KK, Shimada H, Grupp SA, Seeger R, Reynolds CP, Buxton A, Reisfeld RA, Gillies SD, Cohn SL, Maris JM, Sondel PM; Children's Oncology Group. Anti-GD2 antibody with GM-CSF, interleukin-2, and isotretinoin for neuroblastoma. N Engl J Med. 2010 Sep 30;363(14):1324-34. link to original article link to PMC article **contains verified protocol** PubMed NCT00026312

GM-CSF, IL-2, Isotretinoin, Dinutuximab [edit | edit source]

Semi-structured Regimens

Regimen [edit | edit source]

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Biomarker-driven definitions

Non-small cell lung cancer (NSCLC)

There are several related dedicated pages:

- **Histology-specific:**
  - **NSCLC, Nonsquamous**
  - **NSCLC, Squamous**
- **Biomarker-specific:**
  - **NSCLC, ALK-positive**
  - **NSCLC, BRAF-mutated**
  - **NSCLC, EGFR-mutated**
  - **NSCLC, KRAS-mutated**
  - **NSCLC, MET-mutated**
  - **NSCLC, RET-positive**
  - **NSCLC, ROS1-positive**
- **CNS carcinoma**

Regimen variant #2, 40 mg/day [edit | edit source]

FDA-recommended dose

Study	Years of enrollment	Evidence	Comparator	Comparative Efficacy
Yang et al. 2012 (LUX-Lung 2)	2007-2009	Phase II		ORR: 61%
Sequist et al. 2013 (LUX-Lung 3)	2009-2011	Phase III (E-RT-switch-ooc)	Cisplatin & Pemetrexed	Superior PFS
Wu et al. 2014 (LUX-Lung 6)	2010-2011	Phase III (E-switch-ooc)	Cisplatin & Gemcitabine	Superior PFS
Park et al. 2016 (LUX-Lung 7)	2011-2013	Randomized Phase II (E-switch-ic)	Gefitinib	Seems to have superior PFS

Biomarker Eligibility Criteria [edit | edit source]

- Biomarker:
  - activating EGFR mutations within exons 18–21 (LUX LUNG-2)
  - activating EGFR mutation with 19 deletions in exon 19, L858R, 3 insertions in exon 20, L861Q, G719S, G719A, G719C, T790M and S768I (LUX-LUNG 3, LUX-LUNG 6)
  - activating EGFR mutation with exon 19 deletion and/or L858R (LUX-LUNG 7)

Targeted therapy [edit | edit source]

- Afatinib (Gilotrif) 40 mg PO once per day, given 1 hour before eating food (LUX-Lung 2: "no food intake immediately before or after afatinib")
  - In LUX-Lung 3, patients could be increased to 50 mg PO once per day if they did not experience any grade 2 or higher rash, diarrhea

OHDSI

OBSERVATIONAL HEALTH DATA SCIENCES AND INFORMATICS

OMOP Common Data Model

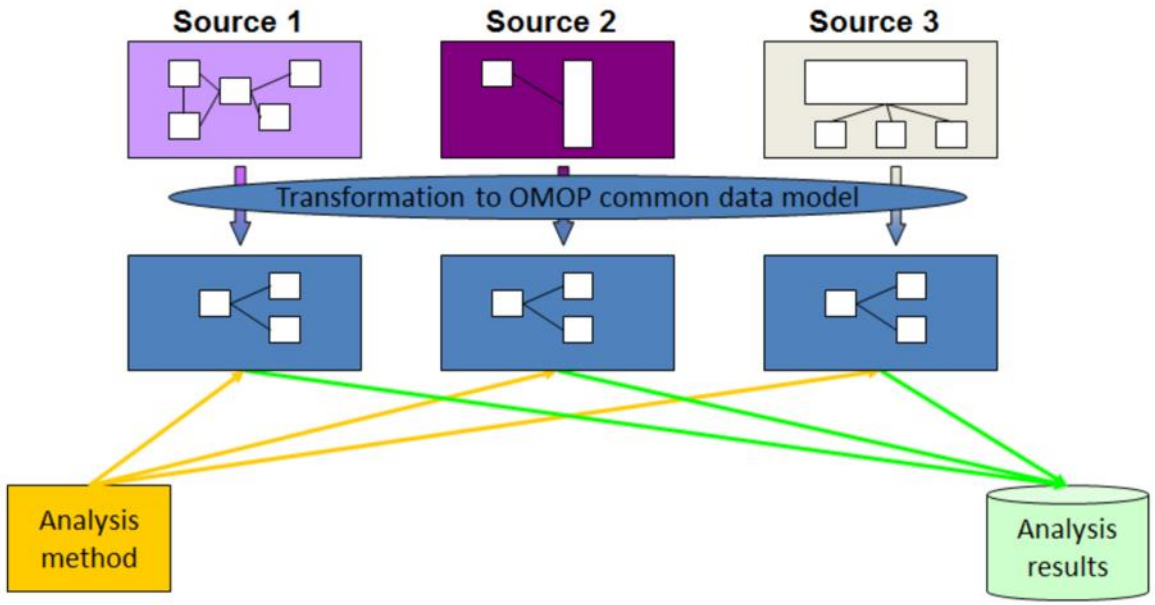


IMAGE: FINE ART IMAGES/HERITAGE IMAGES/GETTY IMAGE

Comparison of existing terminologies/ontologies

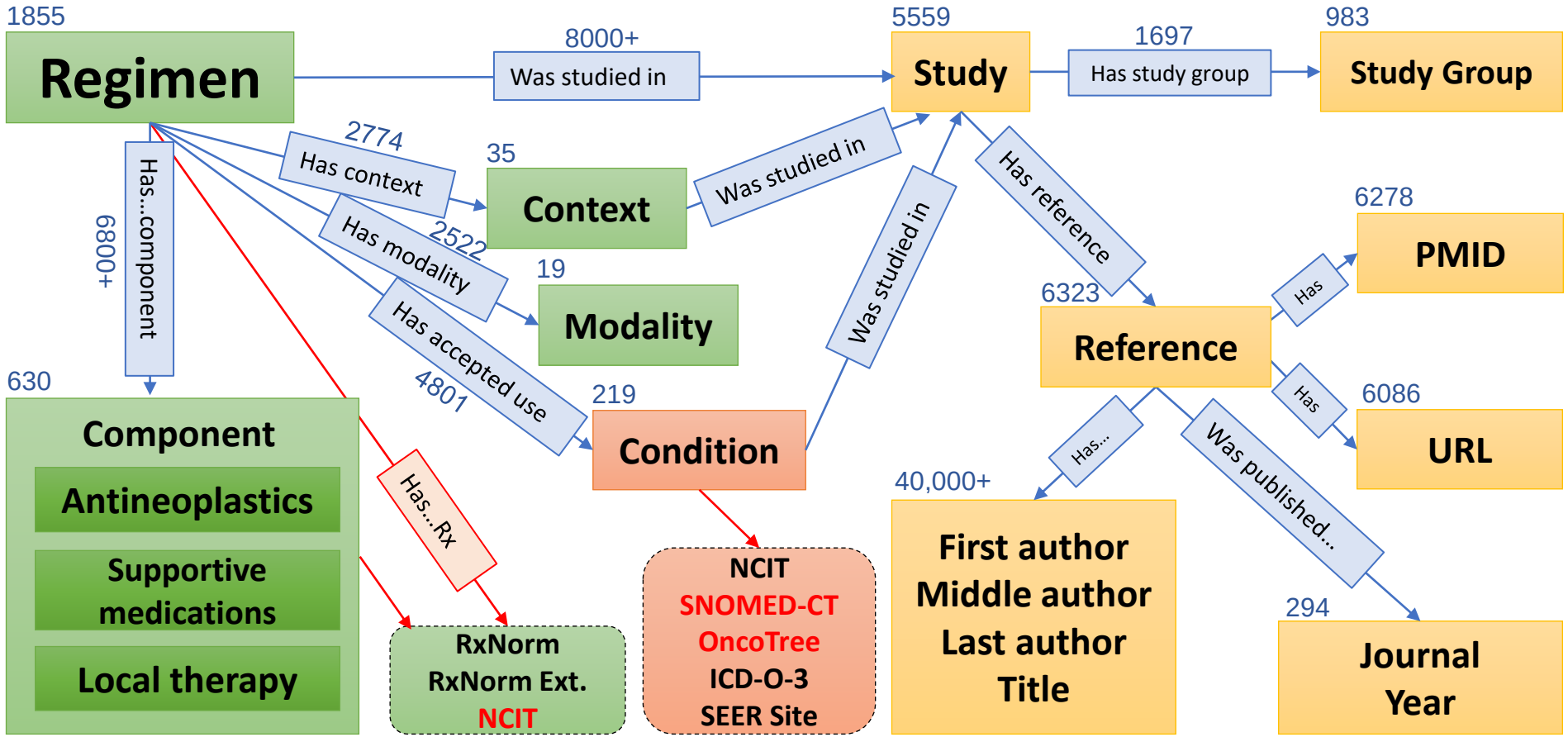
Terminology	Maps to Drugs	Disease Context	Treatment Context	Modality	Link to Evidence	Number of regimens
SNOMED-CT	Yes[1]	No	No	No	No	6
SEER*Rx	Yes[1]	No	No	Yes	No	516
NCI Thesaurus	Yes[1]	Yes	No	No[2]	No	1021
HemOnc	Yes	Yes	Yes	Yes	Yes	3460*

[1]Antineoplastics; HemOnc also maps to supportive medications

[2]In some cases, modality can be inferred

*Includes 1612 regimen "stubs" which that are incompletely defined

HemOnc Regimen Model (simplified)



Concepts: 86,564 **2021-01-27** **Relationships: 230,128**

Warner et al. *J Biomed Inform* 2019 https://doi.org/10.1016/j.jbi.2019.103239

Example for regimen FOLFOX in Athena

FOLFOX

https://athena.ohdsi.org/search-terms/start

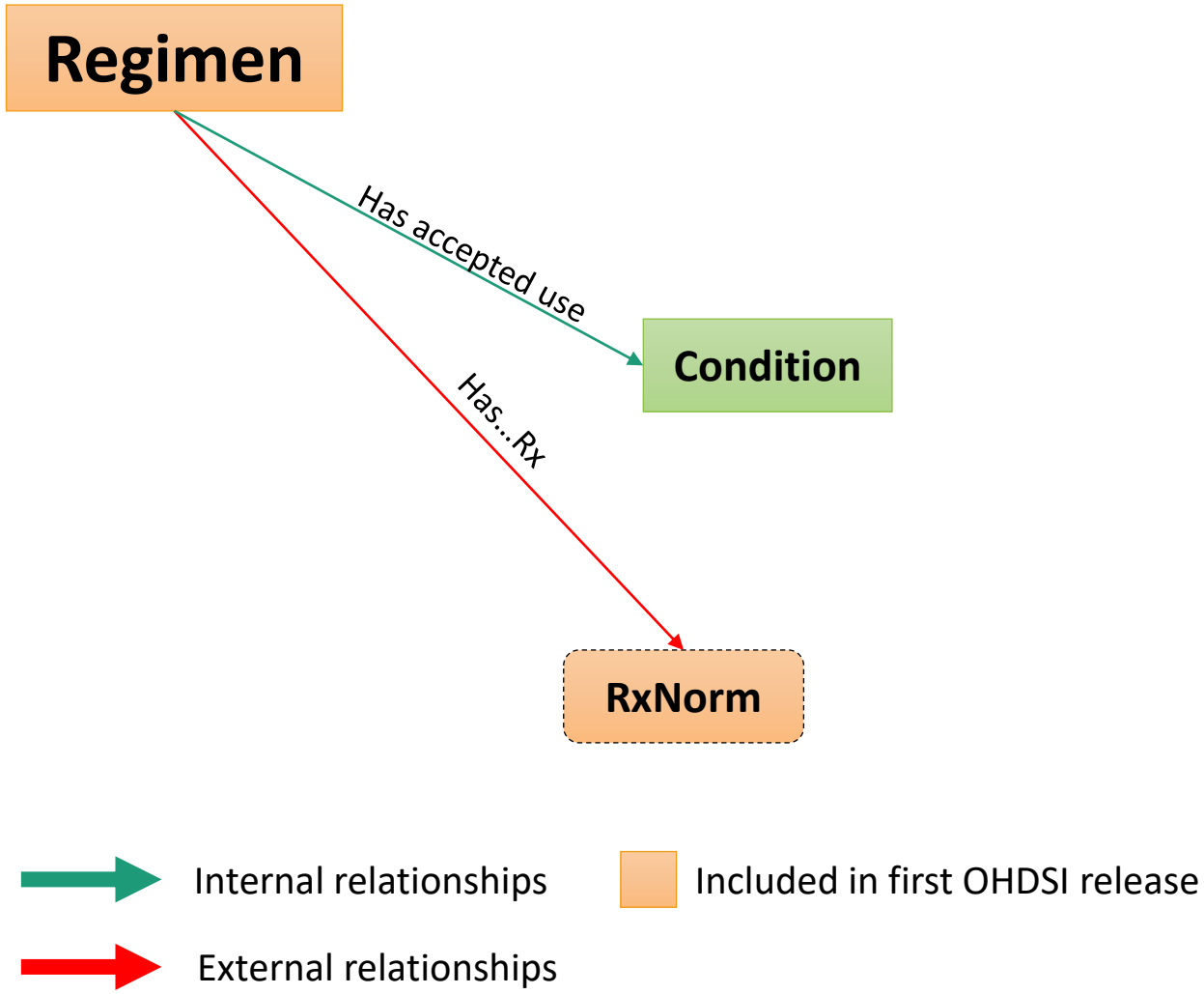
DETAILS

Domain ID	Drug
Concept Class ID	Regimen
Vocabulary ID	HemOnc
Concept ID	35806596
Concept code	33193
Invalid reason	Valid
Standard concept	Standard
Synonyms	FOLFOX
Valid start	05/27/2019
Valid end	12/31/2099

TERM CONNECTIONS (11)

HIERARCHY | RELATED CONCEPTS

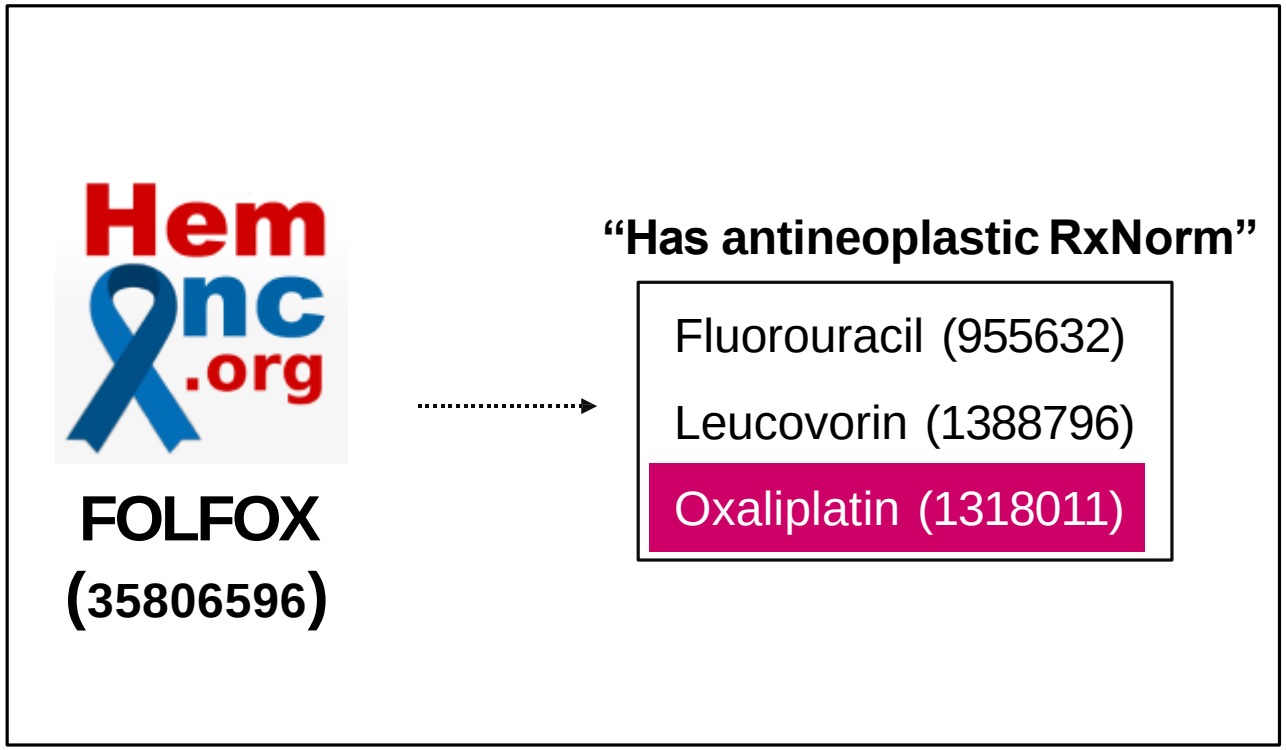
RELATIONSHIP	RELATES TO	CONCEPT ID	VOCABULARY
Has antineoplastic (HemOnc)	Fluorouracil	35803077	HemOnc
	Folinic acid	35803081	HemOnc
	Oxaliplatin	35803227	HemOnc
Has antineoplastic - RxNorm (HemOnc)	Fluorouracil	955632	RxNorm
	Leucovorin	1388796	RxNorm
	oxaliplatin	1318011	RxNorm
Has context (HemOnc)	Adjuvant therapy	35803584	HemOnc
	Non-curative therapy	35803588	HemOnc
Has regimen type (HemOnc)	Chemotherapy	35803401	HemOnc



Use Case #1: Mapping Components to Regimens

Method

Courtesy of Hokyun Jeon, Seng Chan You, Jimyeong Park and Rae Woong Park (Ajou University)



Step 1

Primary drug : Oxaliplatin

Find all the dates that primary drug used.

https://github.com/ABMI/treatmentCycleExtraction

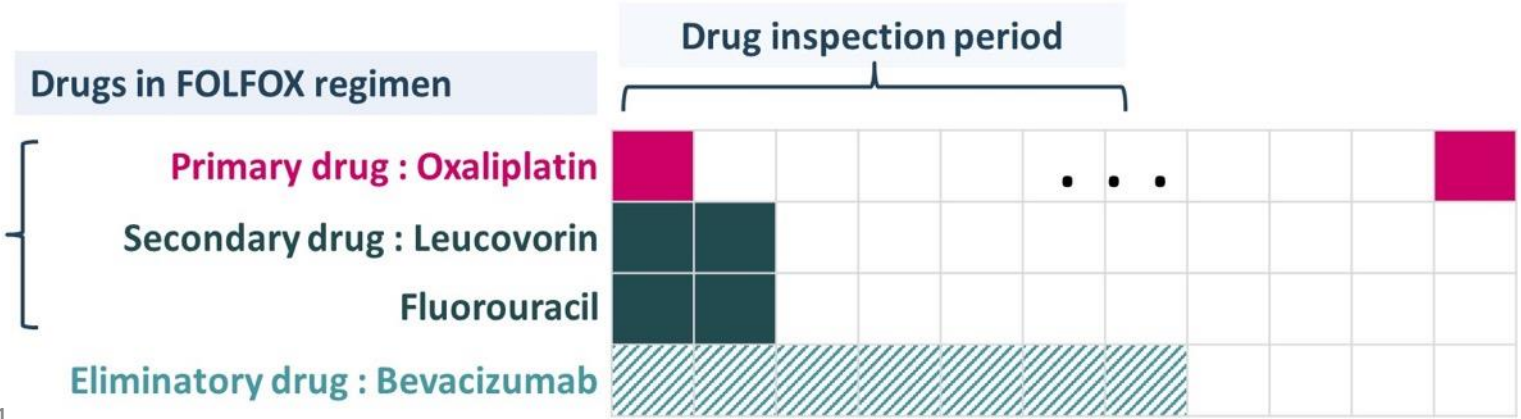
Courtesy of Hokyun Jeon, Seng Chan You, Jimyeong Park and Rae Woong Park

FOLFOX (35806596)

"Has antineoplastic RxNorm"

- Fluorouracil (955632)
- Leucovorin (1388796)
- Oxaliplatin (1318011)

Step 2



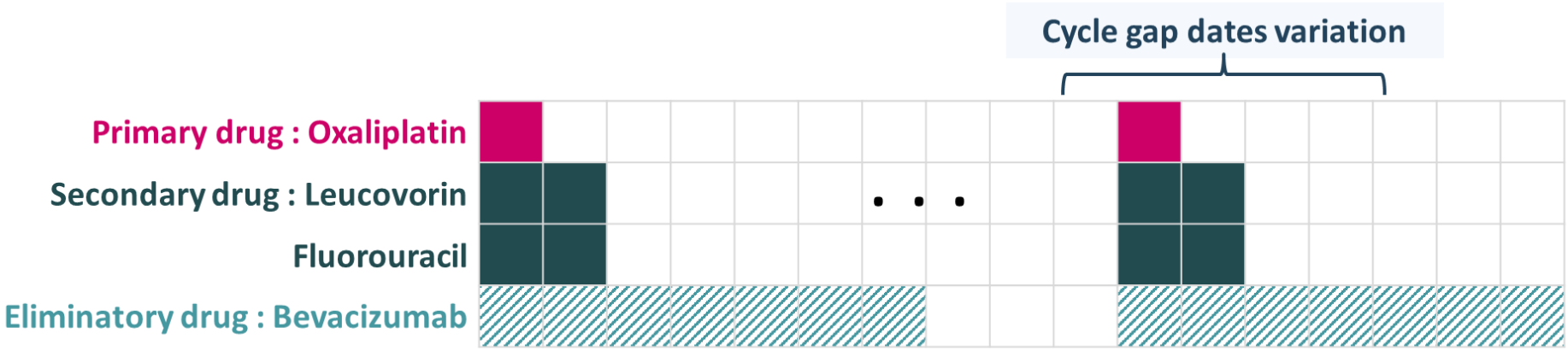
Check the drug conditions

https://github.com/ABMI/treatmentCycleExtraction

Method

Courtesy of Hokyun Jeon, Seng Chan You, Jimyeong Park and Rae Woong Park

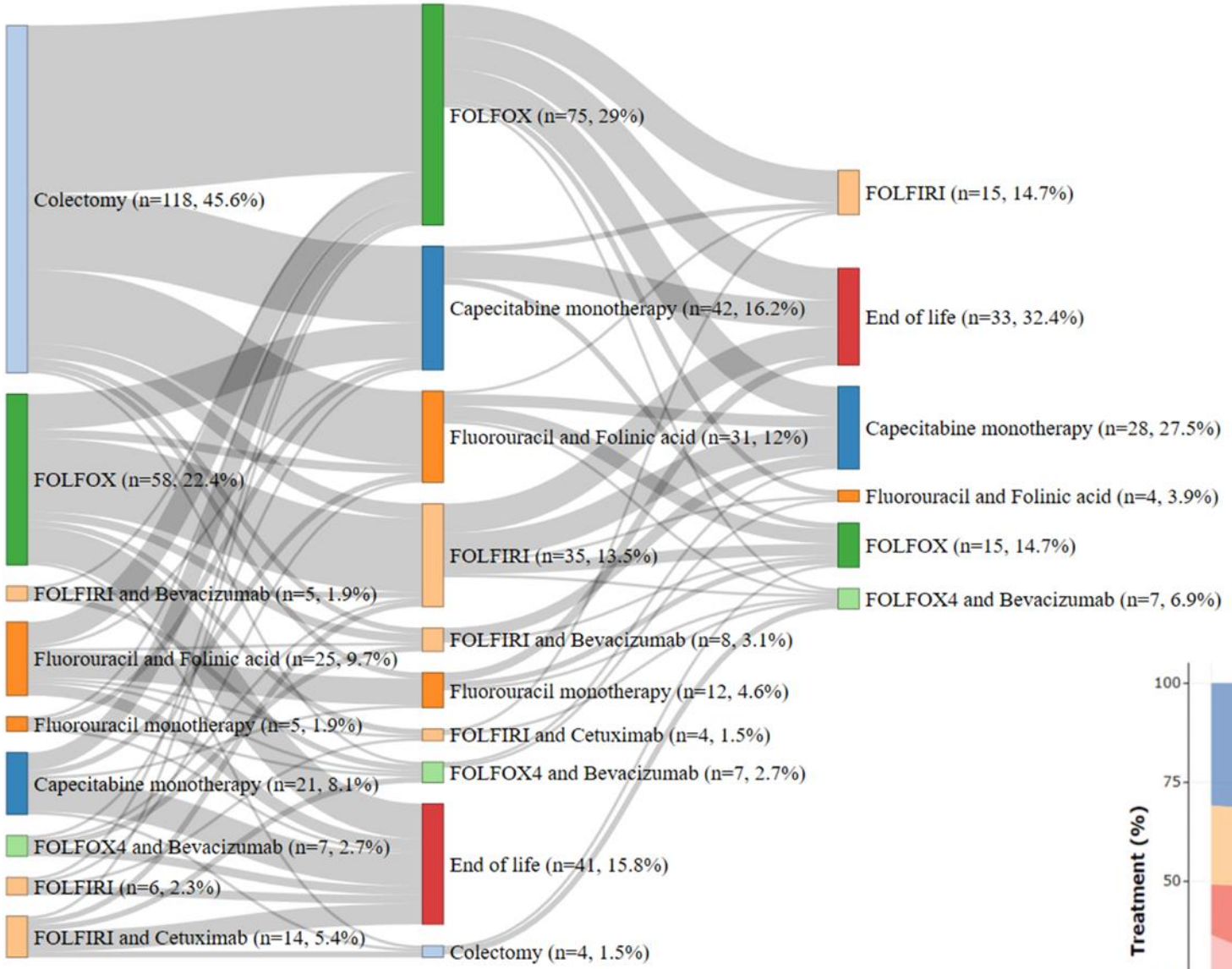
Step 4

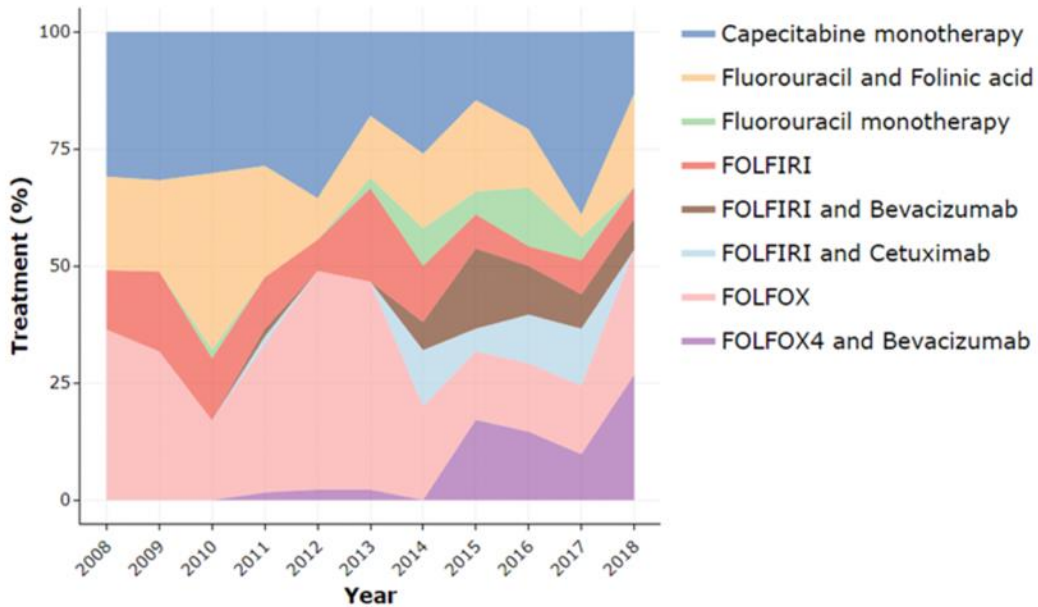


Step 5

https://github.com/ABMI/treatmentCycleExtraction

(a)

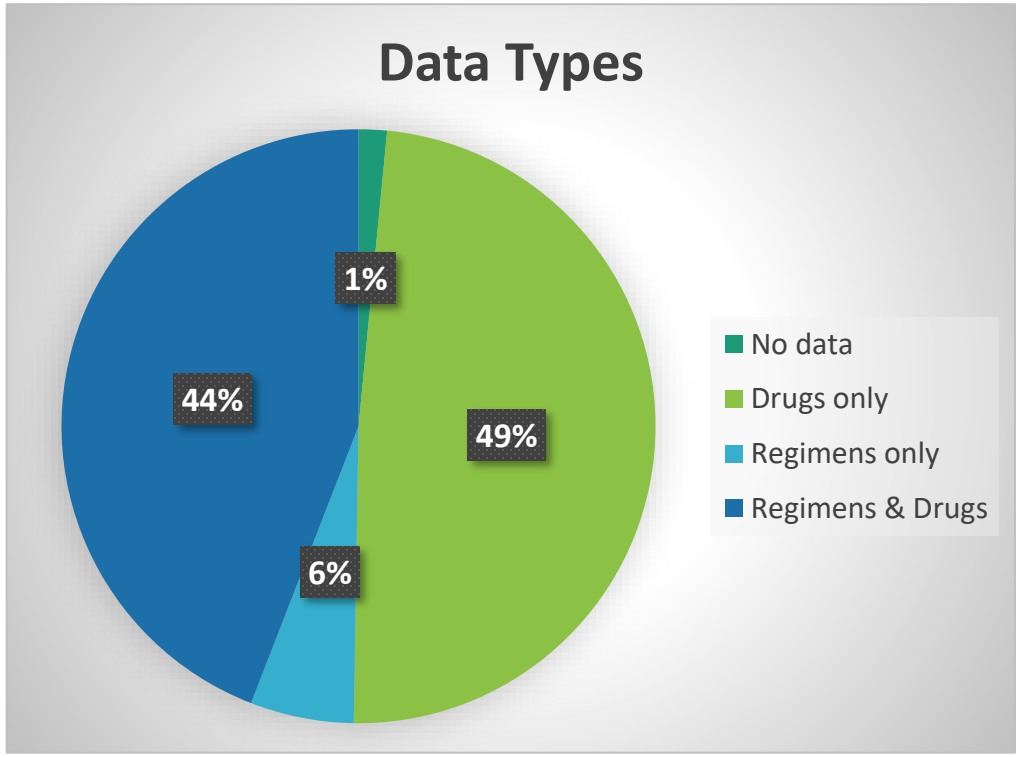




Jeon et al. https://www.jmir.org/preprint/25035/submitted (in press)

Matching drugs to HemOnc regimens in AACR Project GENIE

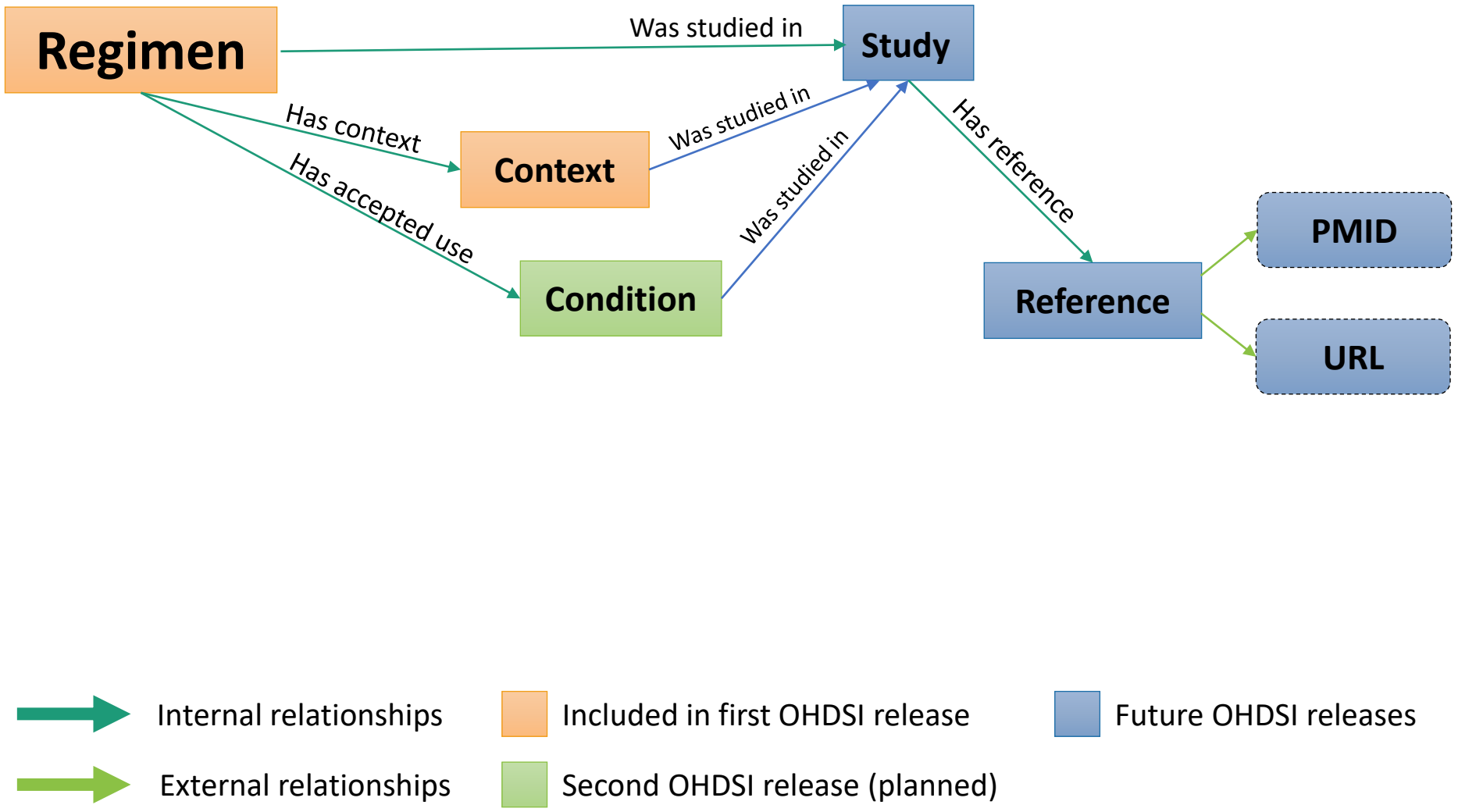
- Small (N=36) breast cancer cohort
- Data had been curated and stored in REDCap by line of therapy
- N=195 treatment exposures



Results, cont.

- 178 (91%) of the lines of therapy matched to a HemOnc regimen
- Of these, ***all but 6 (3.4%) were determined automatically***
- 49 mapped regimens (**84.5%**) had an accepted use in breast cancer

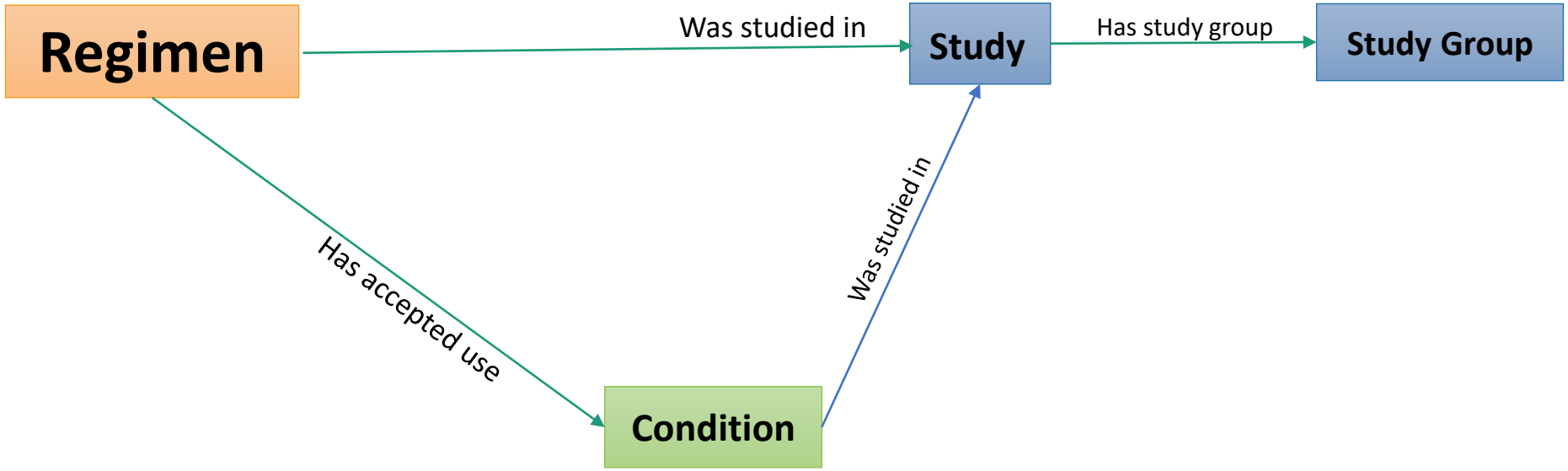
Reason for no match	# of instances	Example
No drug or regimen names	3	N/A
Regimen name only, with only experimental drugs	3	PI3K inhibitor GDC-0032
Regimens modeled differently in HemOnc	1	EC-T
Regimen not present in HemOnc; no data to support combination found	10	Gemcitabine, Vinorelbine, Bevacizumab
Total	**17**	



Use Case #2: HemOnc Regimen Browser (alpha)

LIVE DEMO

https://smartpcm-dev.app.vumc.org/regimen/



Use Case #3: Landscape Analyses

Pediatric oncology studies

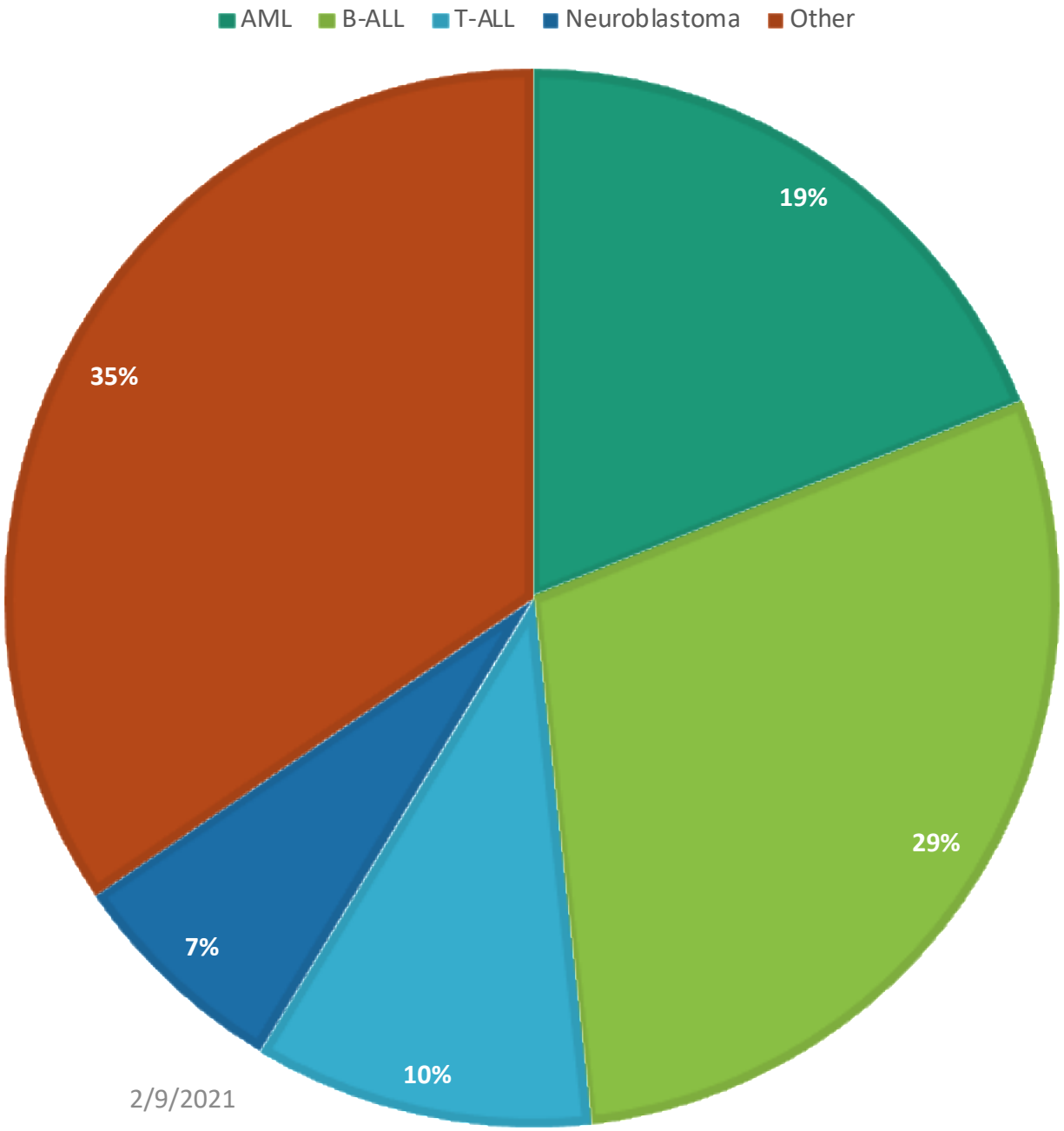
Study Groups (N=15)

Adult and Childhood Leukaemia Working Parties of the Medical Research Council
Children's Cancer Group
Children's Leukemia Cooperative Group of the European Organiztaion for Research and Treatment of Cancer
Children's Leukemia Group of the European Organisation for Research and Treatment of Cancer (EORTC)
Children's Oncology Group
Childrens Cancer Group
Dutch Childhood Oncology Group
EORTC Children Leukemia Group
French Society of Pediatric Oncology (SFCE)
Gruppo Italiano-Malattie Ematologiche Maligne dell'Adulto and Associazione Italiana di Ematologia ed Oncologia Pediatrica Cooperative Groups
Medical Research Council Childhood Leukaemia Working Party
Pediatric Oncology Group
Societe Francaise d'Oncologie Pediatrique (SFOP)
UK Medical Research Council's Working Party on Childhood Leukaemia
United Kingdom Children's Cancer Study Group (UKCCSG) and the Medical Research Council Bone Sarcoma Working Party

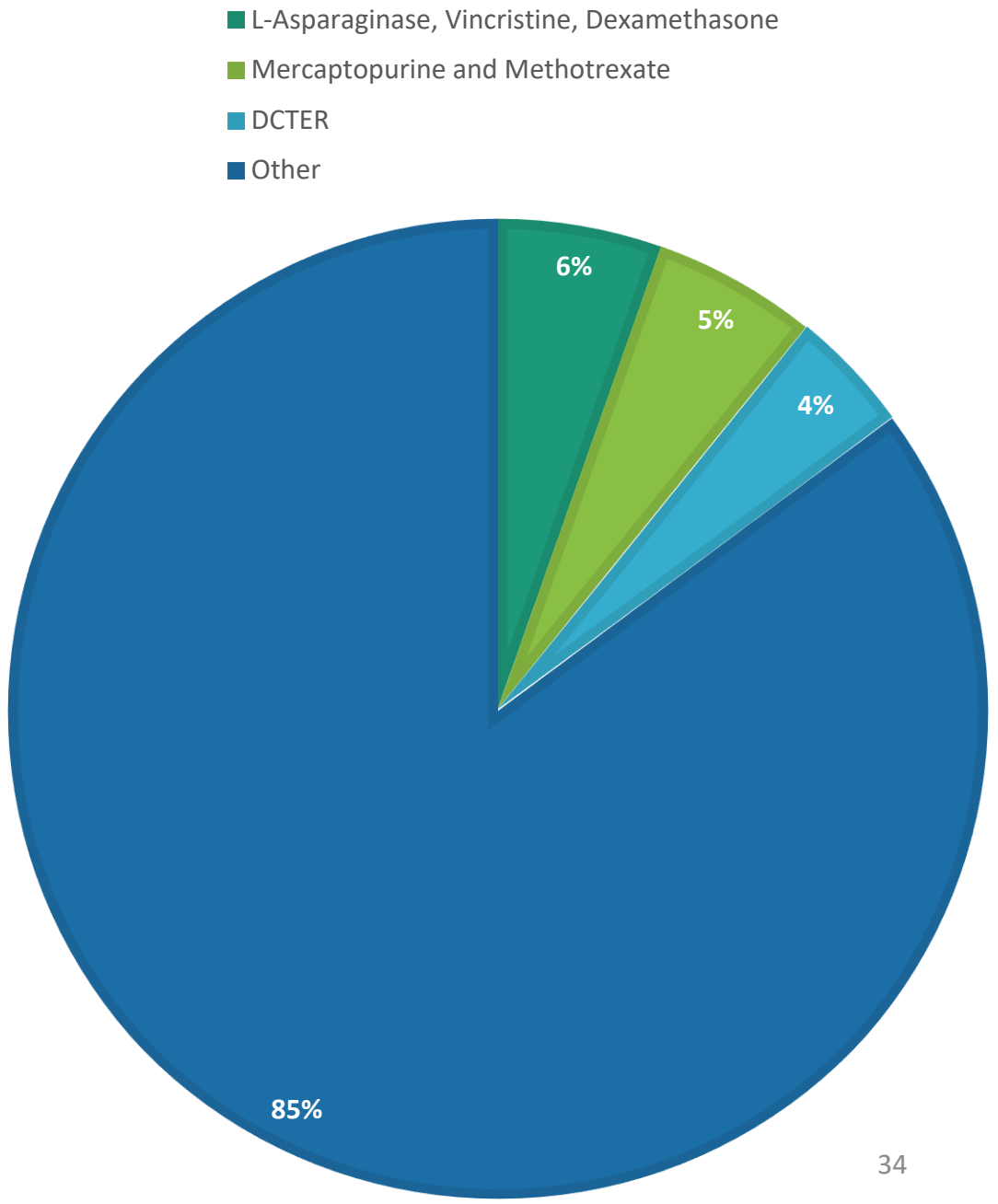
Studies (N=56)

Berg et al. 2005	COG AALL1131	Matthay et al. 1999
CCG 102	COG AALL1231	MRC UKALL XI
CCG 1882	COG AAML0123	OS2006
CCG 1962	COG AAML0531	POG 8101
CCG 213	COG ANBL0032	POG 8615
CCG 241	COG ANBL1221	POG 8704
CCG 251	COG ARST0332 Arm D	POG 9005
CCG 2891	COG ARST0431	POG 9006
CCG 2961	COG CCG-1961	POG 9315
CCG 5942	COG CCG-1991	POG 9404
CCG-105	COG D9803	POG 9457
CCG-106	COG P9425	Ravindranath et al. 1996
CCG-1922	DCOG ALL-9	Saylors et al. 2001
CCG-521	DCOG ALL-VI	SFOP OS94
COG A3961	EORTC 58881	UK MRC ALL97
COG A9952	EORTC 58921	UK MRC AML10
COG AALL0031	EORTC CLG 58951	
COG AALL0232	ET-1	
COG AALL0434	Finlay et al. 1995	
COG AALL07P4	GIMEMA AIDA 0493	

STUDIES BY CONDITION

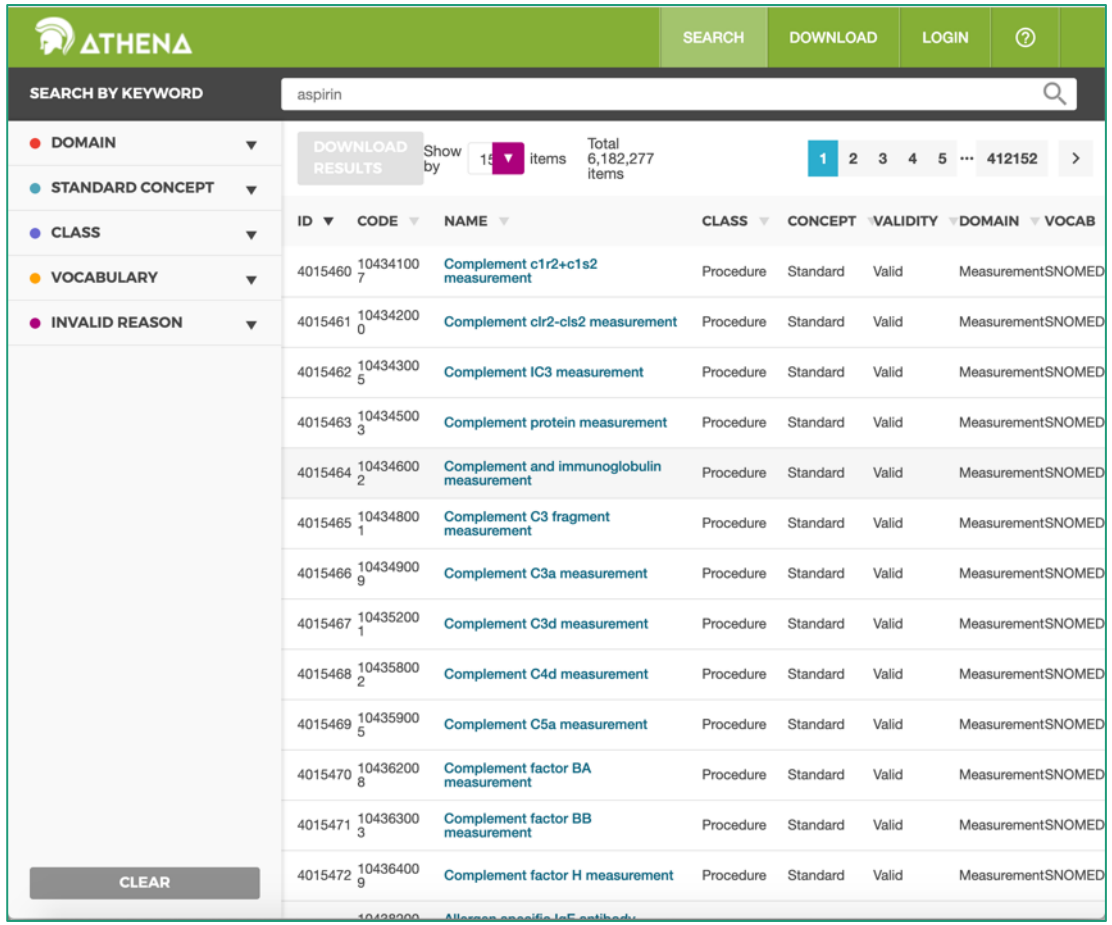


STUDIES BY REGIMEN (N=74)



Ontology Availability

Retrospective research (any user)



http://athena.ohdsi.org/vocabulary/list

Non-commercial user (any use)

Attribution-NonCommercial-ShareAlike 4.0 International (CC BY-NC-SA 4.0)

https://dataverse.harvard.edu/dataverse/HemOnc/

Commercial user (any use other than retrospective)