TrEatment, utiLisation and safEty of medicines for MUltiple Sclerosis (TELEMUS)

***Telemus* is *Eurymus'* son, a prophet and a master at reading signs**

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What is the issue?

Curr Treat Options Neurol (2021) 23:19
DOI 10.1007/s11940-021-00677-1

Multiple Sclerosis and Related Disorders (J Graves, Section Editor)

Early Aggressive Treatment Approaches for Multiple Sclerosis

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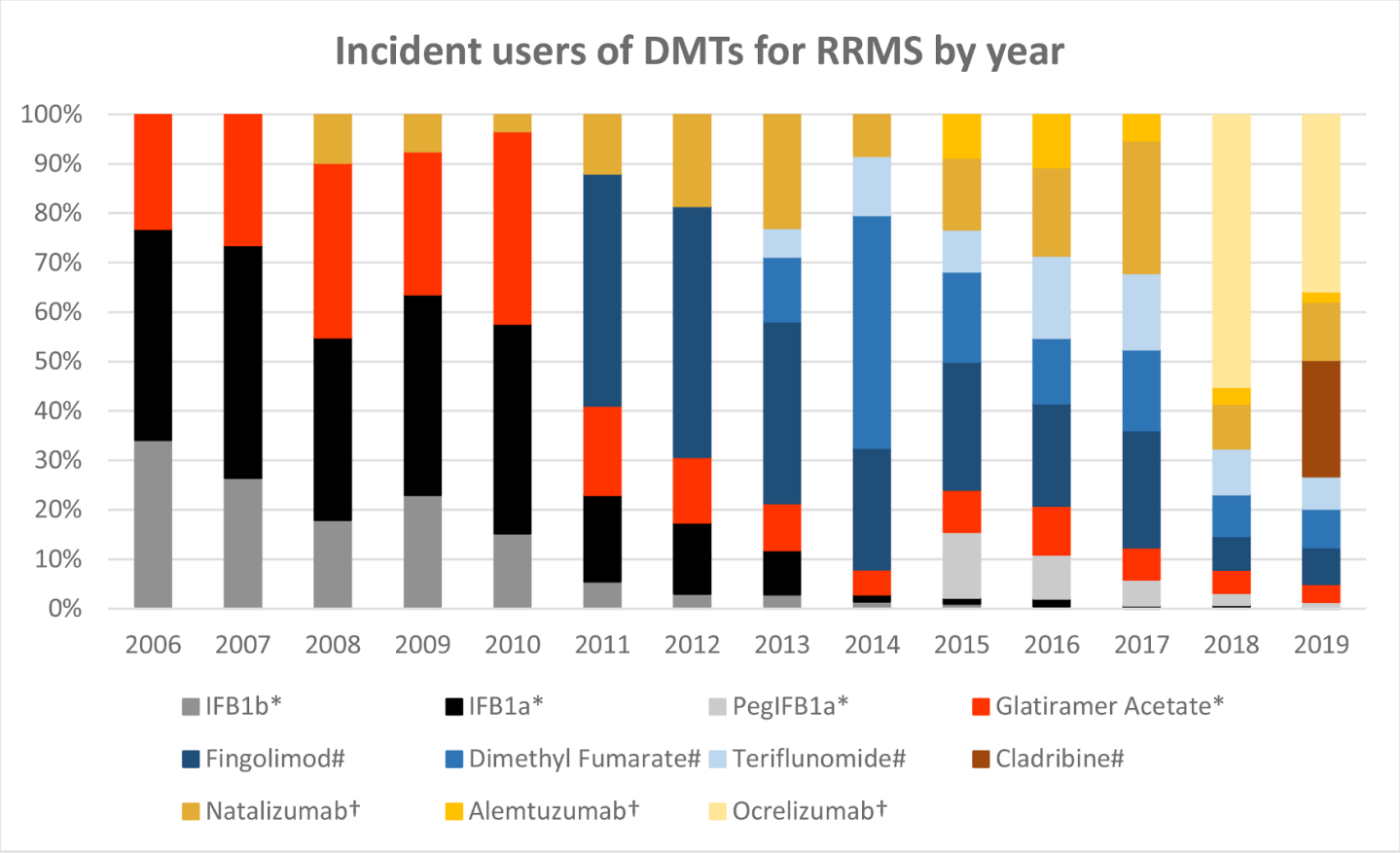
Recent findings

- **Natalizumab** promising efficacy in RCTs and observational studies when compared with placebo, the injectable DMTs, and fingolimod.
- The anti-CD20 B cell depleting therapies (**rituximab, ocrelizumab, and ofatumumab**) demonstrated superiority in RCTs compared to their comparator group (placebo, interferon, and teriflunomide, respectively) and
- **Rituximab** has shown in observational studies to be more effective than older injectable therapies and some of the oral therapies.
- **Alemtuzumab** has shown good efficacy in RCTs and observational studies yet has several potentially severe side effects limiting its use.

Has the increased use of High Efficacy treatments earlier in the treatment pathway led to better outcomes for patients diagnosed with MS?

2. What is the utilisation of multiple sclerosis treatments across the APAC region?

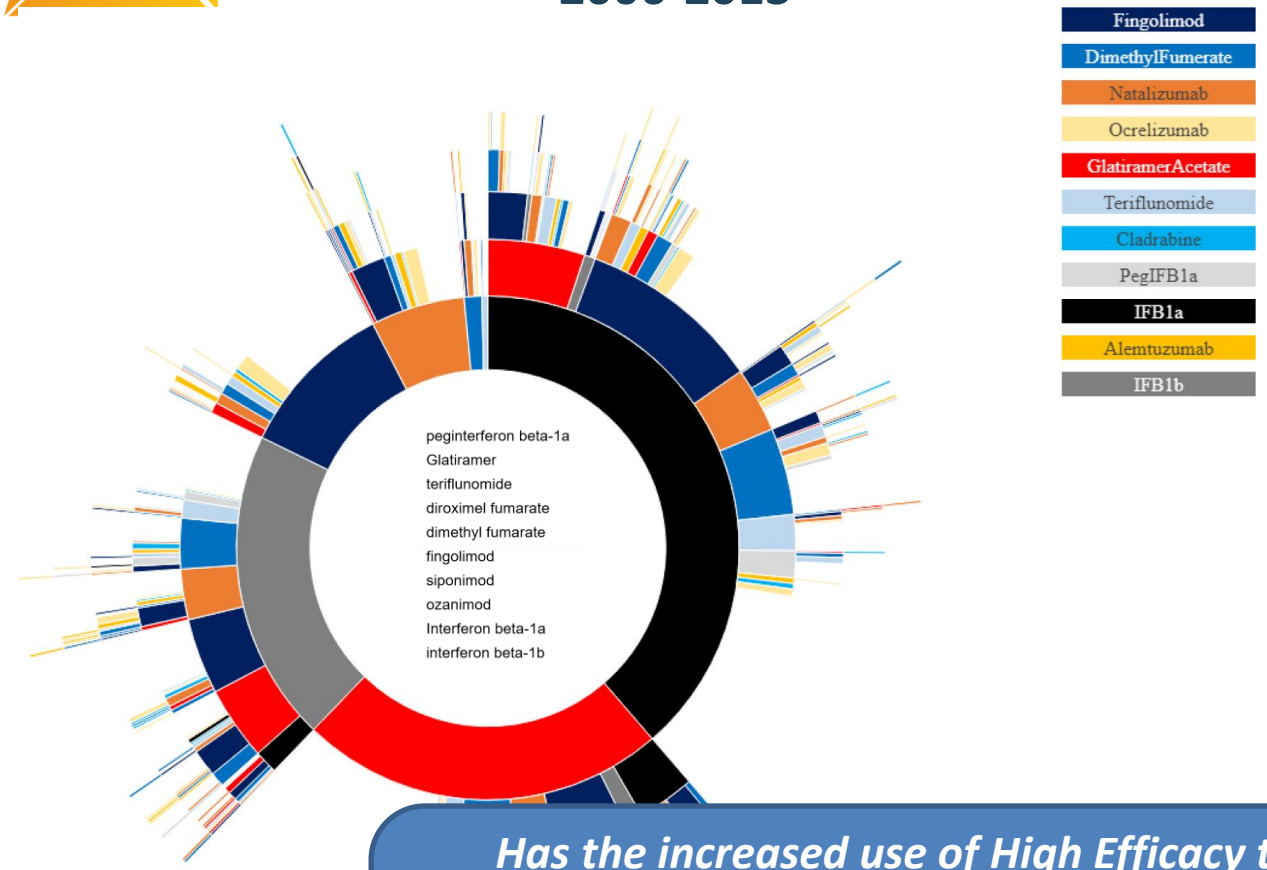


Multiple Sclerosis and Related Disorders 57 (2022) 103412

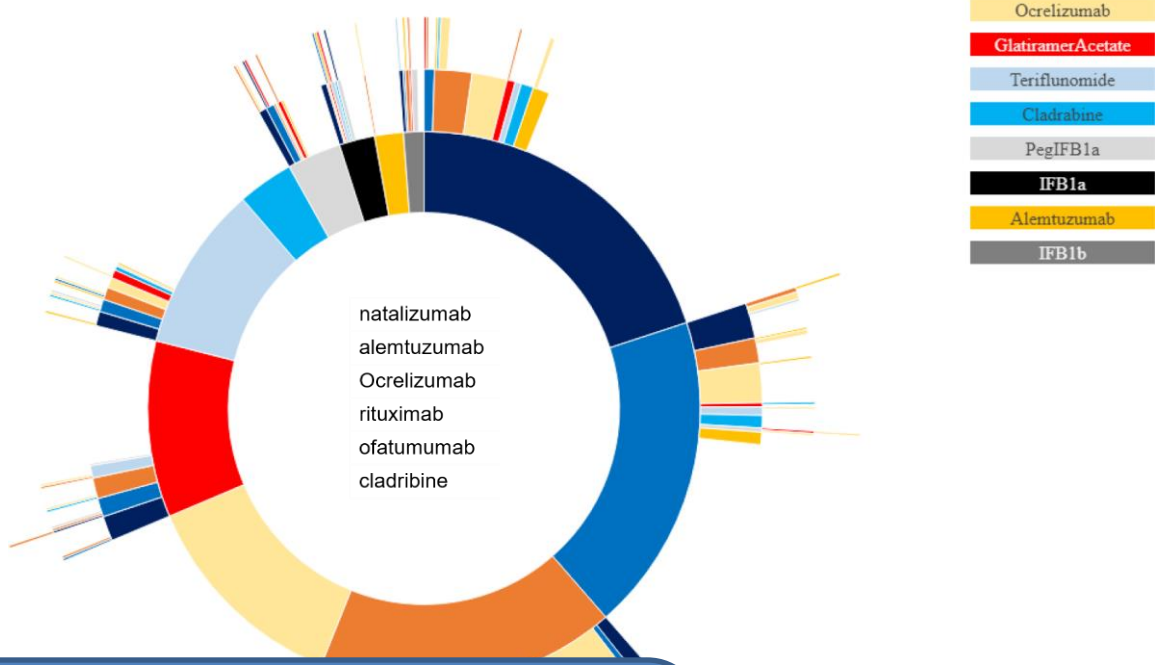
Early aggressive/highly effective

It's a dynamic market!

Traditional Approaches
2006-2013



Early Aggressive Treatment Approaches
2014-2019



Has the increased use of High Efficacy treatments earlier in the treatment pathway led to better outcomes for patients diagnosed with MS?

Escalation approach v early High-Efficacy treatment approach
DELIVER-MS study TREAT-MS study

Hillen J, et al. Utilisation of disease modifying treatment and diversity of treatment pathways in relapsing remitting multiple sclerosis. Mult Scler Relat Disord. 2022;57:103412

RCTs that are investigating the effectiveness of traditional MS treatments with HET strategies

- *The 'Determining the Effectiveness of earLy Intensive Versus Escalation Approaches for the treatment of Relapsing-remitting MS' (DELIVER-MS) (NCT03535298) trial* will directly compare traditional MS with HET strategies and their impact on clinical and radiologic outcomes.
- *The 'TRaditional versus Early Aggressive Therapy for MS' (TREAT-MS*) (NCT03500328) trial aims to 1) evaluate, jointly and independently among patients deemed at higher risk vs. lower risk for disability accumulation, whether an "early aggressive" therapy approach, versus starting with a traditional, first-line therapy, influences the intermediate-term risk of disability, and 2) to evaluate if, among patients deemed at lower risk for disability who start on first-line MS therapies but experience breakthrough disease, those who switch to a higher-efficacy versus a new first-line therapy have different intermediate-term risk of disability."
- The DELIVER-MS study is due for completion in 2025 while the TREAT-MS study is due for completion in 2024.

Utilisation

1. Characterization
   - Characteristics of initiators over time
   - Trends in use over time
   - Treatment pathways
     - Overall
     - By Calendar Era
     - By Traditional/Early aggressive approaches

2. What is the utilisation of multiple sclerosis treatments across the APAC region?

Early aggressive/highly effective

Medicine	Concept_ID
natalizumab	735843
alemtuzumab	1312706
Ocrelizumab	1593457
rituximab	1314273
ofatumumab	40167582
cladribine	19054825

Traditional/escalation

Medicine	Concept_ID
peginterferon beta-1a	45775146
Glatiramer	751889
teriflunomide	42900584
diroximel fumarate	37497593
dimethyl fumarate	43526424
fingolimod	40226579
siponimod	1510913
ozanimod	37499437
Interferon beta-1a	722424
interferon beta-1b	713196

Other FDA approved

Medicine	Concept_ID
Daclizumab	19036892
Mitoxantrone	1309188

Event Cohorts

Each Event Cohort defines the step in a pathway that may occur for a person in the Target Cohort.

Import

Show 10 entries Search:

ID	Name		
41	[MS] interferon beta-1a exposure (1)	Edit cohort	Remove
42	[MS] glatiramer exposure (1)	Edit cohort	Remove
43	[MS] fingolimod exposure (1)	Edit cohort	Remove
44	[MS] dimethyl fumarate exposure (1)	Edit cohort	Remove
45	[MS] ocrelizumab exposure (1)	Edit cohort	Remove
46	[MS] natalizumab exposure (1)	Edit cohort	Remove
47	[MS] mitoxantrone exposure (1)	Edit cohort	Remove
48	[MS] interferon beta-1b exposure (1)	Edit cohort	Remove
49	[MS] daclizumab exposure (1)	Edit cohort	Remove
50	[MS] cladribine exposure (1)	Edit cohort	Remove

Showing 1 to 10 of 16 entries Previous 1 2 Next

Analysis Settings

The following set of parameters will be used when performing the pathway analysis.

Collapse Days:	1	Any dates found within the specified collapse days will be reassigned the earliest date. Collapsing dates reduces pathway variation, leading to a reduction in 'noise' in the result.
Minimum cell count:	0	Minimum number of subjects in the target cohort for a given event in order to be counted in the pathway.
Maximum path length:	10	Maximum number of steps in a given pathway to be included in the sunburst plot.
Allow repeats:	false	Allow cohort events/combos to appear multiple times in the same pathway.

ATLAS

- Home
- Data Sources
- Search
- Concept Sets
- Cohort Definitions
- Characterizations
- Cohort Pathways
- Incidence Rates
- Profiles
- Estimation
- Prediction
- Jobs
- Configuration
- Feedback

Cohort #50

[MS] cladribine exposure (1)

Definition | Concept Sets | Generation | Samples | Reporting | Export | Messages 4

New Concept Set | Import | Export All Concept Sets To CSV

Show 10 entries Filter Concept Sets: Search...

Id	Title
0	[MS] cladribine

Showing 1 to 1 of 1 entries Previous 1 Next

Concept Set Expression | Included Concepts 175 | Included Source Codes | Export | Import

Name: [MS] cladribine

Show 25 entries Search: Search...

Showing 1 to 2 of 2 entries Previous 1 Next

Concept Id	Concept Code	Concept Name	Domain	Standard Concept Caption	Exclude	Descendants	Mapped
43266125	OMOP528444	Cladribine 10 MG Oral Tablet Box of 1	Drug	Standard	☐	☑	☐
19054825	44157	cladribine	Drug	Standard	☐	☑	☐

Classification Non-Standard Standard

Add Concepts | Remove Selected Concepts | Delete Concept Set | Copy To Concept Set Repository | Close Concept Set

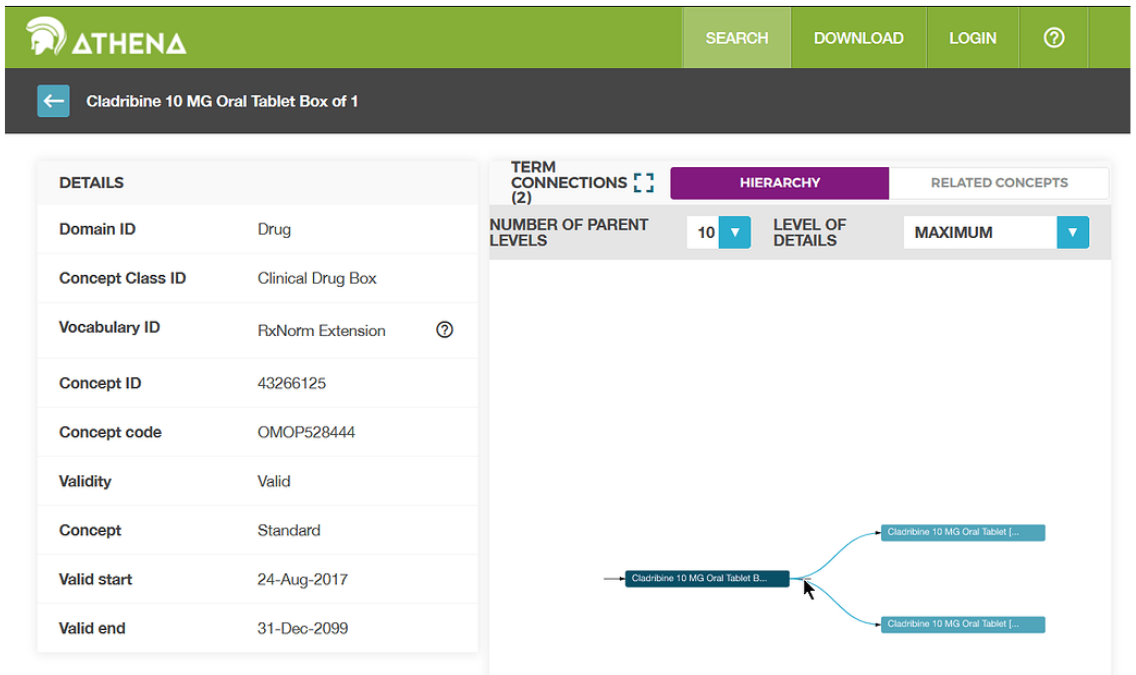
tystan 1y 3d

Hi Vocab Wizzes

I was unsure where/who to reach out with this so apologies if this is not the right place - please feel free to point me in the right direction.

I believe we have come across an orphaned Concept ID for the medication “Cladribine 10 MG Oral Tablet Box of 1”. It’s a standard and valid concept but it does not seem to be a descendant of the more general RXNorm standard concept of “Cladribine” as an ingredient.

I paste a screenshot of the hierarchy diagram on Athena for “Cladribine 10 MG Oral Tablet Box of 1” that does seem to be self-referential/not have a “is a” relationship with the ingredient standard concept.



mik Michael Kallfelz 5d

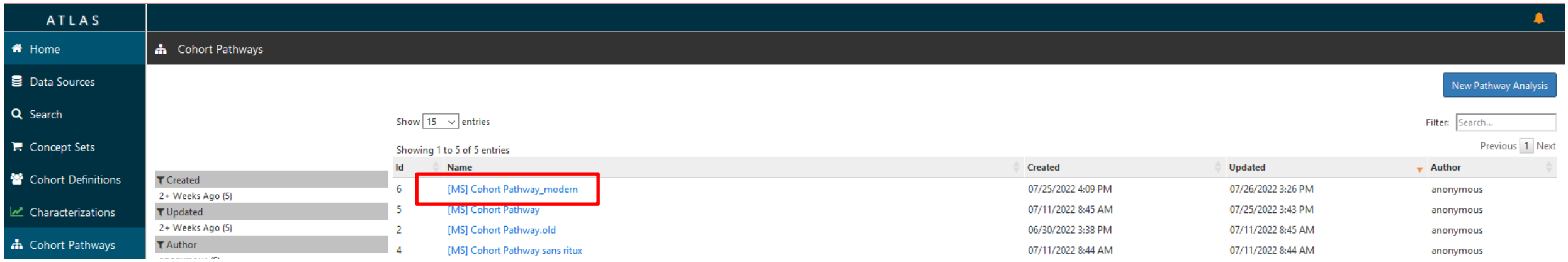
Hi @tystan - for creating a new issue about existing content that needs fixing, go here. For your case the “Faulty content” template is probably best.
You do not have to repeat the whole forum post of course, but just state the facts and insert a link back to the post!
Thanks for spotting this!
~mik

tystan Ty 5d

>  tystan:
>
> create the parent-descendant relationship between the Concept IDs 43266125 and 19054825

Thanks for such a quick and helpful response @mik ! I have submitted a github issue:
https://github.com/OHDSI/Vocabulary-v5.0/issues/678 1

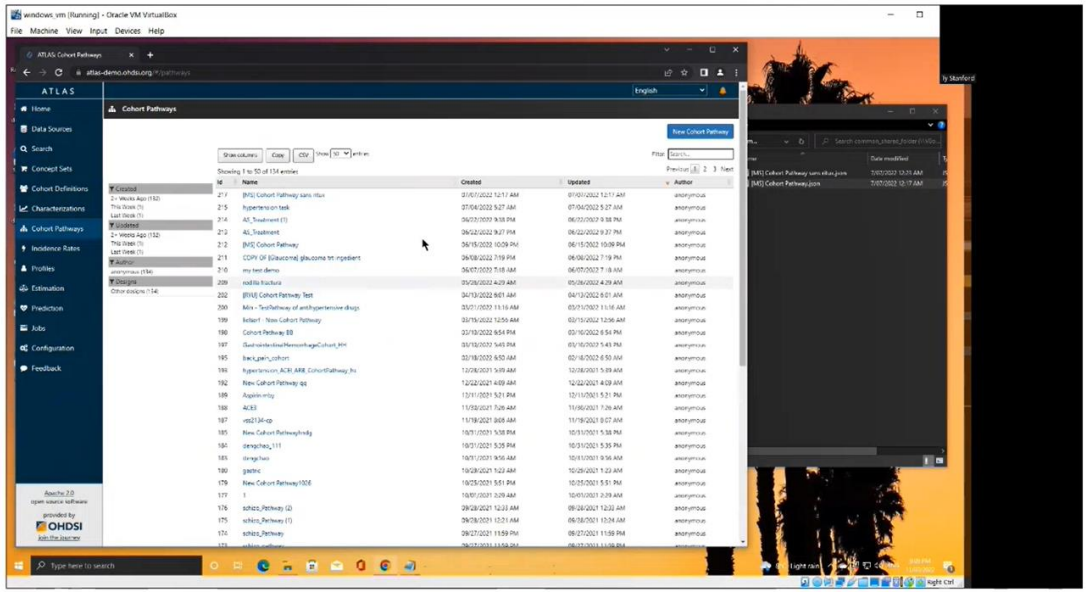
Treatment pathways



Mini-tutorial (building treatment pathways) by Ty Stanford

OHDSI APAC Study 3 (Multiple Sclerosis) Meeting-20220713_110558-Meeting Recording.mp4

Treatment Pathways

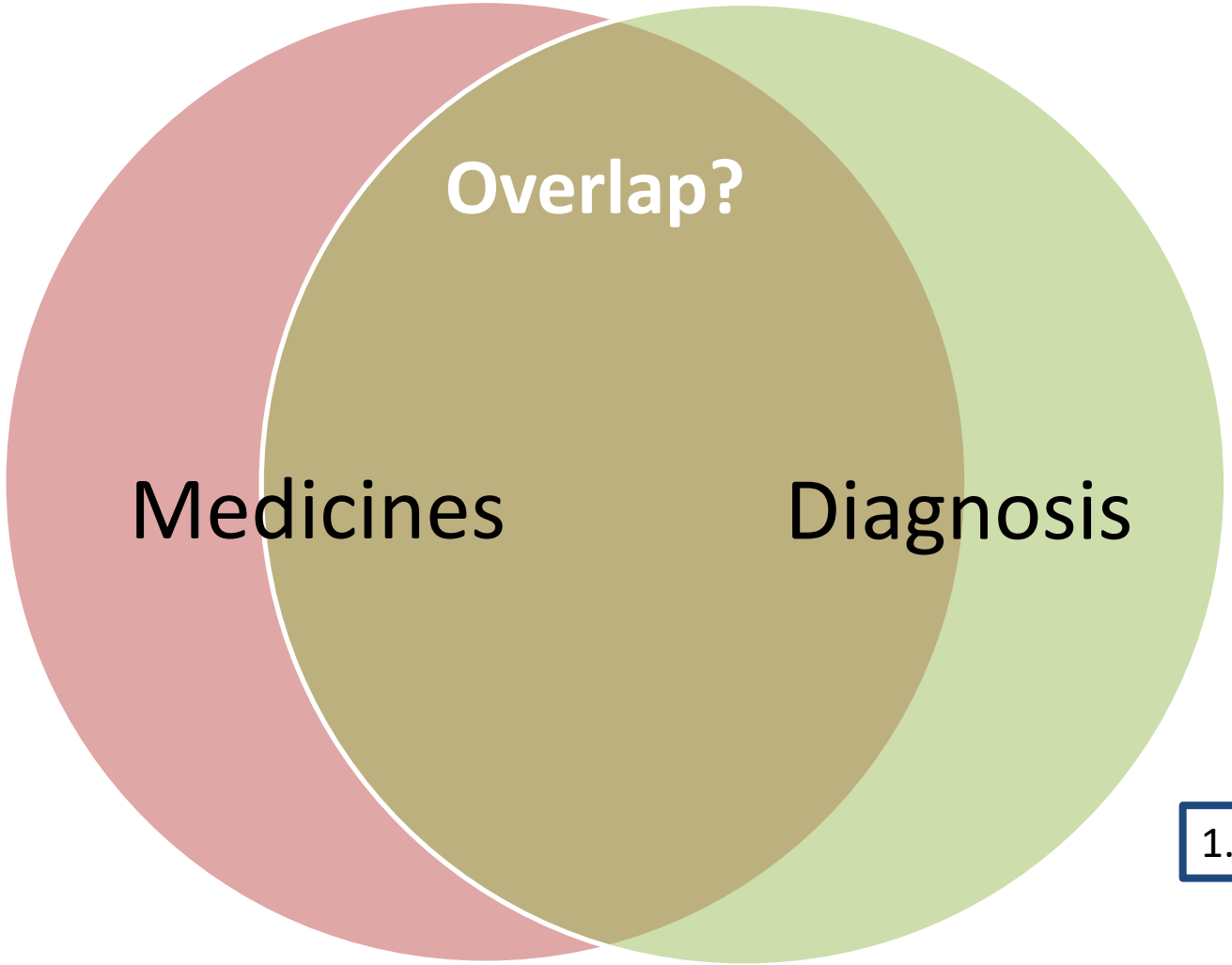


Validation of phenotypes

Cohorts

- Generate cohorts **with** and without diagnosis
- Evaluate treatment schedules for the **3x medicine** condition
  - particularly for medicines that have 6/12month dosing schedules or limited dose eg alemtuzumab (12 months), ocrelizumab (6 months)

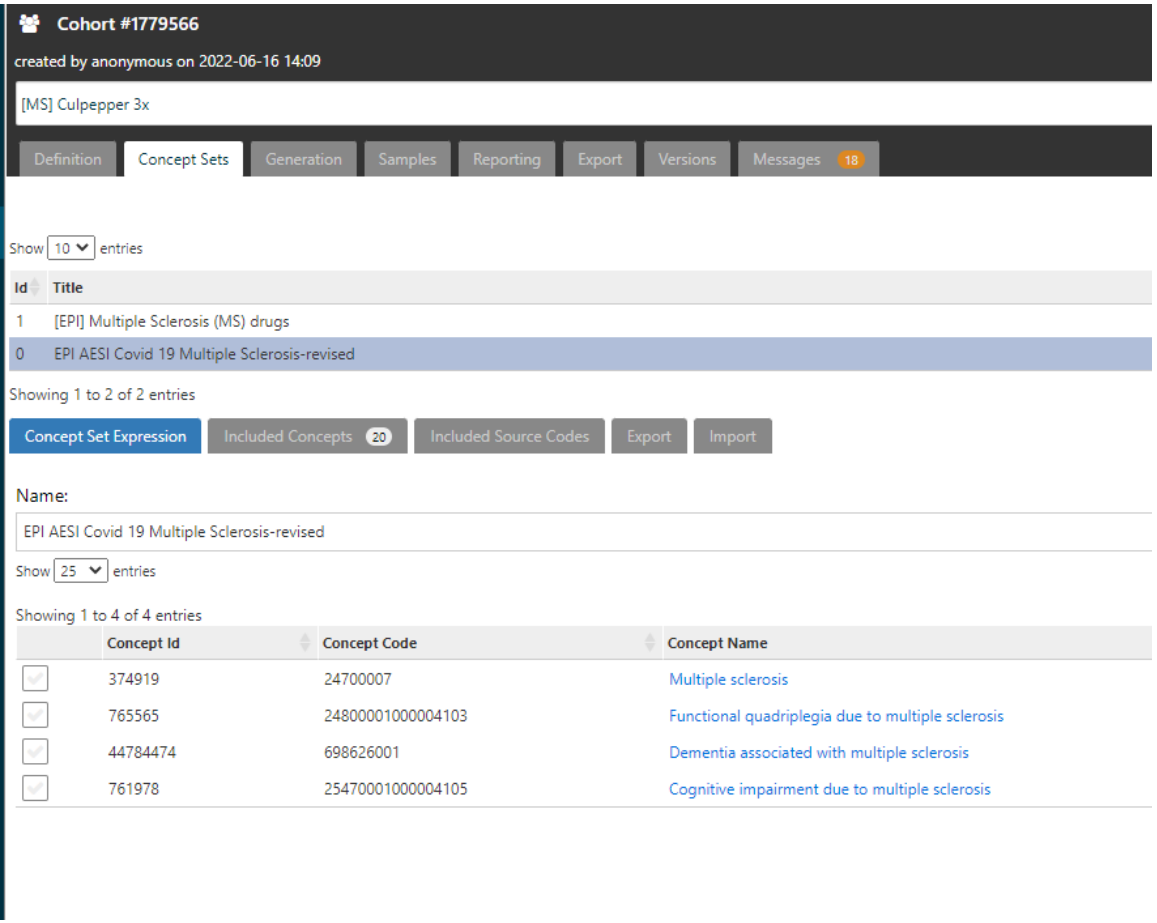
MS Phenotype



Culpepper:
Earliest occurrence of MS diagnosis, requiring ≥3
[
MS-related occurrences of any combination of inpatient or outpatient diagnosis
OR
specific disease-modifying therapies (DMT)
]
within a 1-year time period

1. Determine overlap between diagnosis and treatment

Diagnosis



In the absence of diagnostic information:

- Must be treated by a neurologist (*provider specialty*).
- Magnetic resonance imaging of the brain and/or spinal cord (*procedure*)

Disease-modifying therapies (DMT)

Show 10 entries

Id	Title
1	[EPI] Multiple Sclerosis (MS) drugs

Showing 1 to 1 of 1 entries

Concept Set Expression | Included Concepts 3736 | Included Source Codes | Export | Import

Name:

[EPI] Multiple Sclerosis (MS) drugs

Show 25 entries

Showing 1 to 16 of 16 entries

Concept Id	Concept Code	Concept Name	Domain	Standard Concept Caption
42900584	1310520	teriflunomide	Drug	Standard
1510913	2121085	siponimod	Drug	Standard
1314273	121191	rituximab	Drug	Standard
45775146	1546168	peginterferon beta-1a	Drug	Standard
1593457	1876366	ocrelizumab	Drug	Standard
735843	354770	natalizumab	Drug	Standard
1309188	7005	mitoxantrone	Drug	Standard
713196	72257	interferon beta-1b	Drug	Standard
722424	75917	interferon beta-1a	Drug	Standard
751889	214582	glatiramer	Drug	Standard
40226579	1012892	fingolimod	Drug	Standard
37497593	2261783	diroximel fumarate	Drug	Standard
43526424	1373478	dimethyl fumarate	Drug	Standard
19036892	190353	daclizumab	Drug	Standard
19054825	44157	cladribine	Drug	Standard
1312706	117055	alemtuzumab	Drug	Standard

Explore 3x medicine condition (particularly for medicines that have 6mth/12month dosing schedules or limited dose eg **alemtuzumab, ocrelizumab**)

Explore inclusion of **rituximab mitoxantrone cladribine** (others) may be problematic if we are unable to use diagnoses as they can be used for multiple indications (eg cancer)

Early aggressive/early highly effective	Concept_ID	Formulation	Treatment	Indication
natalizumab	735843	infusion	Monthly (30)	Potentially used in Crohns
alemtuzumab	1312706	infusion	**12 months**	
Ocrelizumab	1593457	infusion	**6 monthly**	
rituximab	1314273			Potentially used in RA
ofatumumab	40167582	injection	30 days	
cladribine	19054825	Oral (table)	30 days	Also used in cancer (L01BB04 injection)
Traditional/escalation treatments	Concept_ID	Formulation	Treatment	Indication
peginterferon beta-1a	45775146	injection	30 days	
Glatiramer (acetate)	751889	injection	30 days	
teriflunomide	42900584	oral	30 days	
diroximel fumarate	37497593	delayed-release capsules		
dimethyl fumarate	43526424	oral	30 days	
fingolimod	40226579	oral	30 days	
siponimod	1510913	oral	30 days	
ozanimod	37499437	oral	30 days	
Interferon beta-1a	722424	injection	30 days	
interferon beta-1b	713196	injection	30 days	
Other Approved	Concept_ID	Formulation	Treatment	Indication
Daclizumab	19036892	injection	30 days	
Mitoxantrone	1309188		?	
ponesimod	740121	oral	?	

Next Steps

1. Finalise characterization and treatment pathway package
2. Develop phenotype cohorts considering dosing schedules (3x dispensing requirement) & validation with and without MS diagnosis

Thank you!

- Fortnightly meetings at 11am Korean Time on Wednesday