



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

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

nicole.pratt@unisa.edu.au



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

Alexandra Simpson, MD¹
Ellen M. Mowry, MD, MCR¹
Scott D. Newsome, DO^{1,2,*}

Address

¹Department of Neurology, Johns Hopkins School of Medicine, Baltimore, MD, USA
²Division of Neuroimmunology and Neurological Infections, Johns Hopkins Hospital, 600 North Wolfe St., Pathology 627, Baltimore, MD, 21287, USA
Email: snewsom2@jhmi.edu

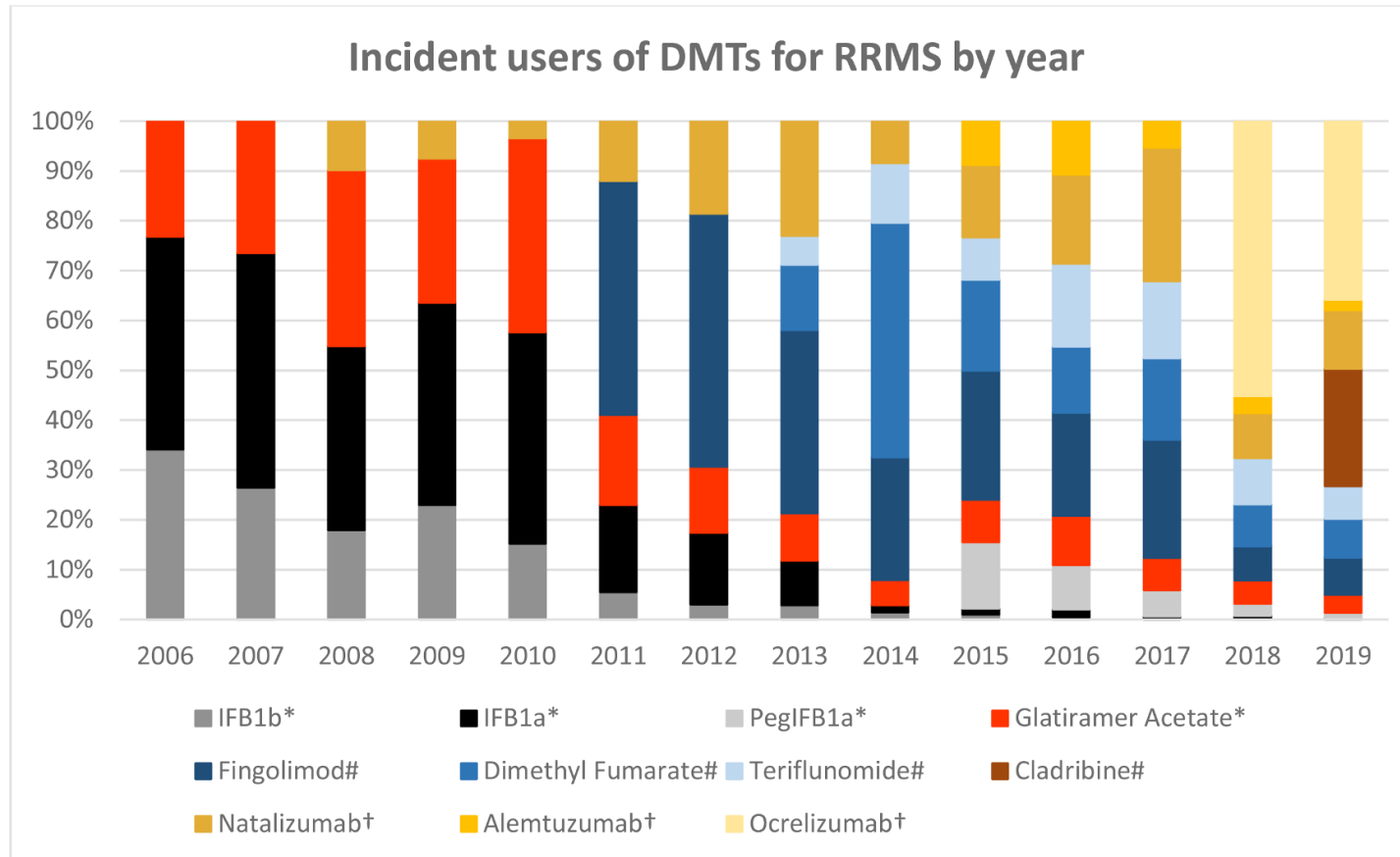
Recent findings

- **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?

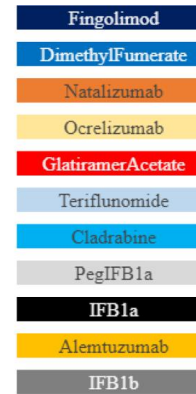
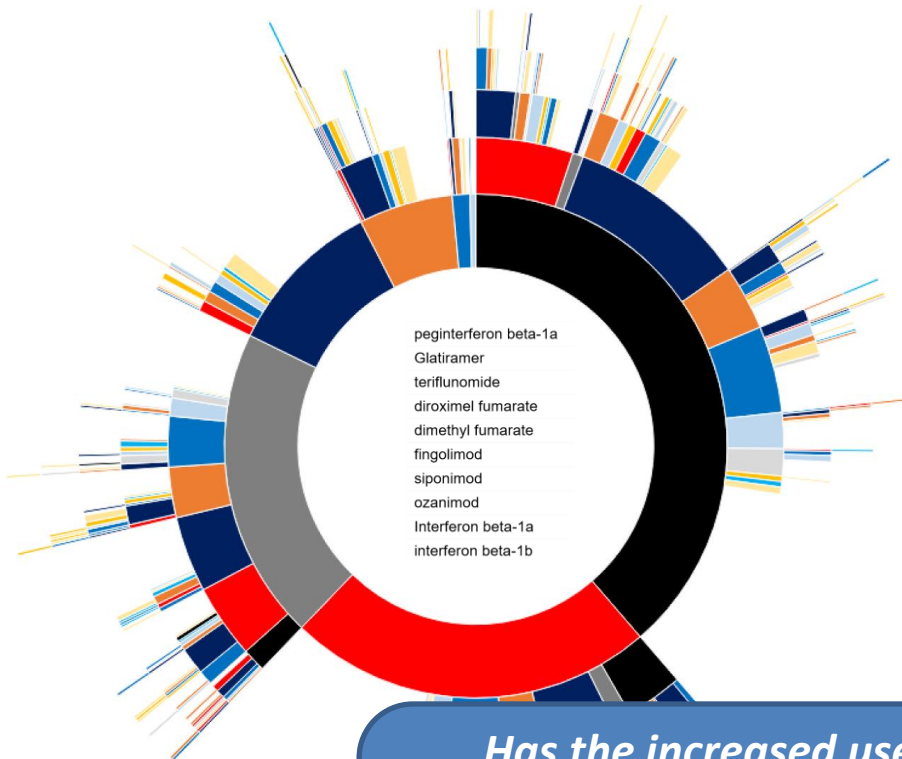


Early aggressive/highly effective

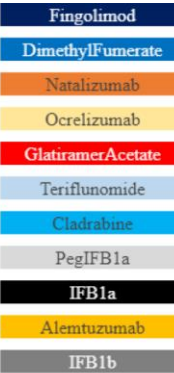
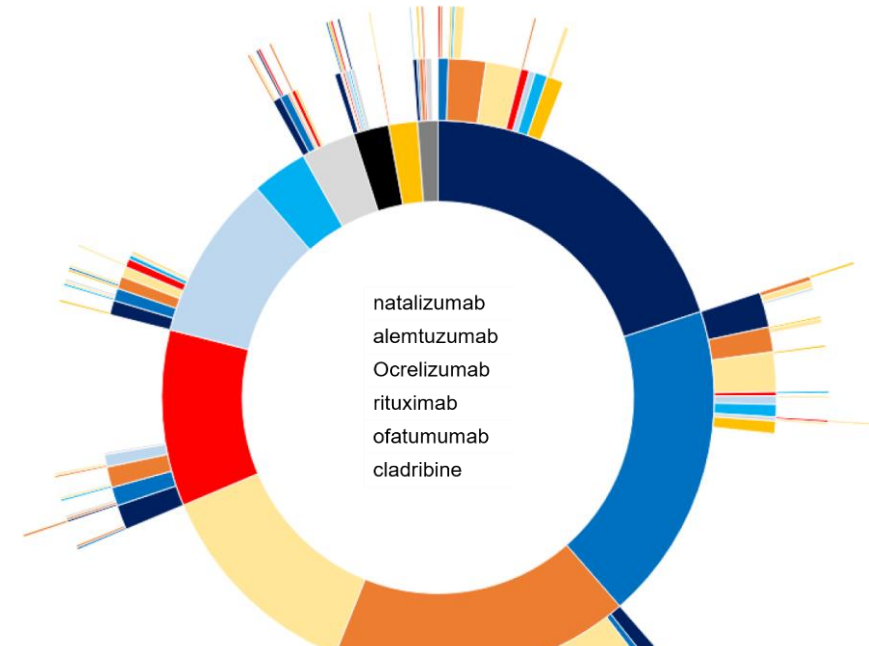
It's a dynamic market!



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



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

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

New Concept Set Import Export All Concept Sets To CSV

Show 10 entries

Filter Concept Sets

Id Title

0 [MS] cladribine

Showing 1 to 1 of 1 entries

Concept Set Expression Included Concepts 175 Included Source Codes Export Import

Name: [MS] cladribine

Show 25 entries

Showing 1 to 2 of 2 entries

<input type="checkbox"/>	Concept Id	Concept Code	Concept Name	Domain	Standard Concept Caption	<input type="checkbox"/> Exclude	<input checked="" type="checkbox"/> Descendants	<input type="checkbox"/> Mapped
<input checked="" type="checkbox"/>	43266125	OMOPS28444	Cladribine 10 MG Oral Tablet Box of 1	Drug	Standard	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>
<input checked="" type="checkbox"/>	19054825	44157	cladribine	Drug	Standard	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>

Classification Non-Standard Standard

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



tystan ty


30

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.

 ATHENA

SEARCH

DOWNLOAD

LOGIN

?

← Cladribine 10 MG Oral Tablet Box of 1

DETAILS

Domain ID	Drug
Concept Class ID	Clinical Drug Box
Vocabulary ID	RxNorm Extension ?
Concept ID	43266125
Concept code	OMOP528444
Validity	Valid
Concept	Standard
Valid start	24-Aug-2017
Valid end	31-Dec-2099

TERM CONNECTIONS (2)

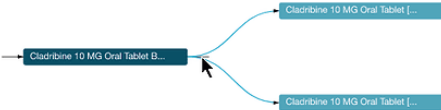
HIERARCHY

RELATED CONCEPTS

NUMBER OF PARENT LEVELS 10

LEVEL OF DETAILS

MAXIMUM





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

ATLAS		Cohort Pathways			
Home					
Data Sources					
Search					
Concept Sets					
Cohort Definitions					
Characterizations					
Cohort Pathways					

Showing 1 to 5 of 5 entries

Show 15 entries

Filter: Search...

Previous 1 Next

Created	Updated	Author
2+ Weeks Ago (5)		
Updated		
2+ Weeks Ago (5)		
Author		

Id	Name	Created	Updated	Author
6	[MS] Cohort Pathway_modern	07/25/2022 4:09 PM	07/26/2022 3:26 PM	anonymous
5	[MS] Cohort Pathway	07/11/2022 8:45 AM	07/25/2022 3:43 PM	anonymous
2	[MS] Cohort Pathway.old	06/30/2022 3:38 PM	07/11/2022 8:45 AM	anonymous
4	[MS] Cohort Pathway sans ritux	07/11/2022 8:44 AM	07/11/2022 8:44 AM	anonymous

New Pathway Analysis

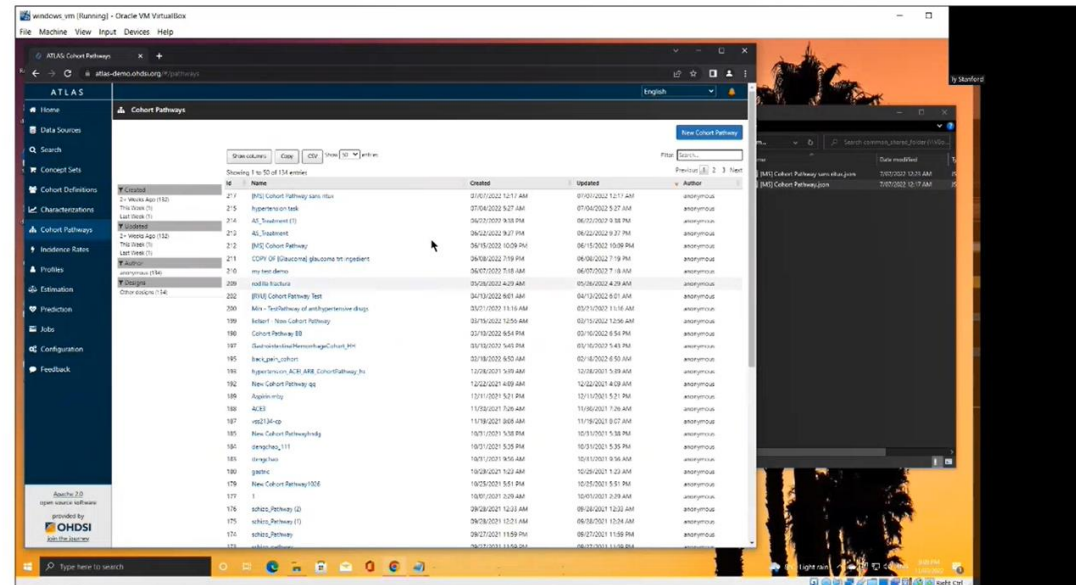


Mini-tutorial (building treatment pathways) by Ty Stanford

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



Treatment Pathways



The screenshot shows the ATLAS Cohort Pathways interface. The left sidebar contains navigation options: Home, Data Sources, Search, Concept Sets, Cohort Definitions, Cohort Pathways, Incidence Rates, Profiles, Estimations, Prediction, Jobs, Configuration, and Feedback. The main panel displays a table of cohort pathways.

ID	Name	Created	Updated	Author
217	[BNC] Cohort Pathway: new risk	01/01/2022 12:17 AM	01/01/2022 12:17 AM	anonymous
215	Hypernatremia test	07/04/2022 9:27 AM	07/04/2022 9:27 AM	anonymous
214	AC Treatment (?)	06/01/2022 9:18 PM	06/01/2022 9:18 PM	anonymous
213	ALL Treatment	06/02/2022 9:27 PM	06/02/2022 9:27 PM	anonymous
212	[BNC] Cohort Pathway	06/15/2022 10:09 PM	06/15/2022 10:09 PM	anonymous
211	CCPV OR Education glucose test ingredient	06/06/2022 7:19 PM	06/06/2022 7:19 PM	anonymous
210	my test demo	06/07/2022 7:18 AM	06/07/2022 7:18 AM	anonymous
209	Initial Feature	02/06/2022 4:29 AM	02/06/2022 4:29 AM	anonymous
208	[BNC] Cohort Pathway Test	04/13/2022 6:01 AM	04/13/2022 6:01 AM	anonymous
200	Mix - TestPathway of anti-hypertensive drugs	03/11/2022 11:16 AM	03/11/2022 11:16 AM	anonymous
199	Robert - New Cohort Pathway	03/16/2022 12:56 AM	03/16/2022 12:56 AM	anonymous
198	Cohort Pathway: BB	03/16/2022 8:54 PM	03/16/2022 8:54 PM	anonymous
187	Search results for Hypernatremia Cohort_Hist	02/16/2022 5:45 PM	02/16/2022 5:45 PM	anonymous
195	Back_Lookup Cohort	02/16/2022 6:50 AM	02/16/2022 6:50 AM	anonymous
196	Hypernatremia ACB: ABE Cohort Pathway: Hi	12/06/2021 5:09 AM	12/06/2021 5:09 AM	anonymous
192	New Cohort Pathway: ss	12/02/2021 4:09 AM	12/02/2021 4:09 AM	anonymous
190	Aggravation	12/11/2021 5:21 PM	12/11/2021 5:21 PM	anonymous
188	ACB3	11/06/2021 7:26 AM	11/06/2021 7:26 AM	anonymous
187	rs2134-up	11/09/2021 8:07 AM	11/09/2021 8:07 AM	anonymous
185	New Cohort Pathway: hdy	10/11/2021 5:38 PM	10/11/2021 5:38 PM	anonymous
181	derogates_111	10/11/2021 5:39 PM	10/11/2021 5:39 PM	anonymous
180	longevity	10/11/2021 9:06 AM	10/11/2021 9:06 AM	anonymous
180	glycine	10/09/2021 1:23 AM	10/09/2021 1:23 AM	anonymous
179	New Cohort Pathway: DDE	10/05/2021 5:51 PM	10/05/2021 5:51 PM	anonymous
177	1	10/01/2021 3:29 AM	10/01/2021 3:29 AM	anonymous
176	schizophrenia (2)	09/24/2021 12:22 AM	09/24/2021 12:22 AM	anonymous
175	schizophrenia (1)	09/20/2021 1:23 AM	09/20/2021 1:23 AM	anonymous
174	schizophrenia	09/27/2021 11:59 PM	09/27/2021 11:59 PM	anonymous
173	schizophrenia	09/27/2021 11:59 PM	09/27/2021 11:59 PM	anonymous



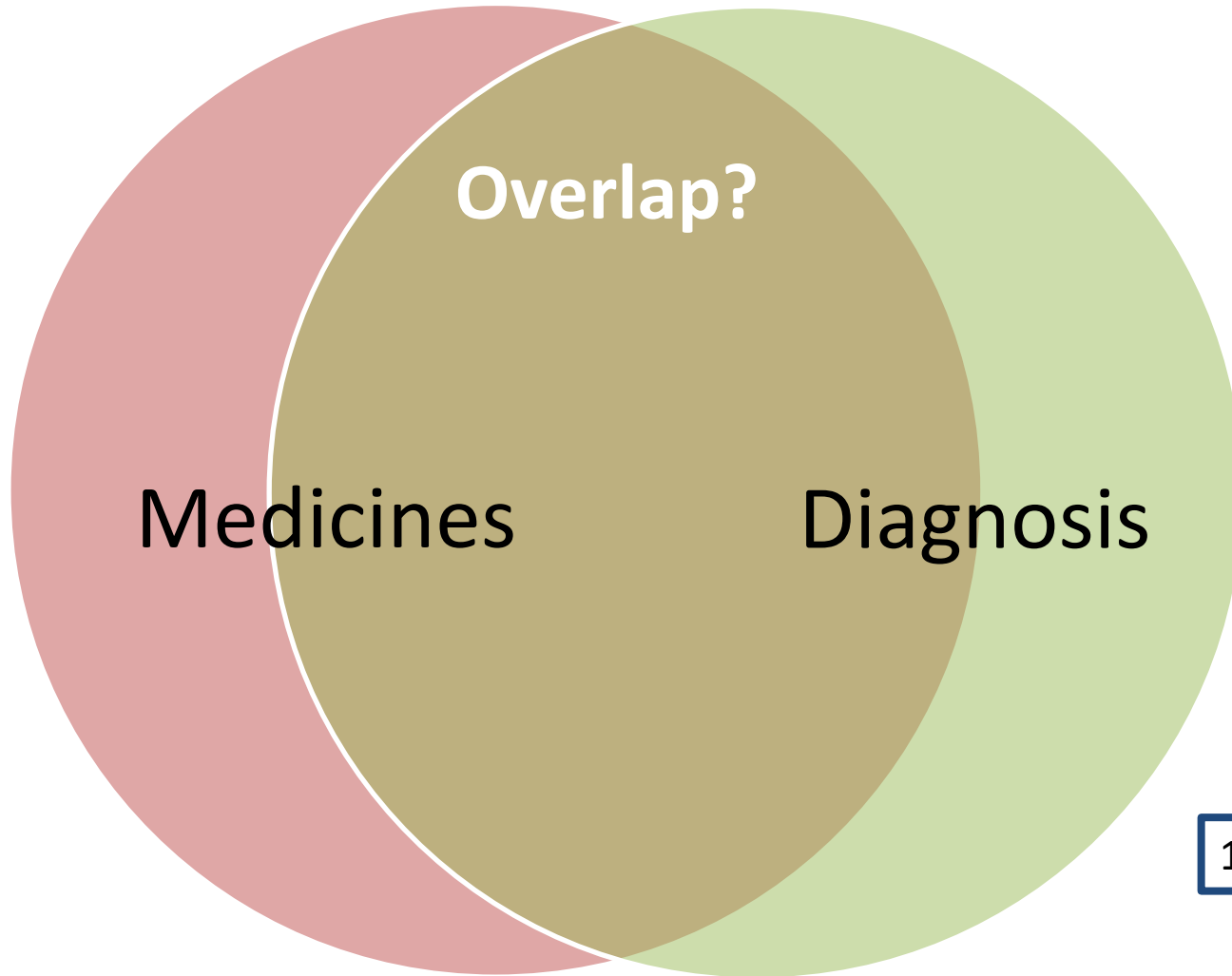
Validation of phenotypes

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

Cohort #1779566
created by anonymous on 2022-06-16 14:09

[MS] Culpepper 3x

Definition Concept Sets Generation Samples Reporting Export Versions Messages 18

Show 10 entries

Id	Title
1	[EPI] Multiple Sclerosis (MS) drugs
0	EPI AESI Covid 19 Multiple Sclerosis-revised

Showing 1 to 2 of 2 entries

Concept Set Expression Included Concepts 20 Included Source Codes Export Import

Name:

EPI AESI Covid 19 Multiple Sclerosis-revised

Show 25 entries

Showing 1 to 4 of 4 entries

	Concept Id	Concept Code	Concept Name
<input checked="" type="checkbox"/>	374919	24700007	Multiple sclerosis
<input checked="" type="checkbox"/>	765565	24800001000004103	Functional quadriplegia due to multiple sclerosis
<input checked="" type="checkbox"/>	44784474	698626001	Dementia associated with multiple sclerosis
<input checked="" type="checkbox"/>	761978	25470001000004105	Cognitive impairment due to multiple sclerosis

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
<input checked="" type="checkbox"/>	42900584	1310520	teriflunomide	Drug	Standard
<input checked="" type="checkbox"/>	1510913	2121085	siponimod	Drug	Standard
<input checked="" type="checkbox"/>	1314273	121191	rituximab	Drug	Standard
<input checked="" type="checkbox"/>	45775146	1546168	peginterferon beta-1a	Drug	Standard
<input checked="" type="checkbox"/>	1593457	1876366	ocrelizumab	Drug	Standard
<input checked="" type="checkbox"/>	735843	354770	natalizumab	Drug	Standard
<input checked="" type="checkbox"/>	1309188	7005	mitoxantrone	Drug	Standard
<input checked="" type="checkbox"/>	713196	72257	interferon beta-1b	Drug	Standard
<input checked="" type="checkbox"/>	722424	75917	interferon beta-1a	Drug	Standard
<input checked="" type="checkbox"/>	751889	214582	glatiramer	Drug	Standard
<input checked="" type="checkbox"/>	40226579	1012892	fingolimod	Drug	Standard
<input checked="" type="checkbox"/>	37497593	2261783	diroximel fumarate	Drug	Standard
<input checked="" type="checkbox"/>	43526424	1373478	dimethyl fumarate	Drug	Standard
<input checked="" type="checkbox"/>	19036892	190353	daclizumab	Drug	Standard
<input checked="" type="checkbox"/>	19054825	44157	cladribine	Drug	Standard
<input checked="" type="checkbox"/>	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	?	



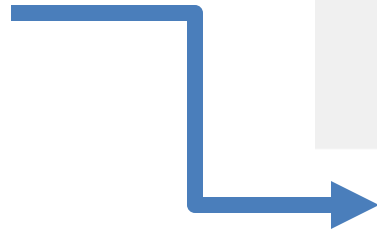
Next Steps

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



OHDSI APAC



General

2022 APAC Study 1 (CHAPTER)

2022 APAC Study 2 (ACESO_Lo...

2022 APAC Study 3 (Multiple S...

2022 APAC Study 4 (Data Qual...