Use of Real-World Evidence (RWE) to Drive Drug Development Strategy and Inform Clinical Trial Design

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Moderator:
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Event
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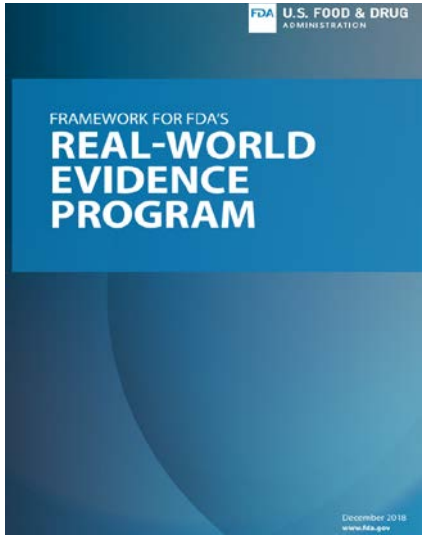
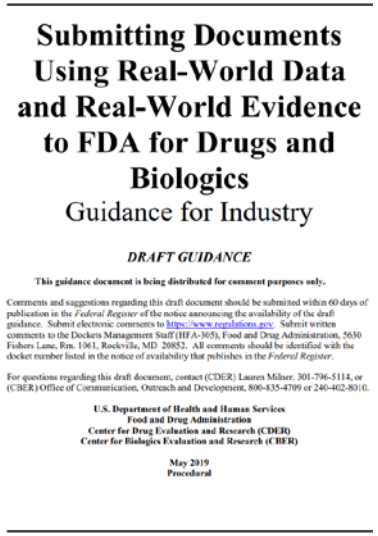
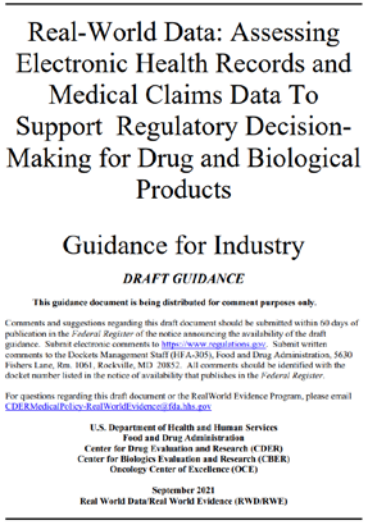
Brief history of RWE in the US

- Congress passed 21st Century Cures Act in December 2016
- Included a provision on Real World Evidence (Section 3022)
- Modified Federal Food, Drug, and Cosmetic Act to add section 505F
- Instructed FDA to evaluate use of RWE in drug approval process and:
  1. Develop framework for using RWE in drug approvals within 2 years
  2. Draft guidance on using RWE in drug approvals within 5 years
  3. Pursue RWE partnerships with industry, academia, professional organizations, etc.




Submitting Documents Using Real-World Data and Real-World Evidence to FDA for Drugs and Biologics
Guidance for Industry
DRAFT GUIDANCE
This guidance document is being distributed for comment purposes only.


Real-World Data: Assessing Electronic Health Records and Medical Claims Data To Support Regulatory Decision-Making for Drug and Biological Products
Guidance for Industry
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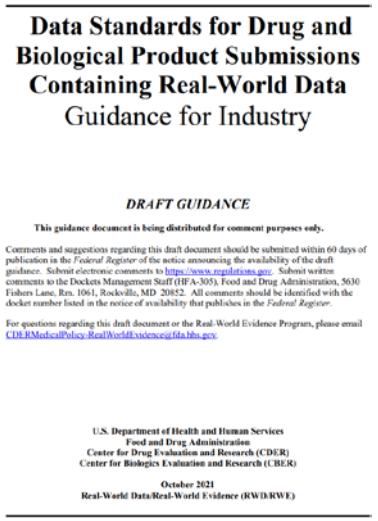
Data Standards for Drug and Biological Product Submissions Containing Real-World Data
Guidance for Industry
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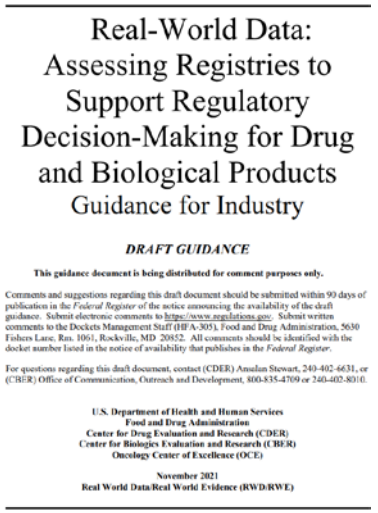
Real-World Data: Assessing Registries to Support Regulatory Decision-Making for Drug and Biological Products
Guidance for Industry
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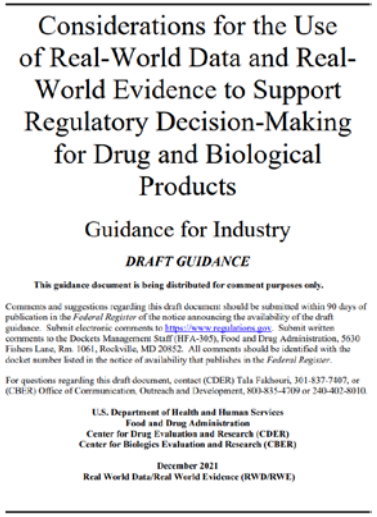

Considerations for the Use of Real-World Data and Real-World Evidence to Support Regulatory Decision-Making for Drug and Biological Products
Guidance for Industry
DRAFT GUIDANCE
This guidance document is being distributed for comment purposes only.

References
https://www.congress.gov/114/bills/hr34/BILLS-114hr34enr.xml
https://www.fda.gov/science-research/science-and-research-special-topics/real-world-evidence

Important terminology related to RWE

	Real world data	Real world insights	Real world evidence
Definition	Data relating to patient health status and/or delivery of health care routinely collected from a variety of sources	Answers to internal research questions derived from analyzing real world data	Clinical evidence about the usage and potential benefits or risks of a medical product derived from analysis of RWD
Examples	• Medical claims and billing • Electronic health records • Patient/product registries • Patient surveys	• Hypothesis generation • Feasibility • Patient journey • Unmet needs	Evidence supporting: • Effectiveness • Safety • Outcomes
Analogy			

References
https://www.fda.gov/media/120060/download

Table 1 Common sources, types, and examples of real-world data

Source	Type	Subtype	Examples
Administrative	Third-party payer claims	Closed networks	IBM MarketScan, IQVIA PharMetrics, Optum Clinformatics
		Open networks	IQVIA LAAD, DRG RWD, Symphony IDV
		Government	CMS FFS Medicare, Medicaid, VA/DOD
	Hospital chargemaster		Premier, Vizient, IQVIA CDM
	Pharmacy		Surescripts, IQVIA NDTI
Electronic health records	Care setting	Hospitals	Cerner, Epic, Athena
		Clinics	IQVIA AEMR, Optum Panther, IBM Explorys
		Long-term care/Home health	PointClickCare Lighthouse, Optima/Net Health
	Disease	Oncology	Flatiron, Ontada, ConcertAI
		Behavioral health	Kareo, SimplePractice, Valant
		Other	Praxis, TSI Healthcare, Phillips
Patients	Health surveys	Private	Kantar Health NHWS, Gallup National Health
		Public	NHANES, MEPS
	Outcome measures		Kantar Health, Evidation Health
	Multidimensional		PatientsLikeMe, Ciitizen
	Consumer genetic testing		23andMe, Ancestry.com
	Social determinants of health		IQVIA/Experian, MarketScan HPM, Optum SES
	Medical devices		Glooko, Livongo
	Mobile device biometrics	Smartphones	iPhone (HealthKit), Android (Google Fit)
		Smart watches	Apple Watch (HealthKit), Fitbit (Google Fit)
Diagnostics	Laboratory testing	Genetic testing	Invitae, Neogenomics, Ambry Genetics
		Other	Quest, LabCorp
	Clinicogenomics	Oncology	AACR GENIE, Optum Clinicogenomics
	Population genomics		NHGRI 1000 Genomes Project, NIH All of Us
	Diagnostic imaging		Life Image, Ambra Health
Other	Disease registries	Traditional	CorEvitas, Target RWE
		Other	OM1, COTA Healthcare
	Adverse event reports	Regulatory	FDA FAERS, FDA VAERS
		Social media	Twitter, Facebook
	Mortality	Public/Private	CDC WONDER, ObituaryData.com
	Tokenization		HealthVerity, Datavant, Komodo

RWE can be a powerful tool at every step of the product development process

Early | **Mid** | **Late**

1. R&D
2. Pre-clinical
3. FIH
4. Phase 2
5. Phase 3
6. Submission
7. Post-approval
8. LCM

Understanding patient population

- Prevalence
- Incidence
- Population size
- Comorbidities
- Temporal trends
- Diagnostic journey

Understanding health care utilization

- Quantity/quality of health care
- Standard of care
- Unmet needs
- Clinical trial sites
- Adherence/persistence

Understanding disease

- Natural history
- Disease progression
- Disease segmentation
- Endpoints
- Sample size

- Trial feasibility
- Trial modeling
- Trial design
- Generating hypotheses
- Effect size

Received: 13 March 2019 | Revised: 17 September 2019 | Accepted: 11 November 2019
DOI: 10.1002/pds.4932

REVIEW

WILEY

Trial designs using real-world data: The changing landscape of the regulatory approval process

Elodie Baumfeld Andre[1] | Robert Reynolds[1,2] | Patrick Caubel[1] | Laurent Azoulay[3,4] | Nancy A. Dreyer[5,6]

CLINICAL CANCER RESEARCH | PERSPECTIVES

Real-World Evidence in Support of Oncology Product Registration: A Systematic Review of New Drug Application and Biologics License Application Approvals from 2015–2020

Bhakti Arondekar[1], Mei Sheng Duh[2], Rachel H. Bhak[2], Maral DerSarkissian[2,3], Lynn Huynh[2], Kelsey Wang[2],

The Role of Real-World Evidence in FDA-Approved New Drug and Biologics License Applications

Christina A. Purpura[1], Elizabeth M. Garry[1], Nicholaas Honig[1], Abigail Case[1] and Jeremy A. Rassen[1,*]

Today's Encore Webinar will review R&D applications of RWE based on our article in the January 2022 issue of *Clinical Pharmacology & Therapeutics*

Learning objectives

At the end of this webinar, participants will understand how biopharmaceutical companies can leverage RWD, RWI, and RWE (collectively termed "RWE") to inform internal decisions throughout the product development process, including:

1. Use of RWE to guide pipeline and portfolio strategy
2. Use of novel sources of RWE to inform product development
3. Use of RWE to inform clinical development

1. Use of RWE to guide pipeline and portfolio strategy

While there are many examples of using RWE to guide R&D portfolio strategy, today we will focus on 3 examples

Citation	Study Objective	Data Source(s)	Insight
Broder *et al.* (2018)[17]	Estimate prevalence and incidence of neuroendocrine tumors	IBM MarketScan and IQVIA PharMetrics claims databases	Prevalence and incidence increasing over time.
Dellon *et al.* (2014)[66]	Estimate prevalence of EE	IQVIA PharMetrics claims	Updated estimates for number of patients with EE in the United States following the introduction of a new ICD-9 diagnosis code specific to EE.
Wallin *et al.* (2019)[16]	Estimate national prevalence for MS by analyzing multiple US databases, covering different population segments.	Optum, IBM, Kaiser Permanente, Department of Veterans Affairs, and the Centers for Medicare and Medicaid claims databases	The 3-year prevalence of MS was 309.2 per 100,000, with an estimated 727,344 cases in the United States, higher than previous studies.
Halpern *et al.* (2019)[67]	Estimate prevalence of agitation among patients with AD	Optum EHR database	Prevalence of agitation over a 2-year period was 44.6%. NLP was used to analyze unstructured data for keywords related to agitation.
Chehade *et al.* (2021)[68]	Describe patient journey for individuals with EG/EoD	Symphony Health Patient Source claims database	Many EG/EoD patients initially diagnosed with irritable bowel syndrome or dyspepsia, highlighting the need for improved diagnosis.
Morgan *et al.* (2021)[69]	Describe diagnostic journey of patients with PSP	Patient interviews and physician chart reviews in France, Germany, Italy, Spain, the United Kingdom, and the United States	Diagnostic delays may be related to patients first presenting to primary care providers before being evaluated by movement disorder specialists.

Target population sizing using RWE can support early go/no-go decisions

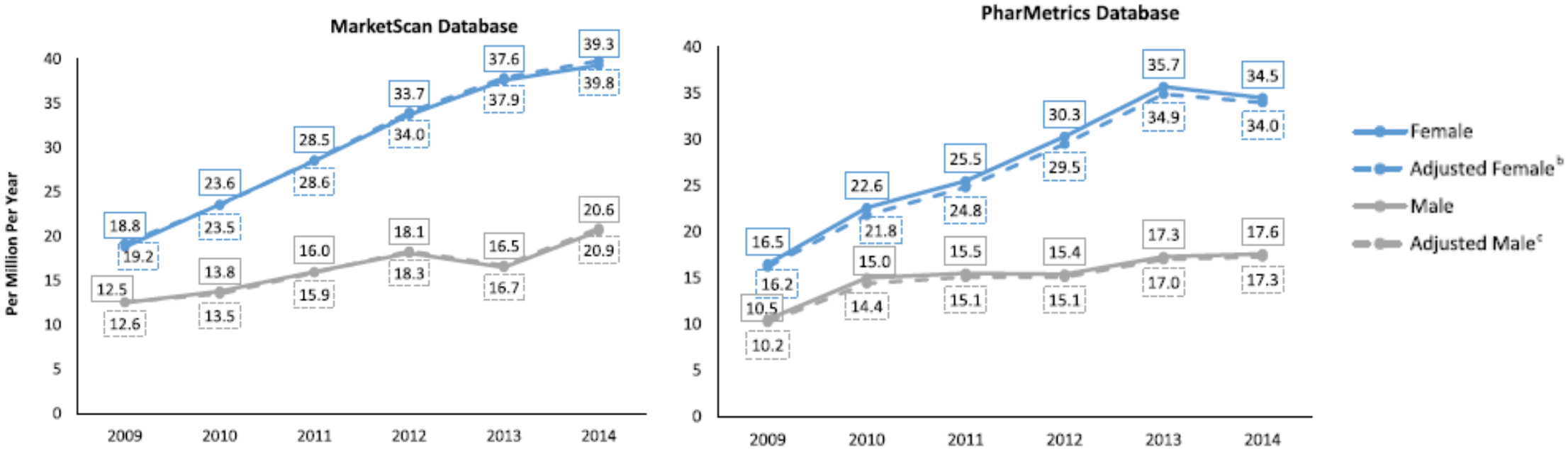
Background

- Estimates on prevalence and incidence of neuroendocrine tumors (NETs) in the US based on SEER registry suggest they are ultra rare
- Objective was to update estimates of NETs using insurance claims in the US

Methods

- Analyzed claims data from MarketScan and PharMetrics that together include ~100 million individuals in the US
- Estimated annual prevalence and incidence rates based on ICD-9 diagnosis codes among insured

Findings



RWD insights

- Although NETs are rare, claims in the US suggest annual prevalence and incidence may be increasing

References
Broder MS, Cai B, Chang E, Neary MP. Incidence and prevalence of neuroendocrine tumors of the lung: analysis of a US commercial insurance claims database. BMC Pulm Med. 2018;18(1):135.

Combining multiple sources of RWE can help size entire target population

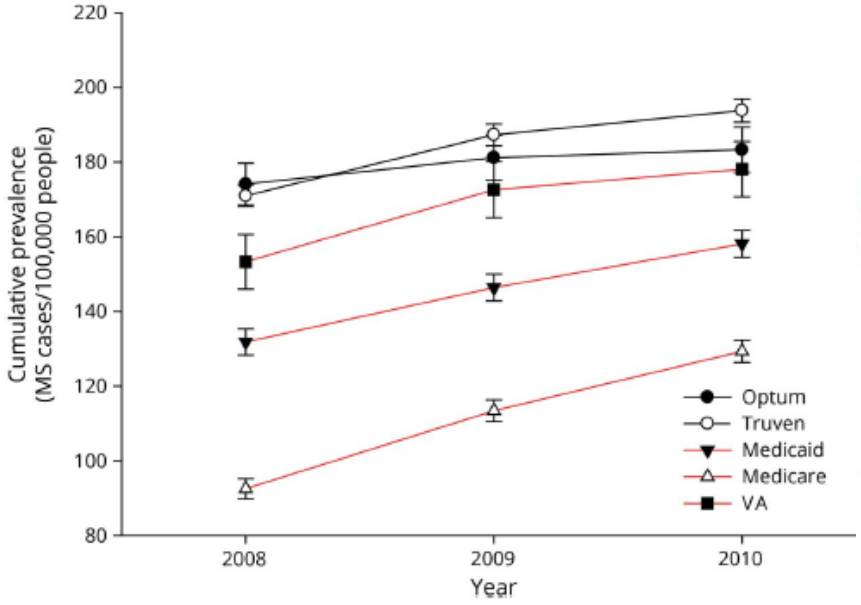
Background

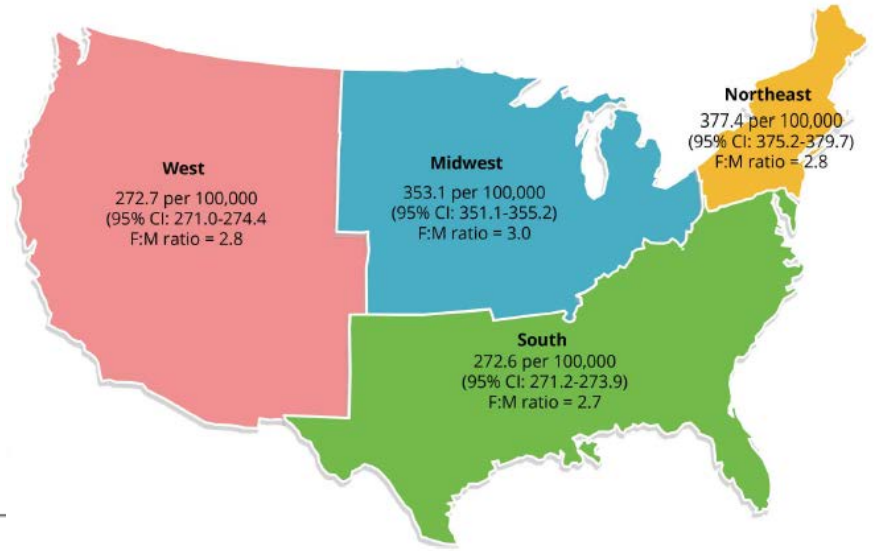
- Older estimates based on literature suggest there are 300,000-400,000 patients with multiple sclerosis (MS) in the US
- Objective was to generate an updated and robust estimate of national prevalence of MS in US using RWD

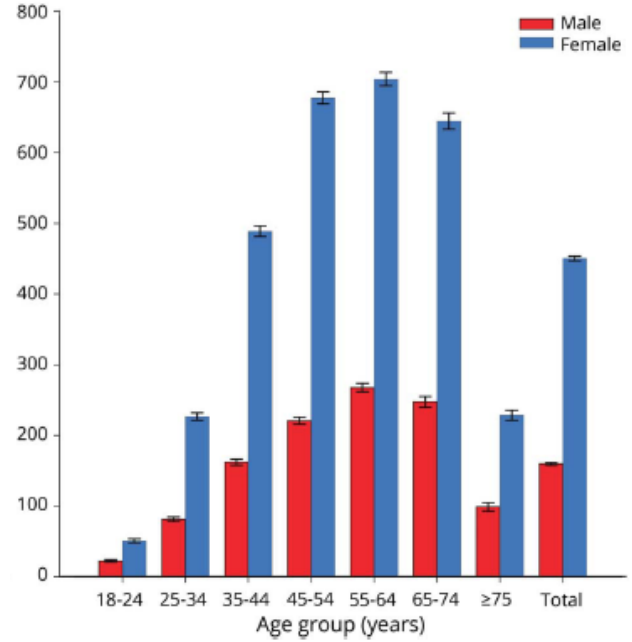
Methods

- Analyzed claims data from Optum, MarketScan, Kaiser, VA, and CMS
- Combined estimates from different population subgroups into comprehensive national estimate

Findings







RWD insights

- Estimates from 5 recent sources of claims data suggest that 727,344 individuals in the US have MS

References

Wallin MT, Culpepper WJ, Campbell JD, Nelson LM, Langer-Gould A, Marrie RA, et al. The prevalence of MS in the United States: A population-based estimate using health claims data. Neurology. 2019;92(10):e1029-e40.

RWE can identify uncover unmet needs that inform product strategy

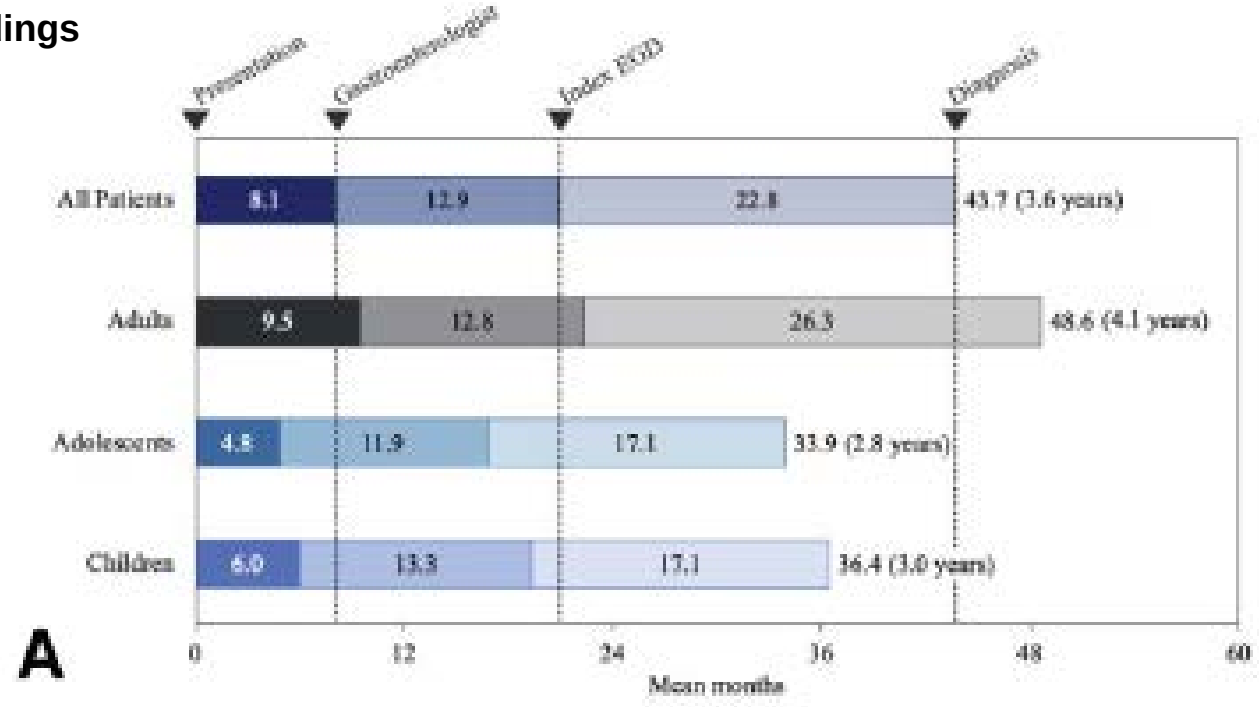
Background

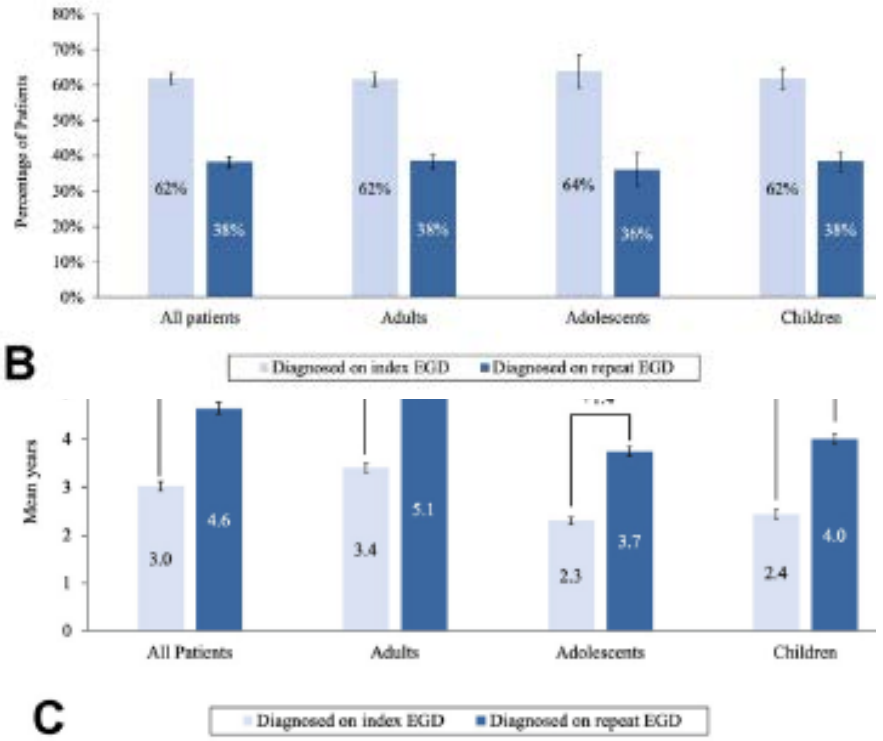
- Literature suggests that eosinophilic gastrointestinal diseases (EG/EoD) are commonly misdiagnosed
- Objective was to understand the diagnostic journey of patients with EG/EoD in the US

Methods

- Analyzed data from Symphony Health, a large database of insurance claims for multiple payers in the US
- Estimated interval between symptom presentation, gastroenterologist visit, diagnostic test (EGD), and diagnosis

Findings





RWD insights

- Mean delay from symptom presentation to diagnosis of EG/EoD was 4.1 years in the US

References

Chehade M, Kamboj AP, Atkins D, Gehman LT. Diagnostic Delay in Patients with Eosinophilic Gastritis and/or Duodenitis: A Population-Based Study. J Allergy Clin Immunol Pract. 2021;9(5):2050-9 e20.

RWE can complement other data to inform risk assessment related to DDIs

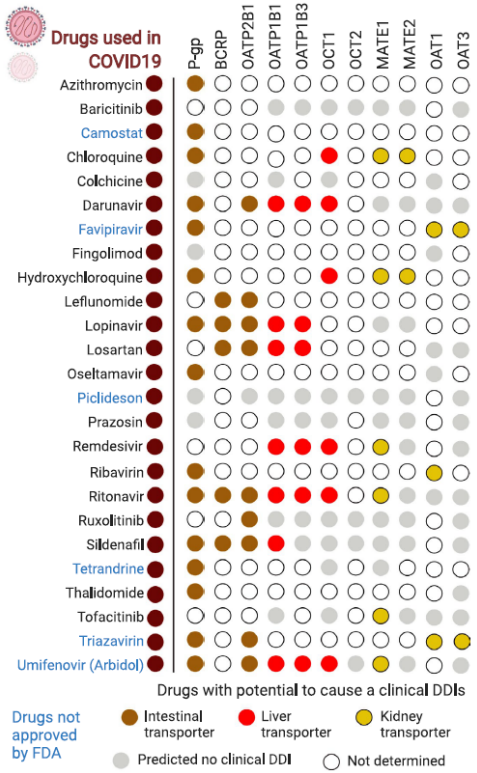
Background

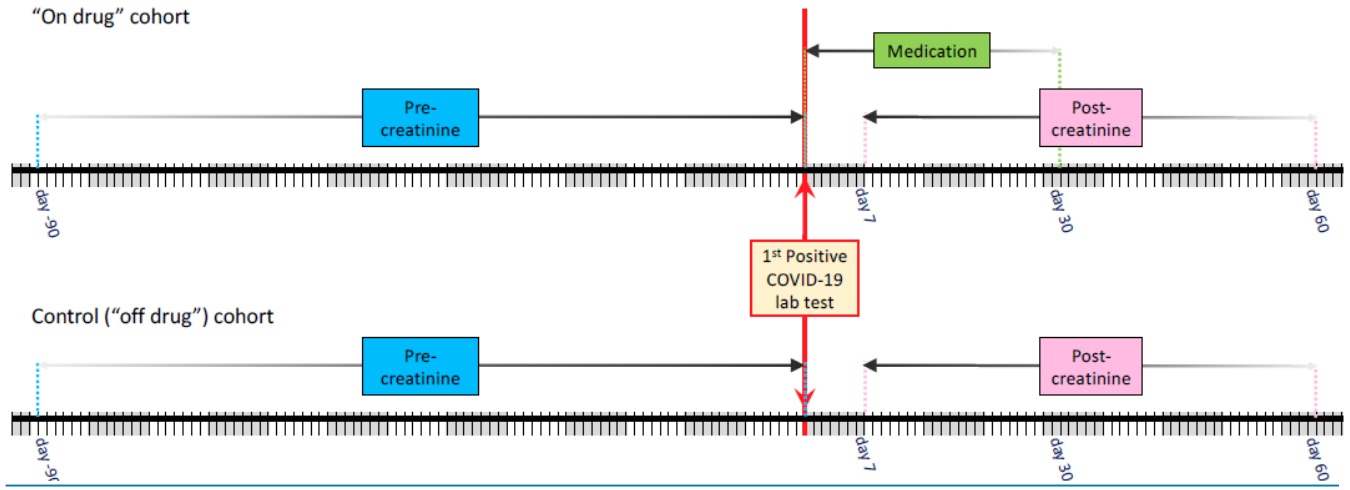
- Early in COVID-19 pandemic, researchers were interested in repurposing existing drugs to minimize development time
- 25 drugs (anti-microbials and anti-inflammatories) were evaluated in clinical trials for COVID-19
- Based on cell line studies, these drugs were predicted to impact 11 transporter pathways that could result in DDIs

Methods

- Analyzed EHR data from Cerner and USCF to determine if predicted DDIs were occurring based on lab test values

Findings





Analysis		Number of patients with creatinine levels above normal level	Total	Creatinine above normal level	χ^2	*P* value
Main	on HCQ/CQ	90	584	15.41%	5.07	0.024
Main	Control	134	1168	11.47%		
1	On HCQ/CQ	74	520	14.23%	12.26	4.6E-04
1	Control	87	1040	8.37%		

RWD insights

- 20/25 (80%) existing drugs evaluated for COVID-19 were predicted to cause transporter-mediated clinical DDIs

References

Yee SW, Vora B, Oskotsky T, Zou L, Jakobsen S, Enogieru OJ, et al. Drugs in COVID-19 Clinical Trials: Predicting Transporter-Mediated Drug-Drug Interactions Using In Vitro Assays and Real-World Data. Clin Pharmacol Ther. 2021;110(1):108-22.

2. Use of novel sources of RWE to inform product development

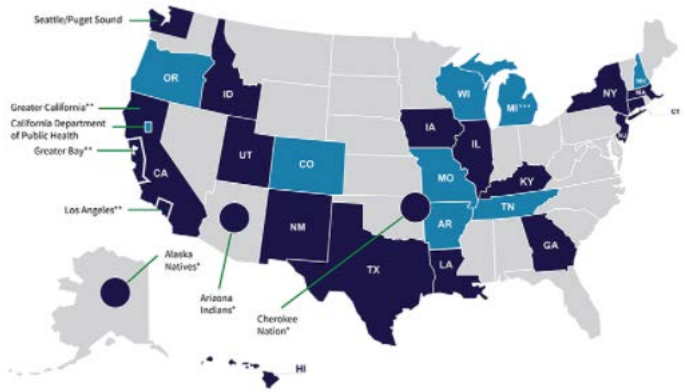
Jennifer Webster

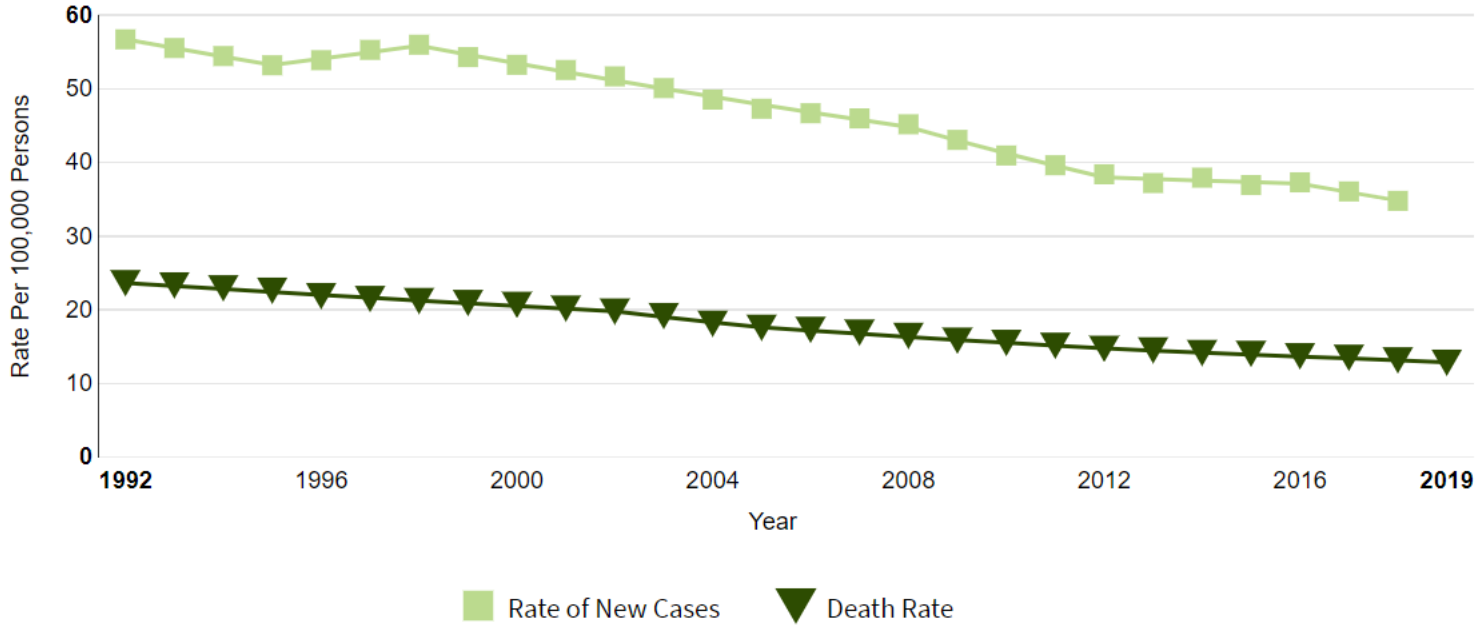
Publicly available resources like SEER & WHO offer high level epi & trends

Scenario: Your team is concerned that incidence rates from the literature give an inaccurate picture within the TPP for MSI-H mCRC, with an opportunity to use large scale RWD for pharmacometric modeling

NIH NATIONAL CANCER INSTITUTE
Surveillance, Epidemiology, and End Results Program

The SEER registry aggregates data from cancer registries in a selection of states. Incidence and death rates per 100,000 for colorectal cancer are shown.





[Colorectal Cancer — Cancer Stat Facts]

Claims and EHR data give insights on more refined subpopulations

Identifying subpopulations in real world data. Example: MSI-H mCRC patients

Option 1: Expert knowledge

- Ontologies beyond ICD-9/10
- Evidence of Molecular Testing
- Line of Therapy Business Rules
- Targeted Therapies as Proxies

Option 2: Machine Learning

ELSEVIER

ImmunoInformatics
Volumes 3–4, December 2021, 100008

Deep learning for the detection of microsatellite instability from histology images in colorectal cancer: A systematic literature review

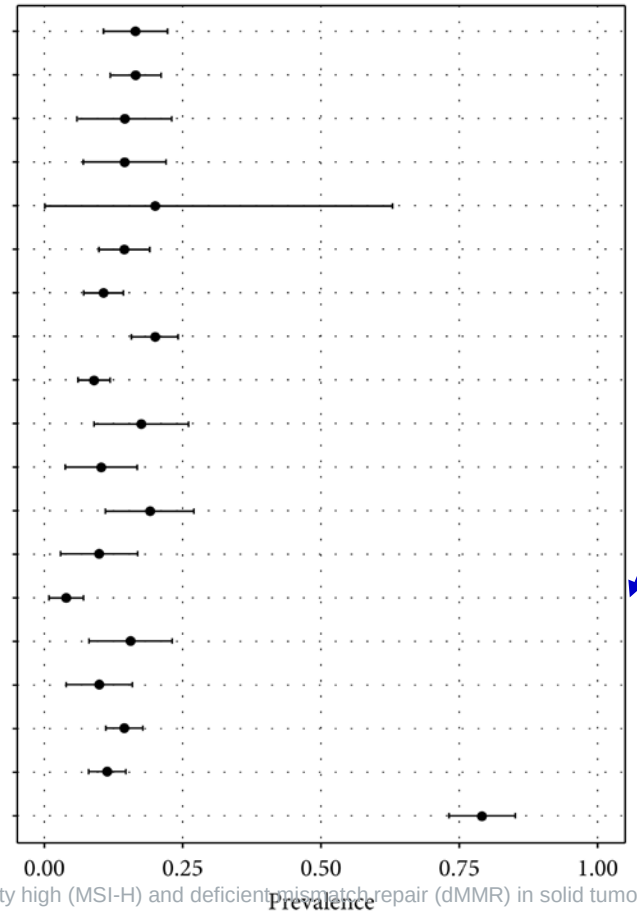
Amelie Echle [a], Narmin Ghaffari Laleh [a], Peter L. Schrammen [a], Nicholas P. West [b], Christian Trautwein [a], Titus J. Brinker [c], Stephen B. Gruber [d], Roman D. Buelow [e], Peter Boor [e], Heike I. Grabsch [b, f], Philip Quirke [b], Jakob N. Kather [a, b, g]

Echle, A., Laleh, N. G., Schrammen, P. L., West, N. P., Trautwein, C., Brinker, T. J., ... & Kather, J. N. (2021). Deep Learning for the detection of microsatellite instability from histology images in colorectal cancer: a systematic literature review. ImmunoInformatics, 100008.

Adding endpoints allows us to understand heterogeneity among subpopulations

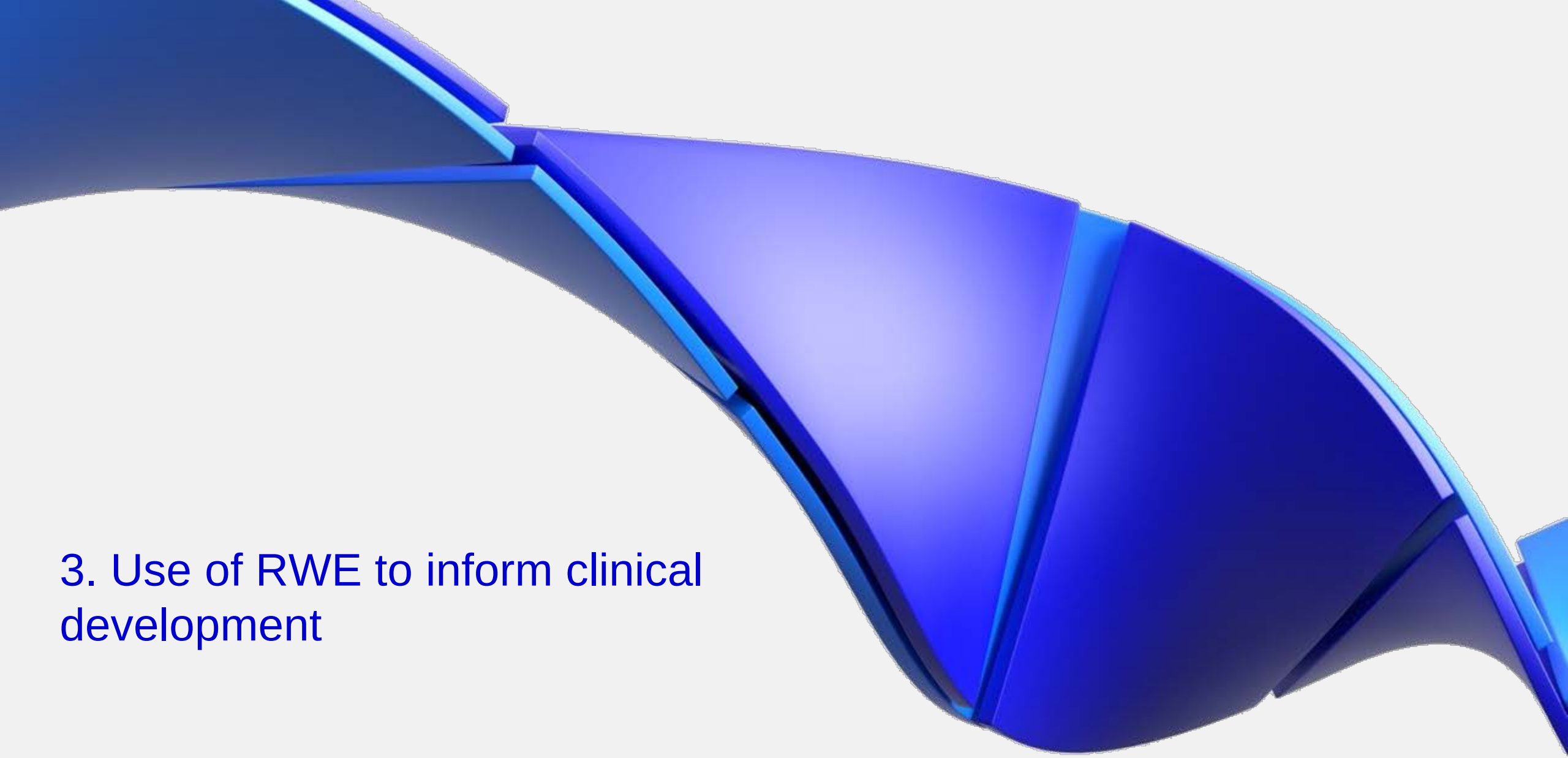
Using real world data to challenge epi assumptions in TPP

Subgroup	Status	*N* study	*N*	*n*	Prevalence	95% CI
Overall	dMMR	54	20383	3279	0.16	0.11–0.22
Overall (sens.)	dMMR	52	20216	3190	0.16	0.12–0.21
Country-United States	dMMR	27	5416	1066	0.14	0.06–0.23
Country-United States (sens.)	dMMR	25	2594	977	0.14	0.07–0.22
Country-Japan	dMMR	2	678	101	0.20	0.00–0.63
Overall (without genomic studies)	MSI-H	90	28213	3494	0.14	0.10–0.19
Overall (with genomic studies)	MSI-H	94	66669	4843	0.10	0.07–0.14
Country-United States	MSI-H	25	5654	1127	0.20	0.16–0.24
Country-Korea	MSI-H	17	14630	1192	0.09	0.06–0.12
Country-Japan	MSI-H	8	1681	198	0.16	0.09–0.26
Stage 1	MSI-H	18	3305	409	0.10	0.04–0.17
Stage 2	MSI-H	18	1535	258	0.19	0.11–0.27
Stage 3	MSI-H	17	1636	157	0.09	0.03–0.17
Stage 4	MSI-H	18	665	36	0.03	0.01–0.07
Stages 1-2	MSI-H	24	5827	915	0.15	0.08–0.23
Stages 3-4	MSI-H	23	2514	246	0.09	0.04–0.16
Overall (without genomic studies)	MSI-H/dMMR	136	47218	6560	0.15	0.11–0.18
Overall (with genomic studies)	MSI-H/dMMR	140	85674	7909	0.11	0.08–0.15
Overall	MSS	79	17613	14056	0.79	0.72–0.85



- MSI-H widely reported to be 15% of CRC
- Only 6% of Stage 4

Lorenzi, M., Amonkar, M., Zhang, J., Mehta, S., & Liaw, K. L. (2020). Epidemiology of microsatellite instability high (MSI-H) and deficient mismatch repair (dMMR) in solid tumors: a structured literature review. Journal of Oncology, 2020.



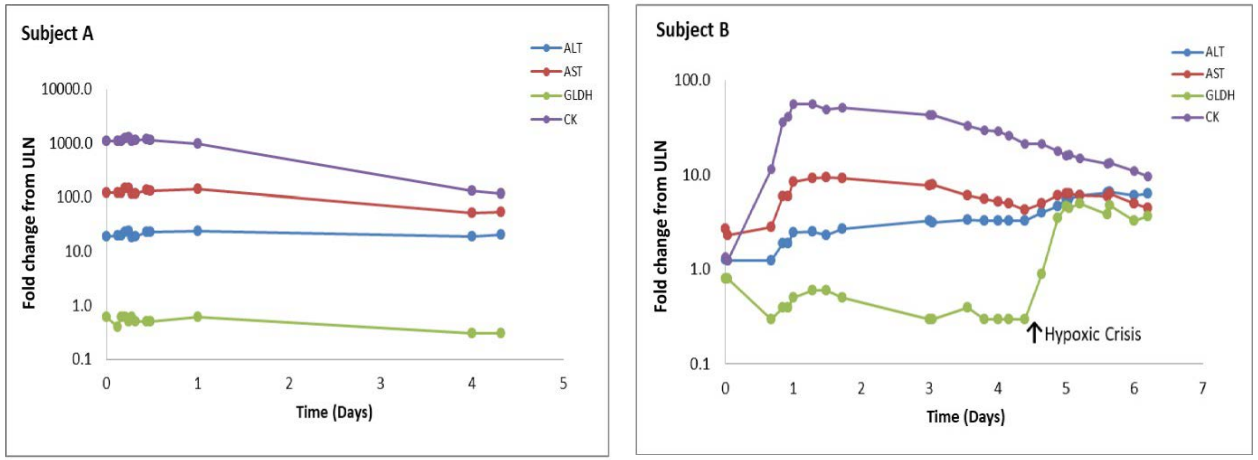
3. Use of RWE to inform clinical development

Data mining for endpoint discovery: hypothesis generation

Scenario: clinical trial planning for Duchenne Muscular Dystrophy

Mining real world clinical data for safety and efficacy biomarkers

GLDH detects the onset of liver injury in a subject with rhabdomyolysis in a real world prospective trial



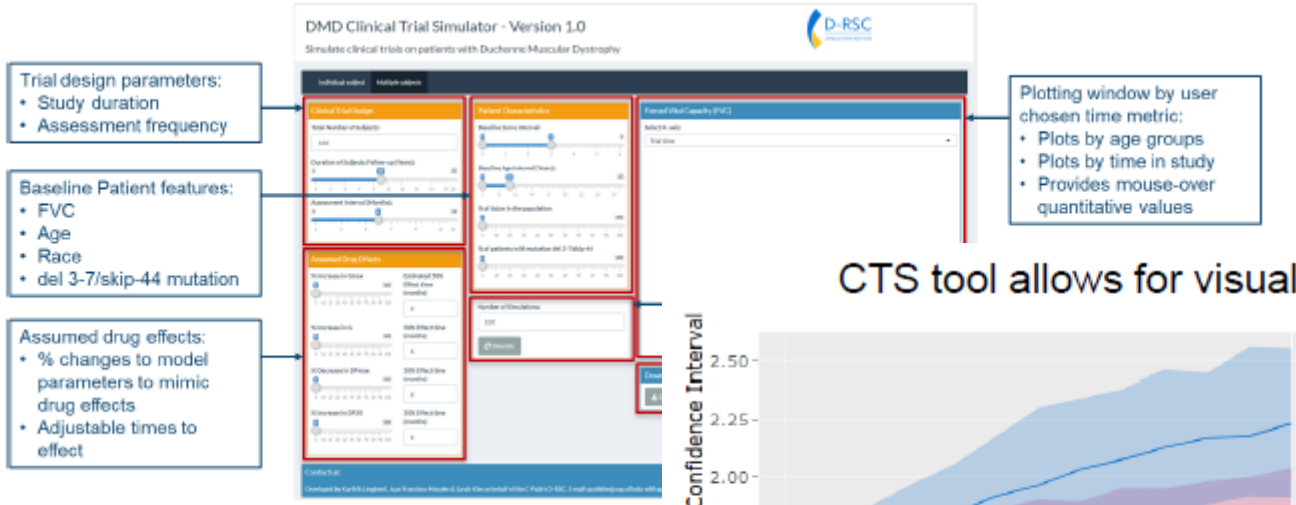
FDA guidance on DMD efficacy endpoints

"FDA encourages sponsors to propose and, if necessary, develop endpoints that can validly and reliably assess patients with a wide spectrum of symptoms and disease stages. Sponsors should engage FDA early during the selection and/or development of efficacy endpoints. The sponsor should include an assessment of multiple efficacy endpoints, when feasible."

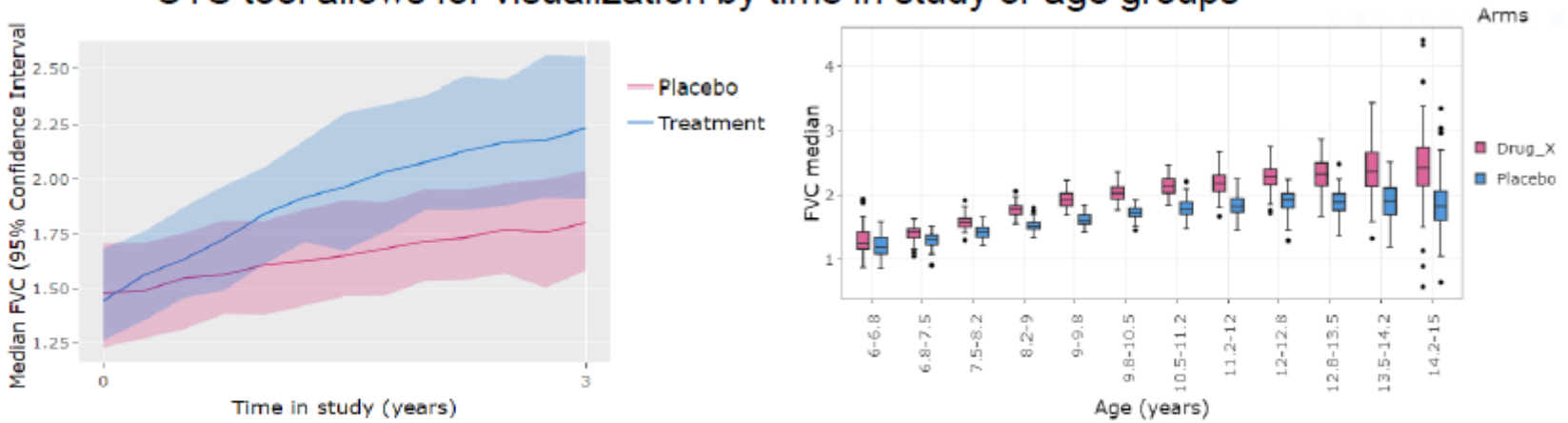
Serum glutamate dehydrogenase activity enables early detection of liver injury in subjects with underlying muscle impairments - PMC (nih.gov)
Duchenne Muscular Dystrophy and Related Dystrophinopathies: Developing Drugs for Treatment Guidance for Industry (fda.gov)

Simulations to explore optimal clinical trial designs

Use to inform trial enrichment strategies throughout all stages of the asset lifecycle



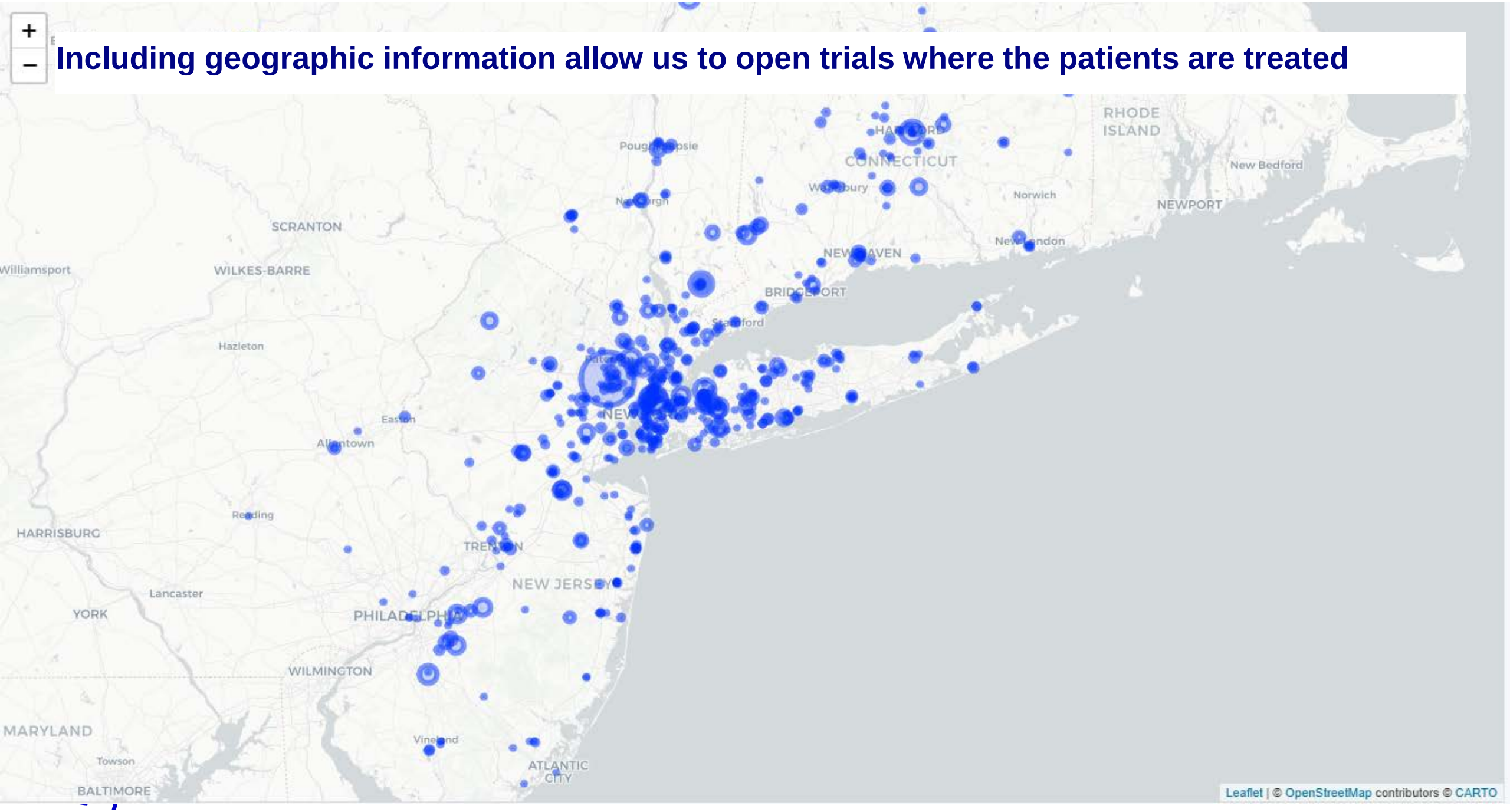
CTS tool allows for visualization by time in study or age groups



Example: Simulation of 100 trials, 50 patients/arm, baseline age 6-12 yrs, duration 3 years, drug predicted to have 30% effect on maximum FVC achieved

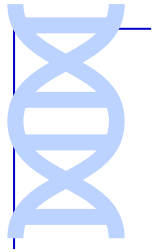
https://c-path.org/wp-content/uploads/2021/04/Development-of-a-regulatory-ready-clinical-trial-simulation-tool-for-Duchenne-muscular-dystrophy_Poster_WMS_2020.pdf

Including geographic information allow us to open trials where the patients are treated



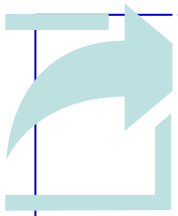
Emerging Opportunities for Incorporating RWE in Drug Development

New data sources, new uses expected to grow over next 3-5 years

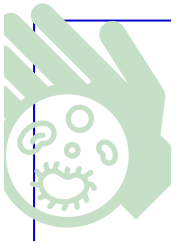


Real world genomics for target discovery and validation

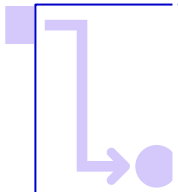
- Genomic data from real world care and from biobanks



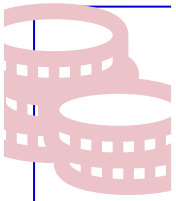
Prospective observational studies can be started as soon as FIH



Use of organoids and xenografts to inform disease model and understand drug response and resistance



Causal Inference Modeling for hypothesis generation



Tokenization for long term follow up

RW Single-cell RNAseq to understand tumor microenvironment throughout patient journey

Thank you!