Data to Evidence: OHDSI in Action!

Rebecca Chandler, MD
Uppsala Monitoring Centre

Patrick Ryan, PhD
Janssen Research and Development
Columbia University Medical Center

The origins of pharmacovigilance

THALIDOMIDE AND CONGENITAL ABNORMALITIES

SIR,—Congenital abnormalities are present in approximately 1·5% of babies. In recent months I have observed that the incidence of multiple severe abnormalities in babies delivered of women who were given the drug thalidomide ('Distaval') during pregnancy, as an antiemetic or as a sedative, to be almost 20%.

These abnormalities are present in structures developed from mesenchyme—i.e., the bones and musculature of the gut. Bony development seems to be affected in a very striking manner, resulting in polydactyly, syndactyly, and failure of development of long bones (abnormally short femora and radii).

Have any of your readers seen similar abnormalities in babies delivered of women who have taken this drug during pregnancy?

Hurstville, New South Wales. W. G. MCBRIDE.

*** In our issue of Dec. 2 we included a statement from the Distillers Company (Biochemicals) Ltd. referring to "reports from two overseas sources possibly associating thalidomide ('Distaval') with harmful effects on the fœtus in early pregnancy". Pending further investigation, the company decided to withdraw from the market all its preparations containing thalidomide.—ED.L.

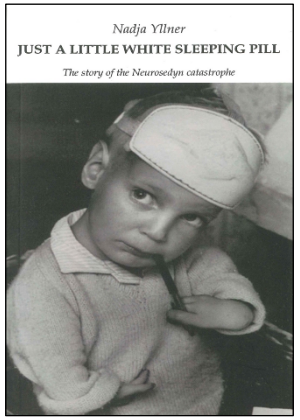
IN THE LAB

STAT+

Scientists find a new clue about how thalidomide caused devastating birth defects

By MEGAN THIELKING @meggophone / AUGUST 3, 2018

WHO Programme for International Drug Monitoring



Thalidomide 1961

World Health Organization

In 1968 WHO creates the Programme for International Drug Monitoring

Uppsala Monitoring Centre

In 1978 Swedish Government and WHO creates UMC and Collaborating Centre

Uppsala Monitoring Centre (UMC)

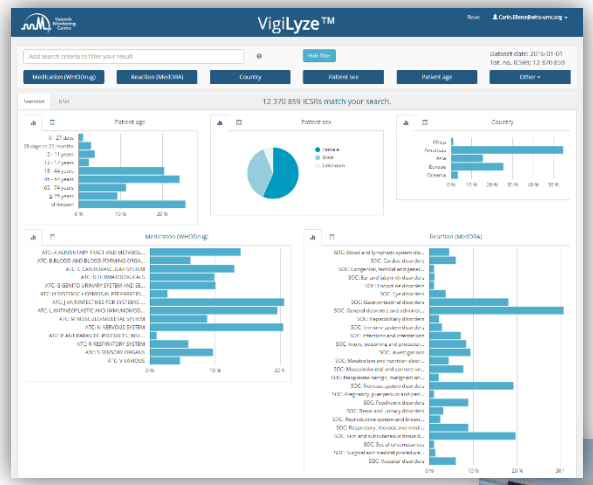
WHO Collaborating Centre for International Drug Monitoring

- Established as a foundation in 1978
- Provider of scientific leadership and operational support to the WHO PIDM
- Custodian and manager of VigiBase®
- Maintenance organization for WHODrug™
- Self funding

UMC's Vision

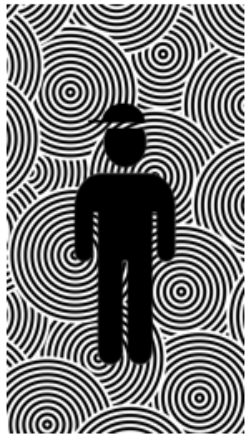
Our vision is a world where all patients and health professionals make wise therapeutic decisions in their use of medicines.

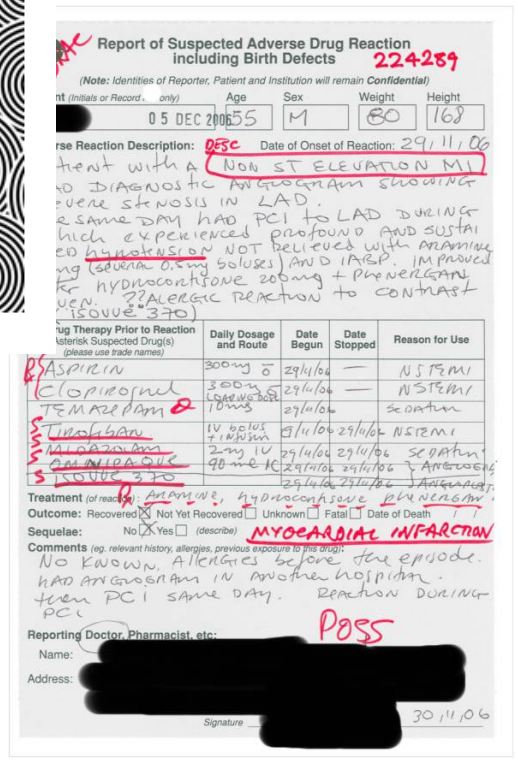
take & tell
Together for safer medicines



INSPIRE. ENGAGE. TRANSFORM.

How patient experiences are transformed to data





Report of Suspected Adverse Drug Reaction including Birth Defects 224289

(Note: Identities of Reporter, Patient and Institution will remain Confidential)

Age 55 | Sex M | Weight 80 | Height 168

05 DEC 2006

Reaction Description: DESC Date of Onset of Reaction: 29/11/06

PATIENT WITH A NON ST ELEVATION MI. HAD DIAGNOSTIC ANGIOGRAM SHOWING SEVERE STENOSIS IN LAD. SAME DAY HAD PCI to LAD DURING WHICH EXPERIENCED PROFOUND AND SUSTAINED HYPOTENSION NOT BELIEVED WITH ARAMINE (SEVERAL 0.5mg BOLUSES) AND IAPB. IMPROVED AFTER HYDROCORTISONE 200mg + PHENERGAN. ?? ALERGIC REACTION to CONTRAST (ISOVUE 370)

Drug Therapy Prior to Reaction (Asterisk Suspected Drug(s)) (please use trade names)	Daily Dosage and Route	Date Begun	Date Stopped	Reason for Use
*ASPIRIN	300mg O	29/11/06	—	NSTEMI
*CLOPIDOGREL	300mg O LOADING DOSE	29/11/06	—	NSTEMI
TEMAZEPAM	10mg	29/11/06		SEDATION
*TIROFIBAN	IV BOLUS + INFUSION	29/11/06	29/11/06	NSTEMI
*MIDAZOLAM	2mg IV	29/11/06	29/11/06	SEDATION
*ARAMINE	90mg IV	29/11/06	29/11/06	? ANGIOGRAM
*ISOVUE 370		29/11/06	29/11/06	ANGIOGRAM

Treatment (of reaction): ARAMINE, HYDROCORTISONE PHENERGAN

Outcome: Recovered ☒ Not Yet Recovered ☐ Unknown ☐ Fatal ☐ Date of Death

Sequelae: No ☒ Yes ☐ (describe) MYOCARDIAL INFARCTION

Comments (eg. relevant history, allergies, previous exposure to this drug): NO KNOWN ALLERGIES before the episode. HAD ANGIOGRAM IN ANOTHER HOSPITAL. THEN PCI SAME DAY. REACTION DURING PCI

Reporting Doctor, Pharmacist, etc: POSS

Name: [redacted]

Address: [redacted]

Signature [redacted] 30/11/06

WHODrug

MedDRA

01001111010
11010100101
01011011011
11111100010
10100111011

VigiBase

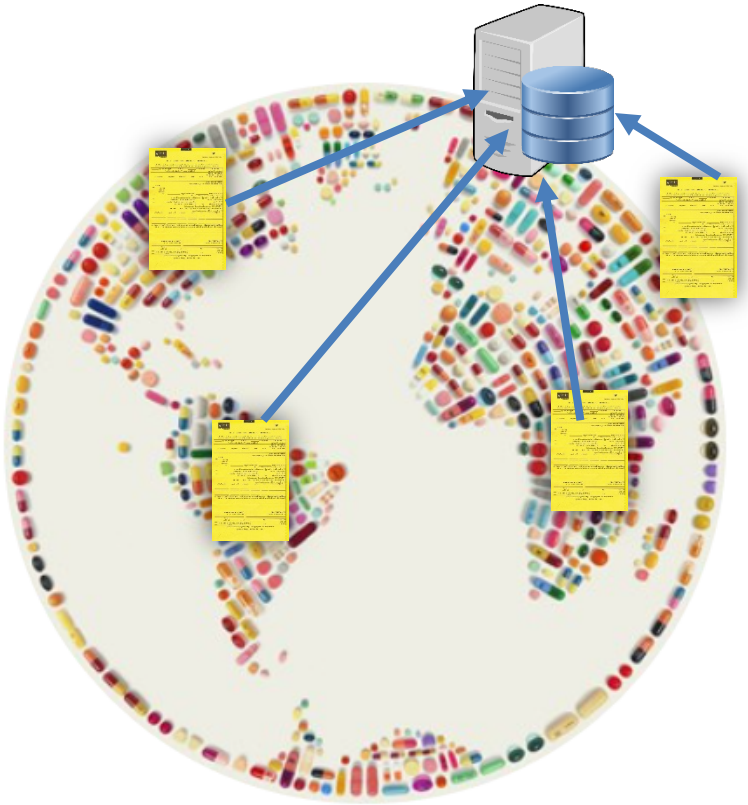
Global collection of reports

Covering 90% of the world

UMC has developed and maintained VigiBase, the WHO global database of individual case safety reports (ICSRs), since 1978. Following the ten founder members of the late 60s, over 130 countries have now joined the WHO Programme, in all representing over 90% of the world's population.

Total reports, as of 25 March 2019:

18 800 662



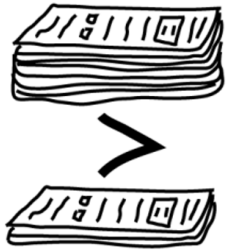
The WHO Programme for International Drug Monitoring

The basis of signal detection in pharmacovigilance

Observed

vs.

Expected



Eur J Clin Pharmacol (1998) 54: 315–321

PHARMACOEPIDEMIOLOGY AND PRESCRIPTION

A. Bate · M. Lindquist · I. R. Edwards · S. Olsson
R. Orre · A. Lansner · R. M. De Freitas

A Bayesian neural network method for adverse drug reaction signal generation

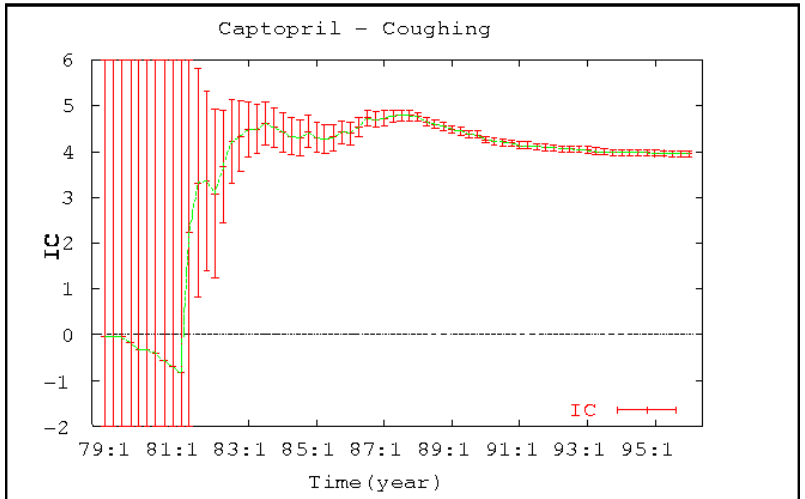
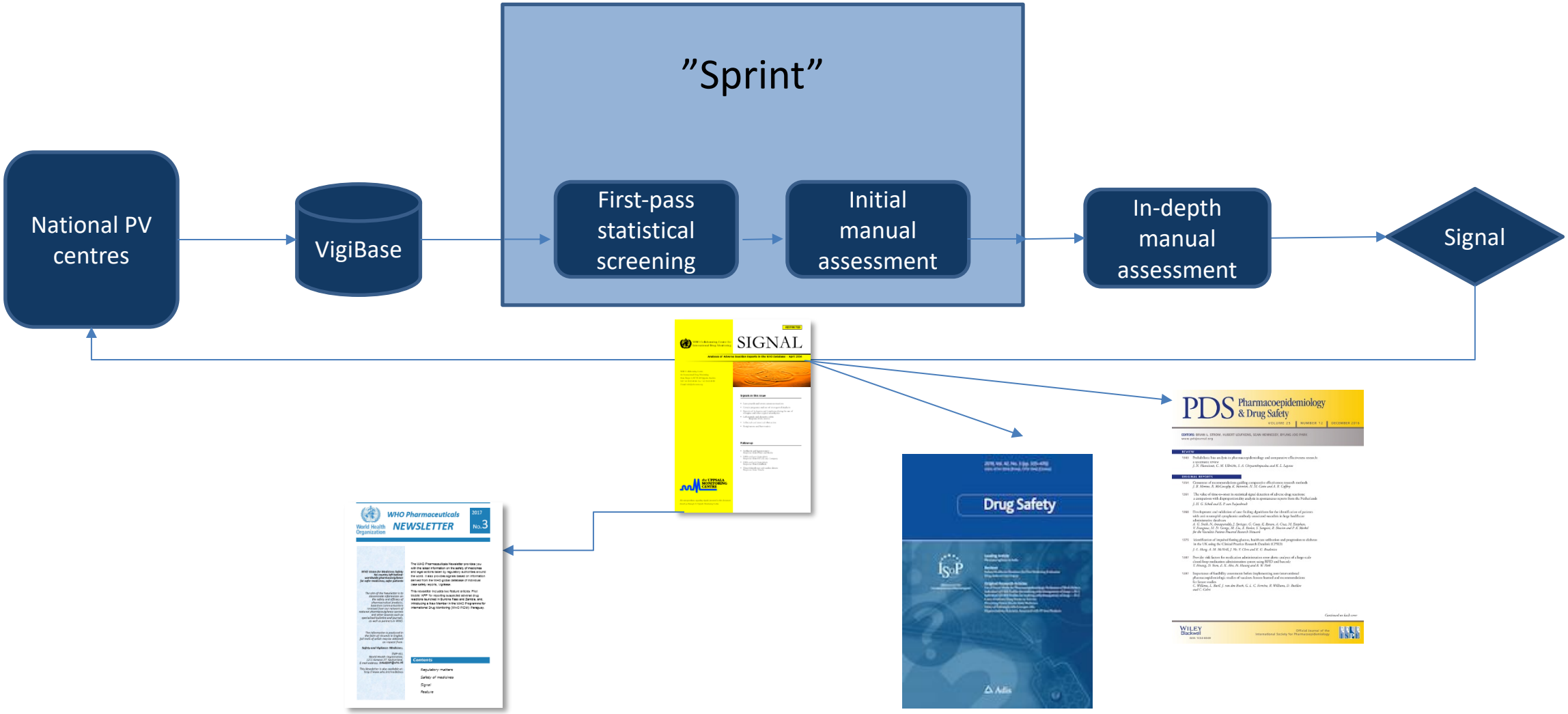


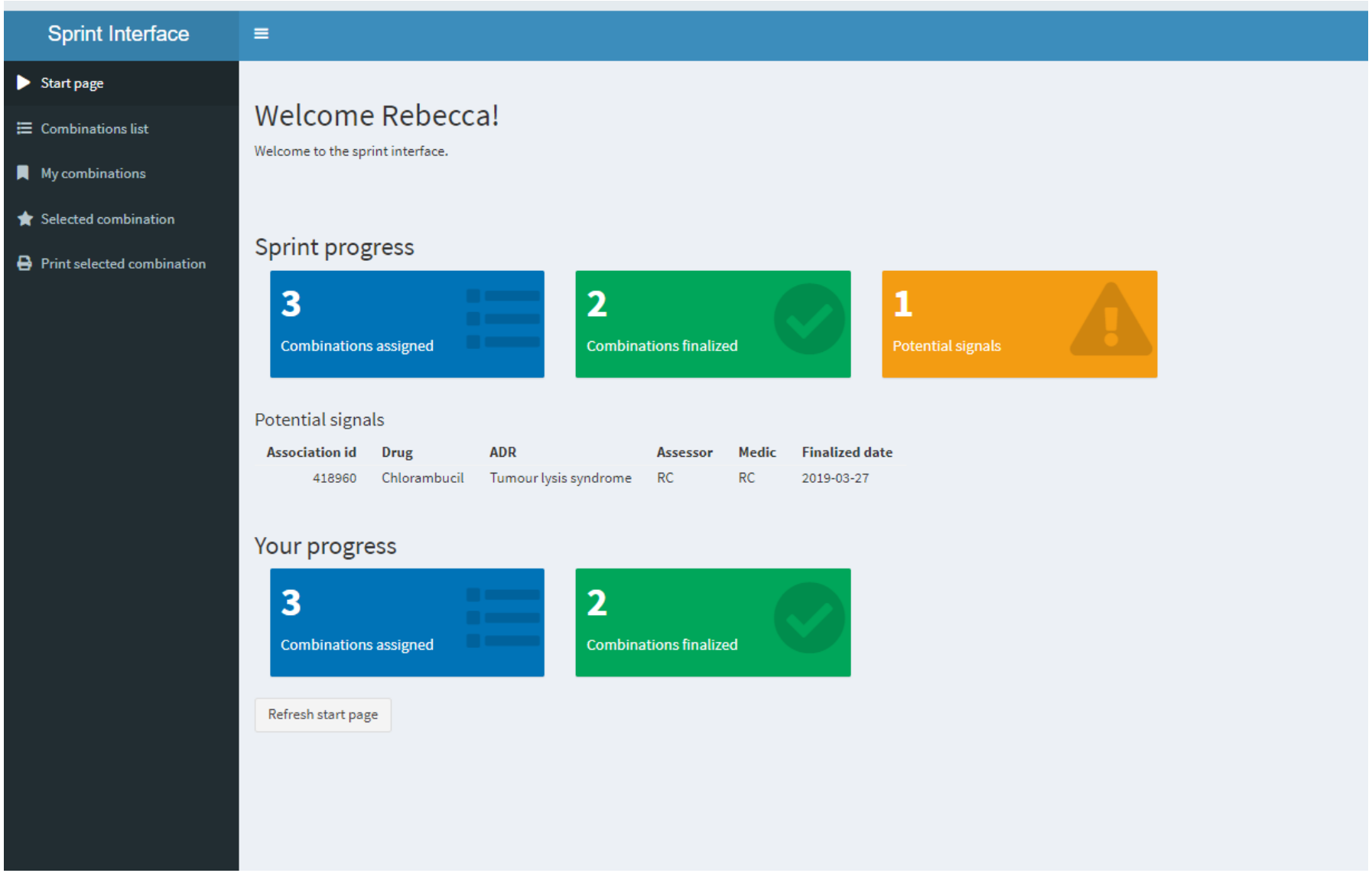
Fig. 1: Shrinkage of CI of IC over time
With increasing data, the confidence interval gets smaller. Once the value 0 is not included in the CI, a signal is flagged.
(Sten Olsson, the Uppsala Monitoring Centre, presentation, 2004)

UMC Signal detection process

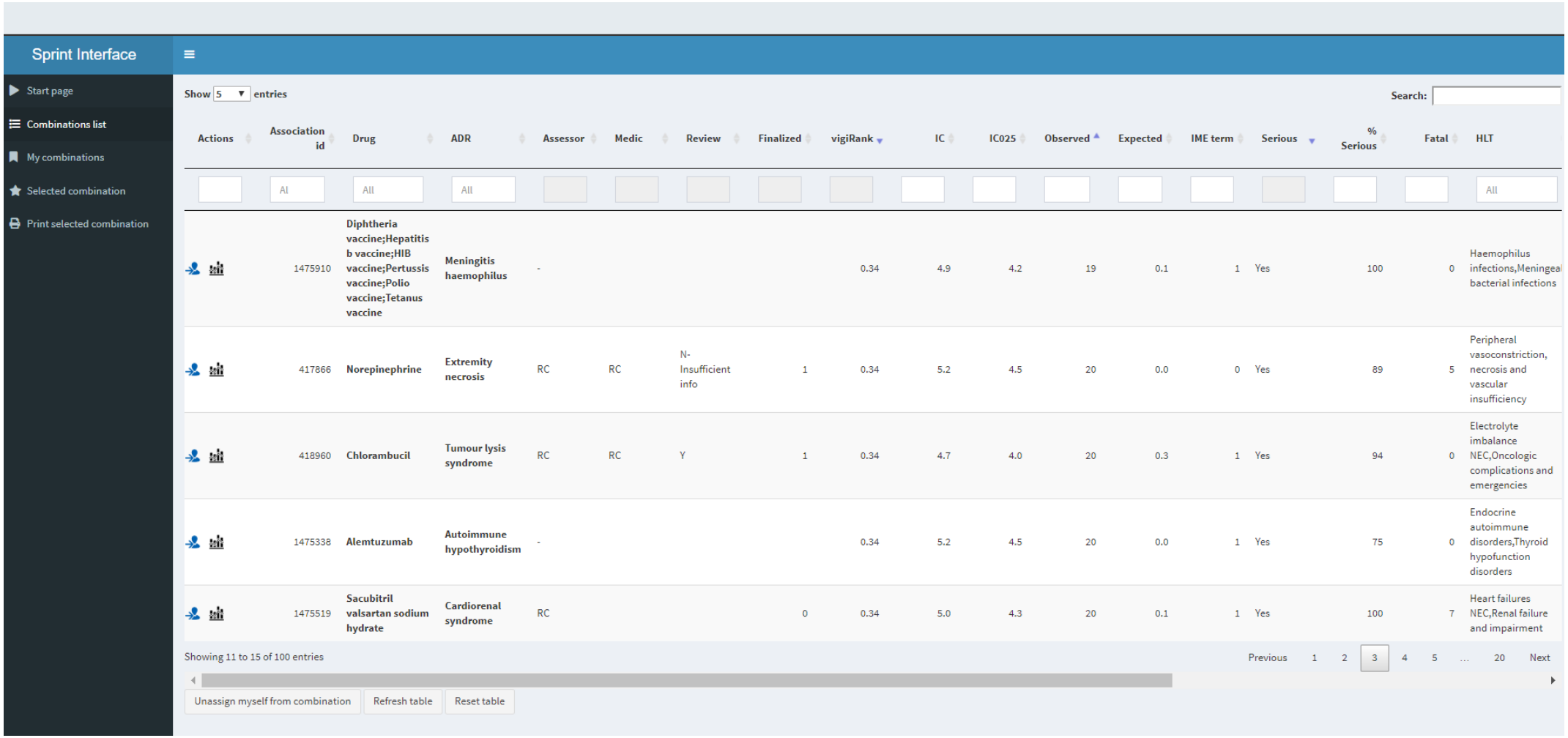


Sprint

Sprint Interface



Sprint Interface



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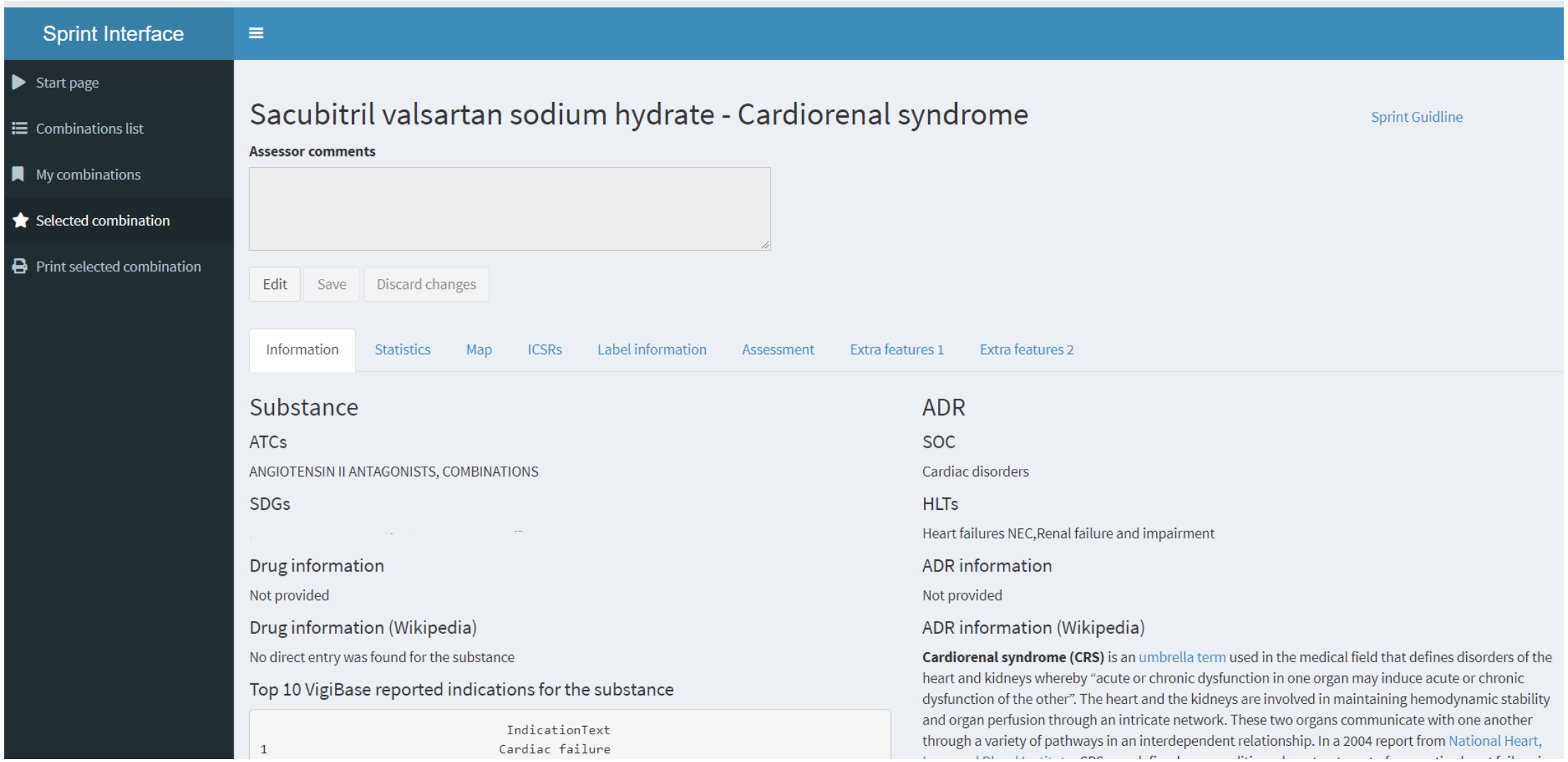

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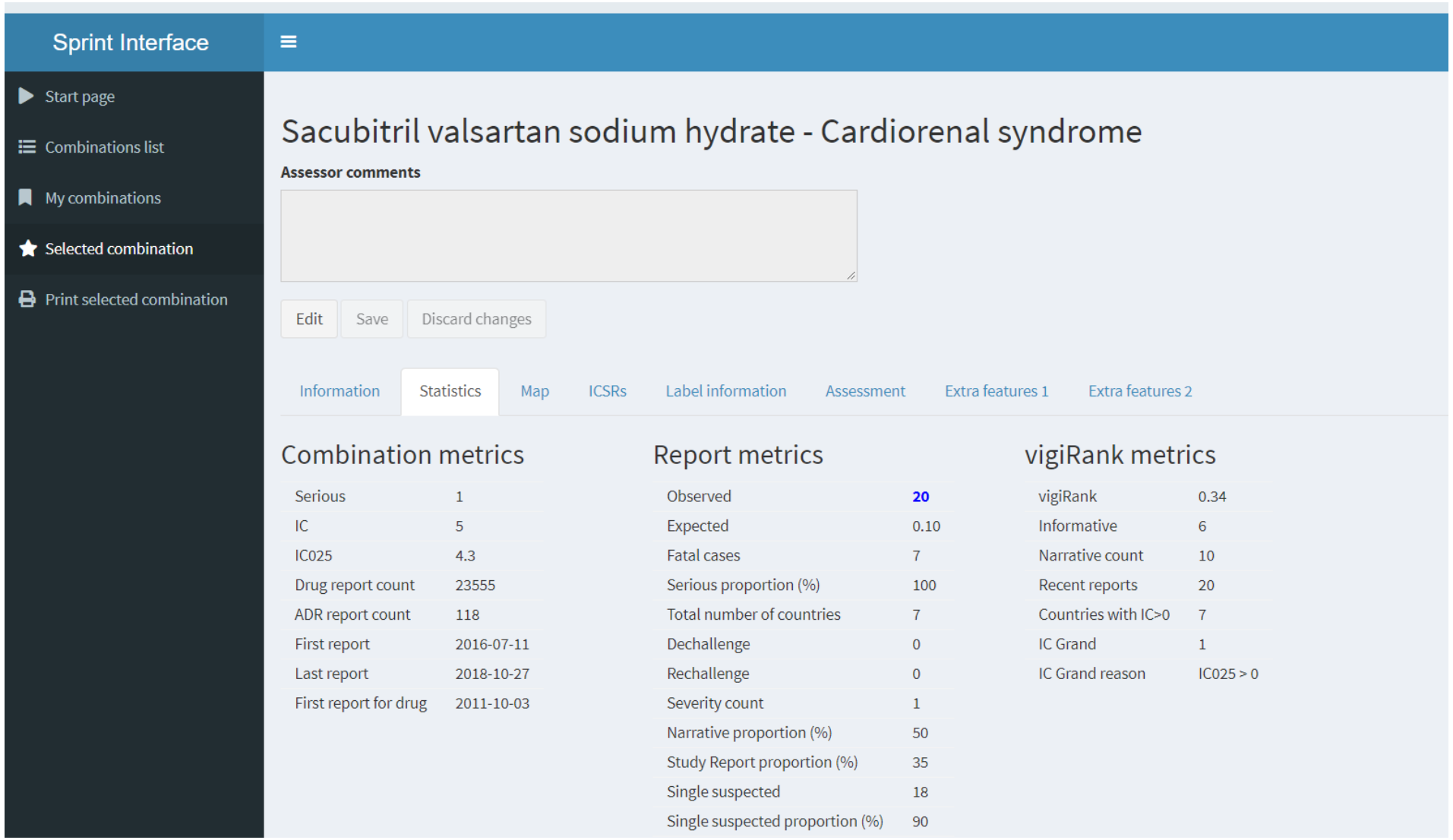
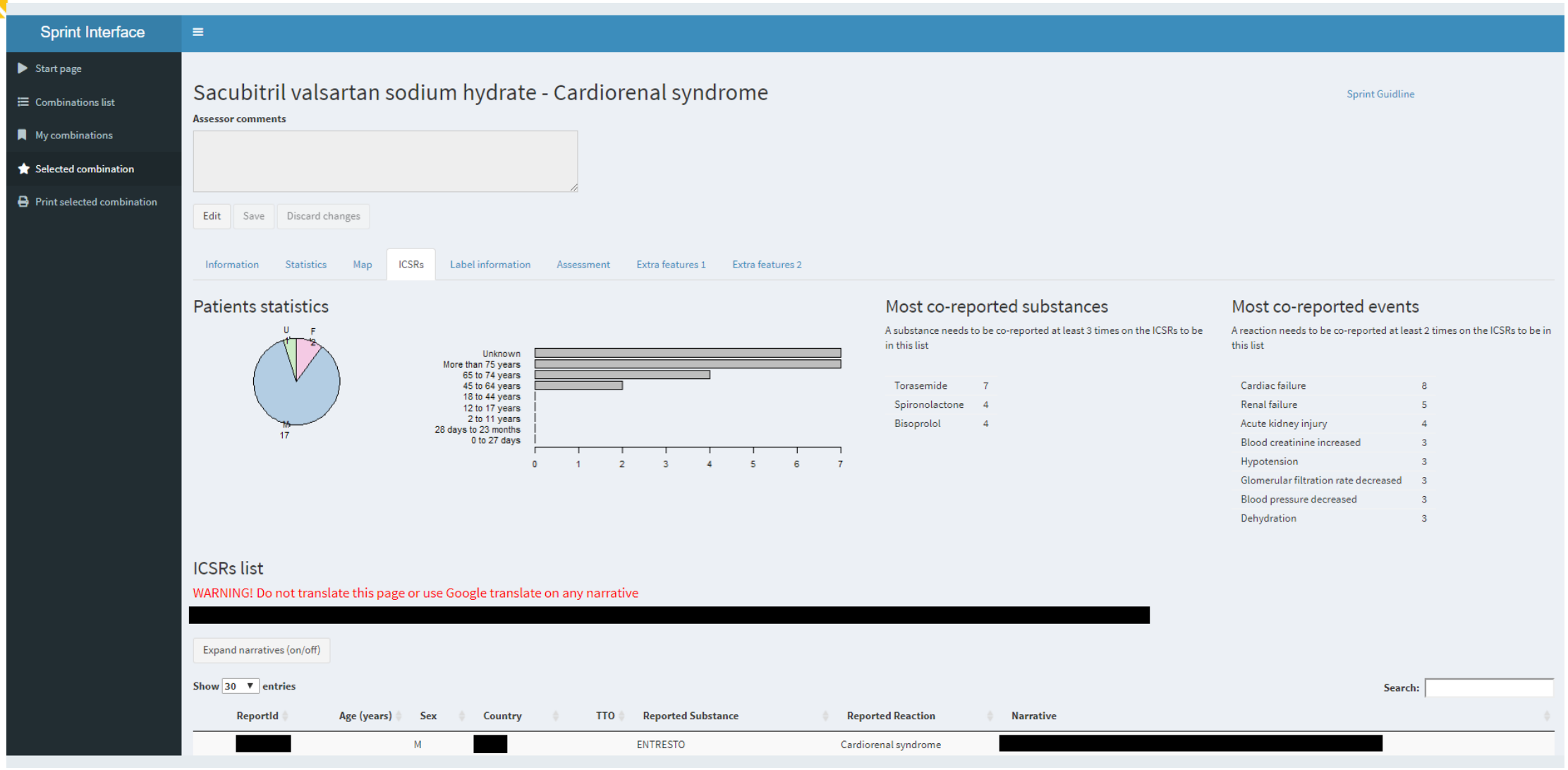


Sprint Interface



The drug-ADR combination in question.....

Uppsala Monitoring Centre — VigiLyze

Substance	Reaction (PT)	$N_{observed}$	$N_{expected}$	IC_{025}	IC
Nintedanib	Colitis	24	8.26	0.85	1.48

NIH U.S. NATIONAL LIBRARY OF MEDICINE

DAILYMED

5.3 Gastrointestinal Disorders

Diarrhea

Diarrhea was the most frequent gastrointestinal event reported in 62% versus 18% of patients treated with OFEV and placebo, respectively *[see Adverse Reactions (6.1)]*. In most patients, the event was of mild to moderate intensity and occurred within the first 3 months of treatment. Diarrhea led to permanent dose reduction in 11% of patients treated with OFEV compared to 0 placebo-treated patients. Diarrhea led to discontinuation of OFEV in 5% of the patients compared to less than 1% of placebo-treated patients.

5.7 Gastrointestinal Perforation

Based on the mechanism of action, OFEV may increase the risk of gastrointestinal perforation. In clinical trials, gastrointestinal perforation was reported in 0.3% of patients treated with OFEV, compared to 0 cases in the placebo-treated patients. In the postmarketing period, cases of gastrointestinal perforations have been reported, some of which were fatal. Use caution when treating patients who have had recent abdominal surgery, previous history of diverticular disease or receiving concomitant corticosteroids or NSAIDs.

Nintedanib

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 MAY 29, 2014 VOL. 370 NO. 22

Efficacy and Safety of Nintedanib in Idiopathic Pulmonary Fibrosis

Luca Richeldi, M.D., Ph.D., Roland M. du Bois, M.D., Ganesh Raghu, M.D., Arata Azuma, M.D., Ph.D., Kevin K. Brown, M.D., Ulrich Costabel, M.D., Vincent Cottin, M.D., Ph.D., Kevin R. Flaherty, M.D., David M. Hansell, M.D., Yoshikazu Inoue, M.D., Ph.D., Dong Soon Kim, M.D., Martin Kolb, M.D., Ph.D., Andrew G. Nicholson, D.M., Paul W. Noble, M.D., Moisés Selman, M.D., Hiroyuki Taniguchi, M.D., Ph.D., Michèle Brun, M.Sc., Florence Le Maulf, M.Sc., Mannaïg Girard, M.Sc., Susanne Stowasser, M.D., Rozsa Schlenker-Herceg, M.D., Bernd Disse, M.D., Ph.D., and Harold R. Collard, M.D., for the INPULSIS Trial Investigators*

ABSTRACT

BACKGROUND

Nintedanib (formerly known as BIBF 1120) is an intracellular inhibitor that targets multiple tyrosine kinases. A phase 2 trial suggested that treatment with 150 mg of nintedanib twice daily reduced lung-function decline and acute exacerbations in patients with idiopathic pulmonary fibrosis.

METHODS

We conducted two replicate 52-week, randomized, double-blind, phase 3 trials (INPULSIS-1 and INPULSIS-2) to evaluate the efficacy and safety of 150 mg of nintedanib twice daily as compared with placebo in patients with idiopathic pulmonary fibrosis. The primary end point was the annual rate of decline in forced vital capacity (FVC). Key secondary end points were the time to the first acute exacerbation and the change from baseline in the total score on the St. George's Respiratory Questionnaire, both assessed over a 52-week period.

RESULTS

A total of 1066 patients were randomly assigned in a 3:2 ratio to receive nintedanib or placebo. The adjusted annual rate of change in FVC was −114.7 ml with nintedanib versus −239.9 ml with placebo (difference, 125.3 ml; 95% confidence interval [CI], 77.7 to 172.8; P<0.001) in INPULSIS-1 and −113.6 ml with nintedanib versus −207.3 ml with placebo (difference, 93.7 ml; 95% CI, 44.8 to 142.7; P<0.001) in INPULSIS-2. In INPULSIS-1, there was no significant difference between the nintedanib and placebo groups in the time to the first acute exacerbation (hazard ratio with nintedanib, 1.15; 95% CI, 0.54 to 2.42; P=0.67); in INPULSIS-2, there was a significant benefit with nintedanib versus placebo (hazard ratio, 0.38; 95% CI, 0.19 to 0.77; P=0.005). The most frequent adverse event in the nintedanib groups was diarrhea, with rates of 61.5% and 18.6% in the nintedanib and placebo groups, respectively, in INPULSIS-1 and 63.2% and 18.3% in the two groups, respectively, in INPULSIS-2.

CONCLUSIONS

In patients with idiopathic pulmonary fibrosis, nintedanib reduced the decline in FVC, which is consistent with a slowing of disease progression; nintedanib was frequently associated with diarrhea, which led to discontinuation of the study medication in less than 5% of patients. (Funded by Boehringer Ingelheim; INPULSIS-1 and INPULSIS-2 ClinicalTrials.gov numbers, NCT01335464 and NCT01335477.)

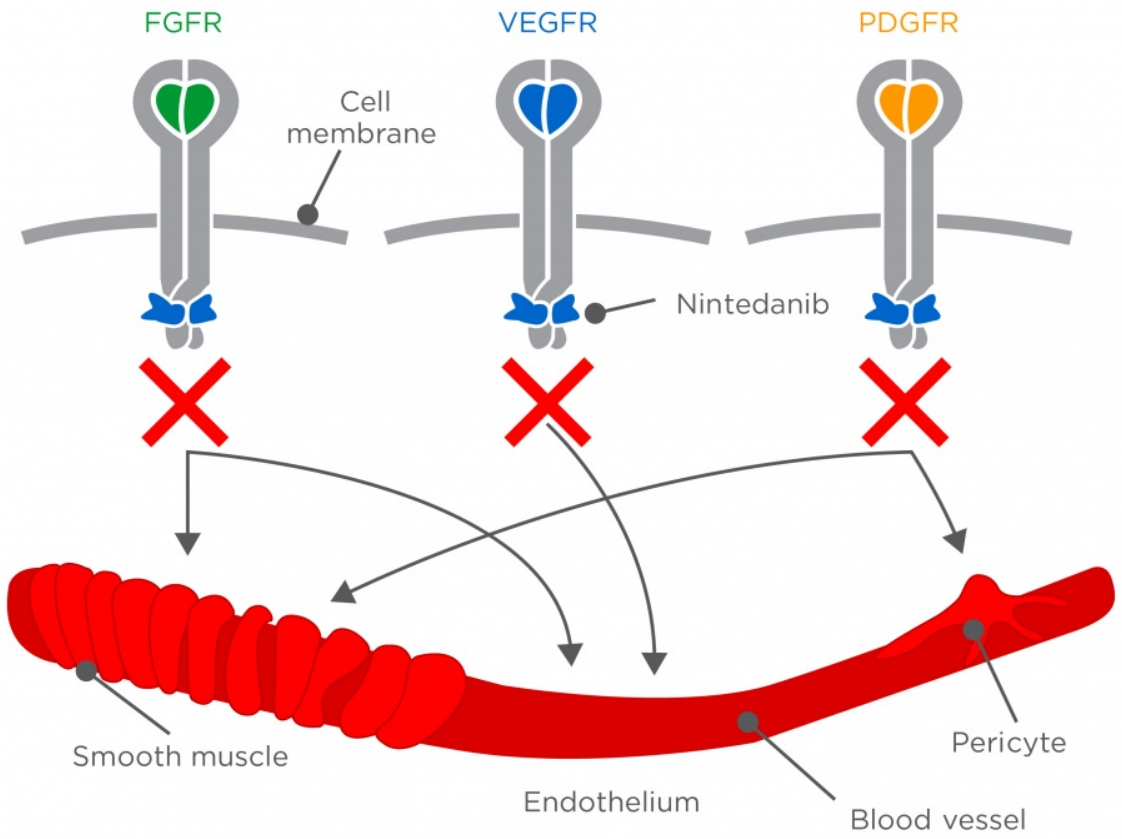
The authors' affiliations are listed in the Appendix. Address reprint requests to Dr. Richeldi at the National Institute for Health Research, Southampton Respiratory Biomedical Research Unit, Mailpoint 813, LE75 E Level, South Academic Block, University Hospital Southampton NHS Foundation Trust, Tremona Rd., Southampton SO16 6YD, United Kingdom, or at l.richeldi@soton.ac.uk.

*A complete list of investigators in the INPULSIS trials is provided in the Supplementary Appendix, available at NEJM.org.

This article was published on May 18, 2014, at NEJM.org.

N Engl J Med 2014;370:2071-82.
DOI: 10.1056/NEJMoa1402584

Nintedanib



OFEV® nintedanib

Product information | Resource libra

Home > Product information > Safety > Adverse Event Management

Adverse Event Management

This section is dedicated to the improvement of possible gastrointestinal side effects of OFEV®.

Treat diarrhea at the first sign[5]

Diarrhea should be treated at first signs with adequate hydration and antidiarrheal medicinal products (eg, loperamide), and may require treatment interruption or reduction of dose.[5]

OFEV®: management of diarrhea[5]

1. Supportive medications

- Initiate antidiarrheals, such as loperamide

2. Dose adjustment

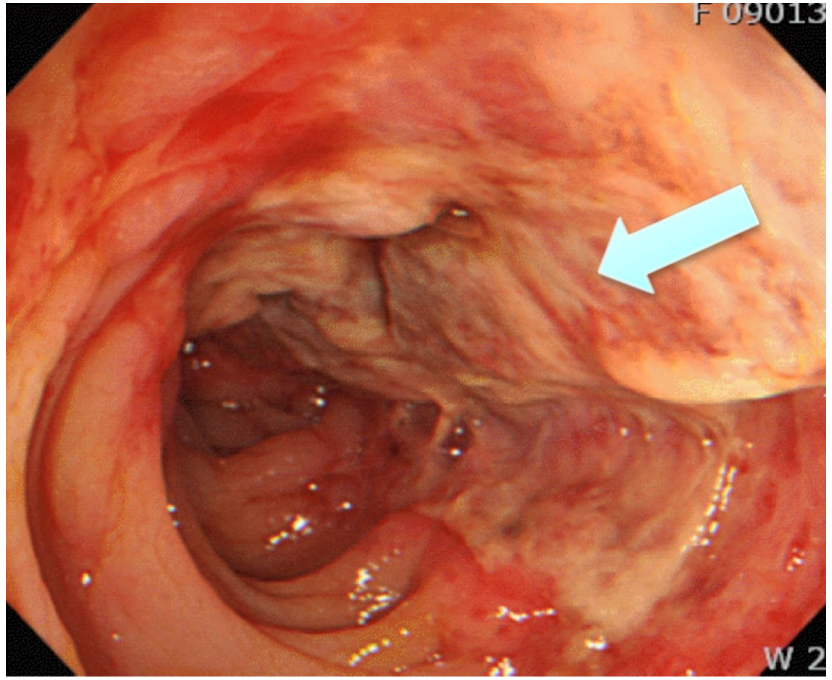
- Interruption or reduction of dose of OFEV® (nintedanib) should be considered if symptomatic treatment is ineffective
- If diarrhea persists despite symptomatic treatment, therapy with OFEV® should be discontinued

3. Dietary changes

- Adequate hydration
- Avoidance of certain foods/drinks

https://www.inoncology.com/compounds/nintedanib/about

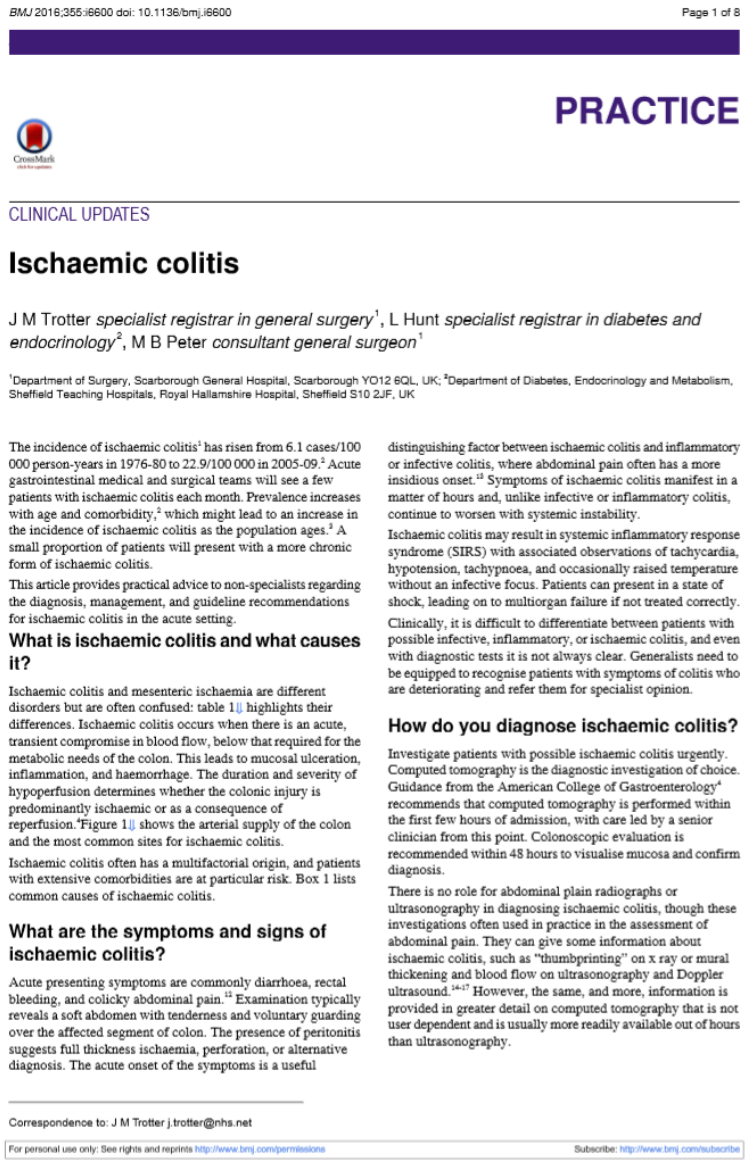
Ischaemic colitis



- A condition which arises with acute, transient compromise in blood flow to the mucosa of the colon
- Leads to mucosal ulceration, inflammation,and haemorrhage.
- It can be difficult to differentiate from other forms, such as infectious or inflammatory colitis
- High mortality rate

Ischaemic colitis

- Acute onset of abdominal pain, colicky in nature, diarrhoea and rectal bleeding
- Causes can be physiological or iatrogenic
- Should be recognised by generalists as colonscopy recommended within 48 hours of onset of symptoms
- Surgical or conservative treatment



BMJ 2016;355:i6600 doi: 10.1136/bmj.i6600

PRACTICE

CLINICAL UPDATES

Ischaemic colitis

J M Trotter *specialist registrar in general surgery*[1], L Hunt *specialist registrar in diabetes and endocrinology*[2], M B Peter *consultant general surgeon*[1]

[1]Department of Surgery, Scarborough General Hospital, Scarborough YO12 6QL, UK; [2]Department of Diabetes, Endocrinology and Metabolism, Sheffield Teaching Hospitals, Royal Hallamshire Hospital, Sheffield S10 2JF, UK

The incidence of ischaemic colitis[1] has risen from 6.1 cases/100 000 person-years in 1976-80 to 22.9/100 000 in 2005-09.[2] Acute gastrointestinal medical and surgical teams will see a few patients with ischaemic colitis each month. Prevalence increases with age and comorbidity,[3] which might lead to an increase in the incidence of ischaemic colitis as the population ages.[3] A small proportion of patients will present with a more chronic form of ischaemic colitis.

This article provides practical advice to non-specialists regarding the diagnosis, management, and guideline recommendations for ischaemic colitis in the acute setting.

What is ischaemic colitis and what causes it?

Ischaemic colitis and mesenteric ischaemia are different disorders but are often confused: table 1⇓ highlights their differences. Ischaemic colitis occurs when there is an acute, transient compromise in blood flow, below that required for the metabolic needs of the colon. This leads to mucosal ulceration, inflammation, and haemorrhage. The duration and severity of hypoperfusion determines whether the colonic injury is predominantly ischaemic or as a consequence of reperfusion.[4]Figure 1⇓ shows the arterial supply of the colon and the most common sites for ischaemic colitis.

Ischaemic colitis often has a multifactorial origin, and patients with extensive comorbidities are at particular risk. Box 1 lists common causes of ischaemic colitis.

What are the symptoms and signs of ischaemic colitis?

Acute presenting symptoms are commonly diarrhoea, rectal bleeding, and colicky abdominal pain.[12] Examination typically reveals a soft abdomen with tenderness and voluntary guarding over the affected segment of colon. The presence of peritonitis suggests full thickness ischaemia, perforation, or alternative diagnosis. The acute onset of the symptoms is a useful distinguishing factor between ischaemic colitis and inflammatory or infective colitis, where abdominal pain often has a more insidious onset.[13] Symptoms of ischaemic colitis manifest in a matter of hours and, unlike infective or inflammatory colitis, continue to worsen with systemic instability.

Ischaemic colitis may result in systemic inflammatory response syndrome (SIRS) with associated observations of tachycardia, hypotension, tachypnoea, and occasionally raised temperature without an infective focus. Patients can present in a state of shock, leading on to multiorgan failure if not treated correctly.

Clinically, it is difficult to differentiate between patients with possible infective, inflammatory, or ischaemic colitis, and even with diagnostic tests it is not always clear. Generalists need to be equipped to recognise patients with symptoms of colitis who are deteriorating and refer them for specialist opinion.

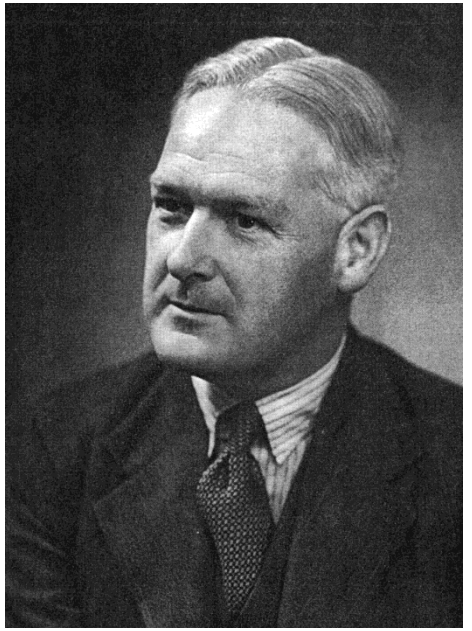
How do you diagnose ischaemic colitis?

Investigate patients with possible ischaemic colitis urgently. Computed tomography is the diagnostic investigation of choice. Guidance from the American College of Gastroenterology[4] recommends that computed tomography is performed within the first few hours of admission, with care led by a senior clinician from this point. Colonoscopic evaluation is recommended within 48 hours to visualise mucosa and confirm diagnosis.

There is no role for abdominal plain radiographs or ultrasonography in diagnosing ischaemic colitis, though these investigations often used in practice in the assessment of abdominal pain. They can give some information about ischaemic colitis, such as "thumbprinting" on x ray or mural thickening and blood flow on ultrasonography and Doppler ultrasound.[14-17] However, the same, and more, information is provided in greater detail on computed tomography that is not user dependent and is usually more readily available out of hours than ultrasonography.

Correspondence to: J M Trotter j.trotter@nhs.net

A question of causality



ORIGINAL RESEARCH ARTICLE

Drug Safety 2007; 30 (4): 333-346
0114-5916/07/0004-0333/$44.95/0

Application of the Bradford Hill Criteria to Assess the Causality of Cisapride-Induced Arrhythmia

A Model for Assessing Causal Association in Pharmacovigilance

Michael Perrio,[1] *Simon Voss*[2] and *Saad AW Shakir*[1,3]

1 Drug Safety Research Unit, Bursledon Hall, Southampton, UK
2 Eli Lilly and Company Limited, Erl Wood Manor, Windlesham, UK
3 University of Portsmouth, Portsmouth, UK

Biological plausibility

Mini Review | OPEN | Published: 22 May 2007

Minireview

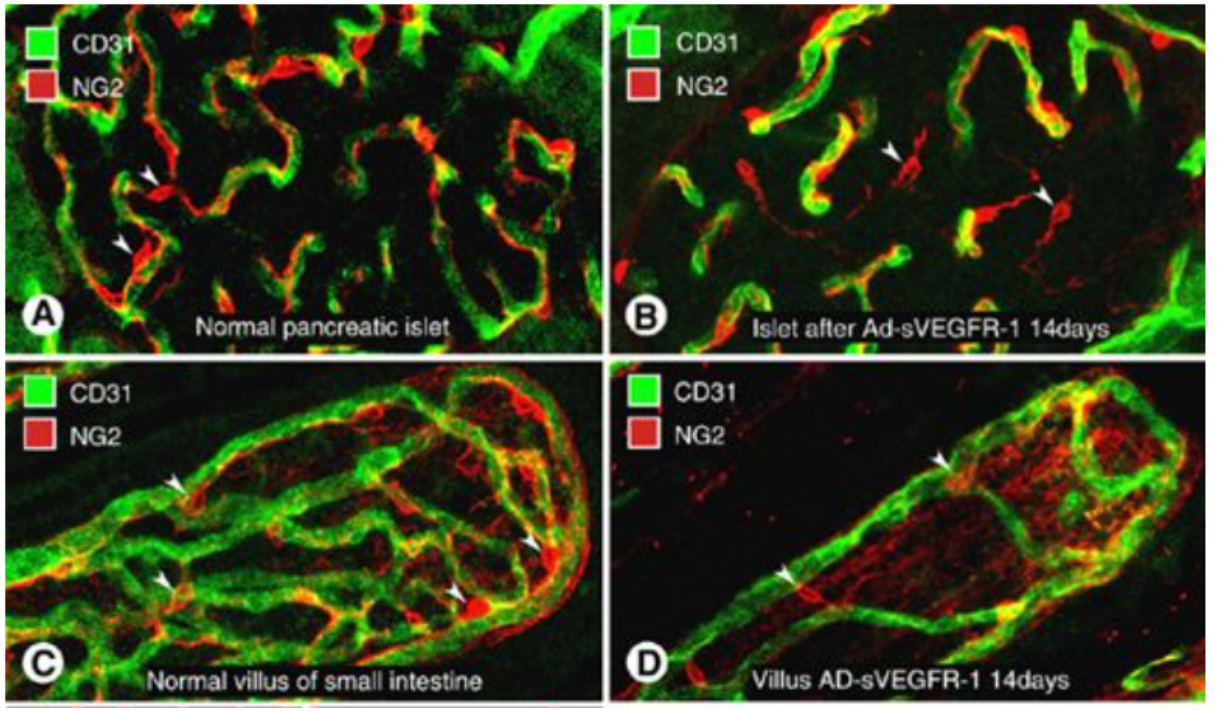
Mechanisms of adverse effects of anti-VEGF therapy for cancer

T Kamba & D M McDonald

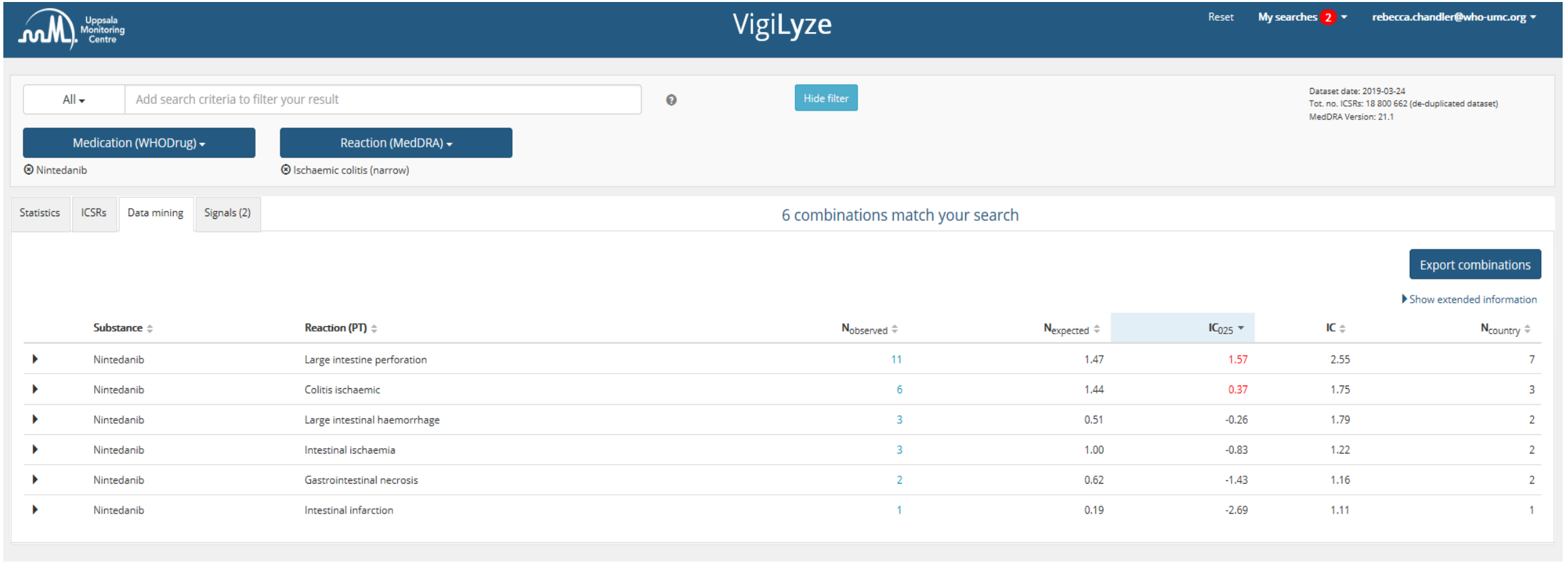
British Journal of Cancer **96**, 1788–1795 (18 June 2007) | Download Citation

A survey of 18 organs of normal adult mice revealed significant regression of capillaries in some organs and not in others (Kamba et al, 2006; Baffert et al, 2006a). After inhibition of VEGF signalling for 1 to 3 weeks, significant capillary regression occurred in pancreatic islets (Figure 2A and B), thyroid, adrenal cortex, pituitary, villi of small intestine (Figure 2C and D), choroid plexus, adipose tissue, and trachea (Kamba et al, 2006; Baffert et al, 2006a). The amount of regression was dose-dependent and varied from organ to organ, with a maximum of 68% in thyroid. But two tumours examined under the same conditions had even greater vascular regression (Inai et al, 2004; Kamba et al, 2006). Little or no capillary regression was detected in brain, retina, skeletal muscle, cardiac muscle, or lung under these conditions. Capillaries that underwent regression had the same pericyte coverage and apparent structural maturity as capillaries that survived.

Figure 2



Strength of association



Uppsala Monitoring Centre

VigiLyze

Reset | My searches 2 | rebecca.chandler@who-umc.org

All | Add search criteria to filter your result | Hide filter

Dataset date: 2019-03-24
Tot. no. ICSRs: 18 800 662 (de-duplicated dataset)
MedDRA Version: 21.1

Medication (WHODrug) | Reaction (MedDRA)

Nintedanib | Ischaemic colitis (narrow)

Statistics | ICSRs | Data mining | Signals (2)

6 combinations match your search

Export combinations

Show extended information

Substance	Reaction (PT)	$N_{observed}$	$N_{expected}$	IC_{025}	IC	$N_{country}$
Nintedanib	Large intestine perforation	11	1.47	1.57	2.55	7
Nintedanib	Colitis ischaemic	6	1.44	0.37	1.75	3
Nintedanib	Large intestinal haemorrhage	3	0.51	-0.26	1.79	2
Nintedanib	Intestinal ischaemia	3	1.00	-0.83	1.22	2
Nintedanib	Gastrointestinal necrosis	2	0.62	-1.43	1.16	2
Nintedanib	Intestinal infarction	1	0.19	-2.69	1.11	1

Analogy

BJCP British Journal of Clinical Pharmacology

SHORT REPORT

Ischaemic colitis associated with intravitreal administration of aflibercept: A first case report

Benjamin Batteux, Valérie Gras, Yanis Mahboud, Sophie Liabeuf, Youssef Bennis, Kamel Masmoudi

First published: 04 January 2019 | https://doi.org/10.1111/bcp.13853

Read the full text > PDF TOOLS SHARE

Abstract

In patients with age-related macular degeneration (AMD), the intravitreal injection of antivascular endothelial growth factor (anti-VEGF) agents reduces disease progression and choroidal neovascularization. We report on a first case of ischaemic colitis associated with intravitreal injection of the anti-VEGF agent aflibercept in an 80-year-old female patient. Conservative treatment resulted in a favourable clinical outcome. The anti-VEGF agent was discontinued, and the symptoms did not recur. Although the intravitreal injection of anti-VEGF agents has not previously been linked to the occurrence of ischaemic colitis, consideration of aflibercept's pharmacological properties and the chronological relationship between the administration of this anti-VEGF agent and the occurrence of this systemic adverse event are strongly suggestive of a causal relationship in the present case. Although systemic complications have been rarely associated with intravitreal injections of anti-VEGF agents, physicians should be aware that novel adverse events can still occur in AMD patients treated with anti-VEGF agents.

Two Cases of Acute Abdomen after an Intravitreal Injection of Bevacizumab

Yasutaka Onoda[a] Tomoaki Shiba[c] Yuichi Hori[c] Takatoshi Maeno[a] Mao Takahashi[b]

[a]Department of Ophthalmology, and [b]Cardiovascular Center, Toho University Sakura Medical Center, Chiba, and [c]Department of Ophthalmology, Toho University School of Medicine, Tokyo, Japan

Key Words
Intravitreal injection of bevacizumab · Acute abdomen · Side effect · Vascular endothelial growth factor · Ischemic colitis · Paralytic ileus

Abstract
We report on a patient with ischemic colitis and another with paralytic ileus, both of whom experienced an acute abdomen after intravitreal injection of bevacizumab (IVB). Case 1 was a 78-year-old woman. Her medical history included surgery for colon carcinoma 10 years earlier. The patient developed acute severe abdominal pain and nausea the day after IVB for retinal vein occlusion with macular edema, and massive lower gastrointestinal bleeding occurred. Ischemic colitis was diagnosed. Case 2 was a 64-year-old man who presented with neovascular glaucoma with proliferative diabetic retinopathy. We performed vitreous surgery on the 9th day after IVB, and we reperformed IVB at the end of the vitreous surgery. On the first postoperative day, severe abdominal distension, vomiting and abdominal pain were observed, and paralytic ileus was diagnosed. It is possible that gastrointestinal disorders are induced after IVB, depending on the patient's background, including for example severe diabetes or a history of surgery for gastrointestinal cancer. Thus, ophthalmologists should apply alternative therapies instead of IVB to patients with severe diabetes mellitus or a history of gastrointestinal cancer.

The pharmacovigilante's dilemma

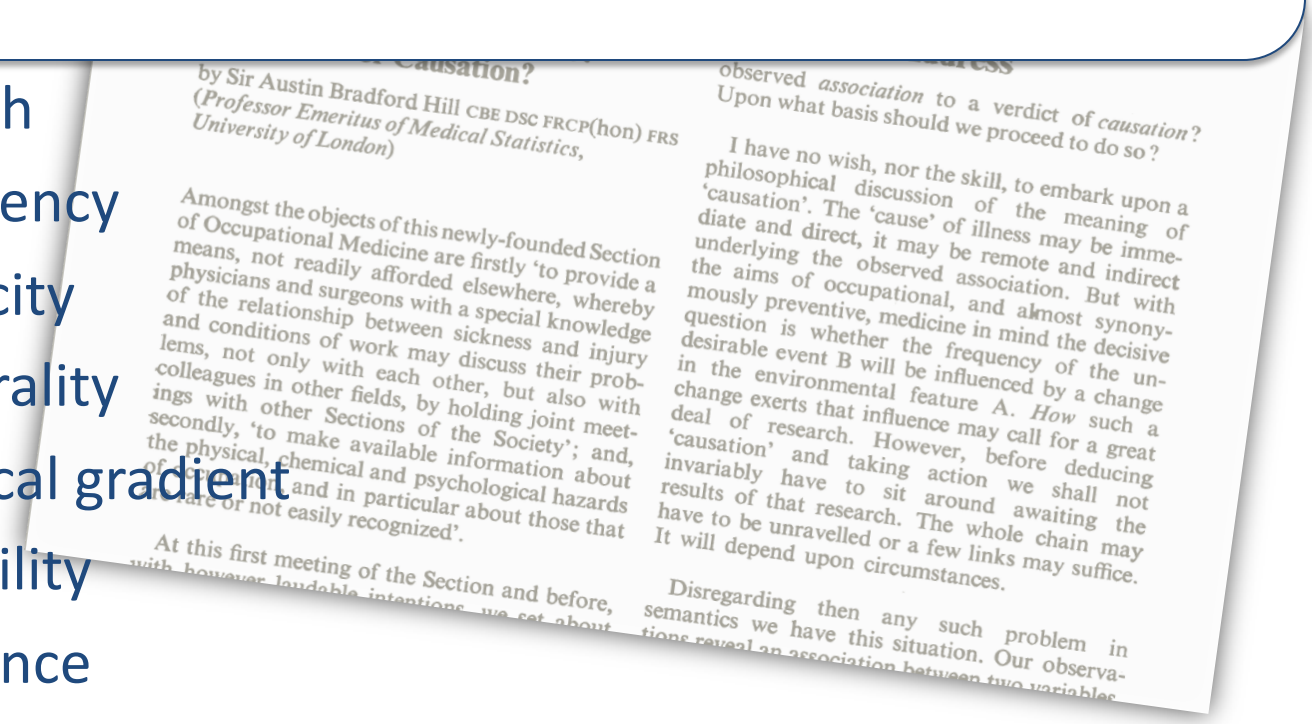
A signal should be identified as soon as possible to allow early warning

but

When is there ENOUGH evidence?

"What aspects of that association should we especially consider before deciding that the most likely interpretation of it is causation?"

- Strength
- Consistency
- Specificity
- Temporality
- Biological gradient
- Plausibility
- Coherence
- Experiment
- Analogy



Austin Bradford Hill, "The Environment and Disease: Association or Causation?," *Proceedings of the Royal Society of Medicine*, 58 (1965), 295-300.

What do we have so far?

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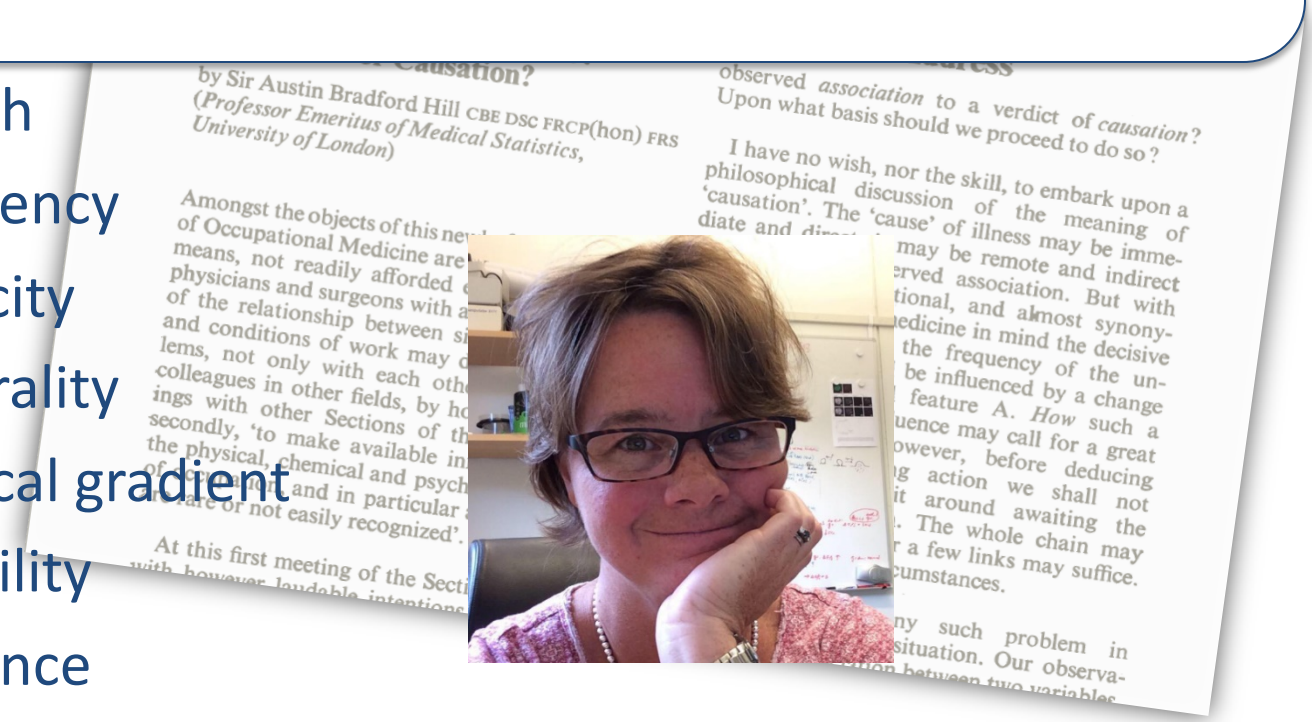

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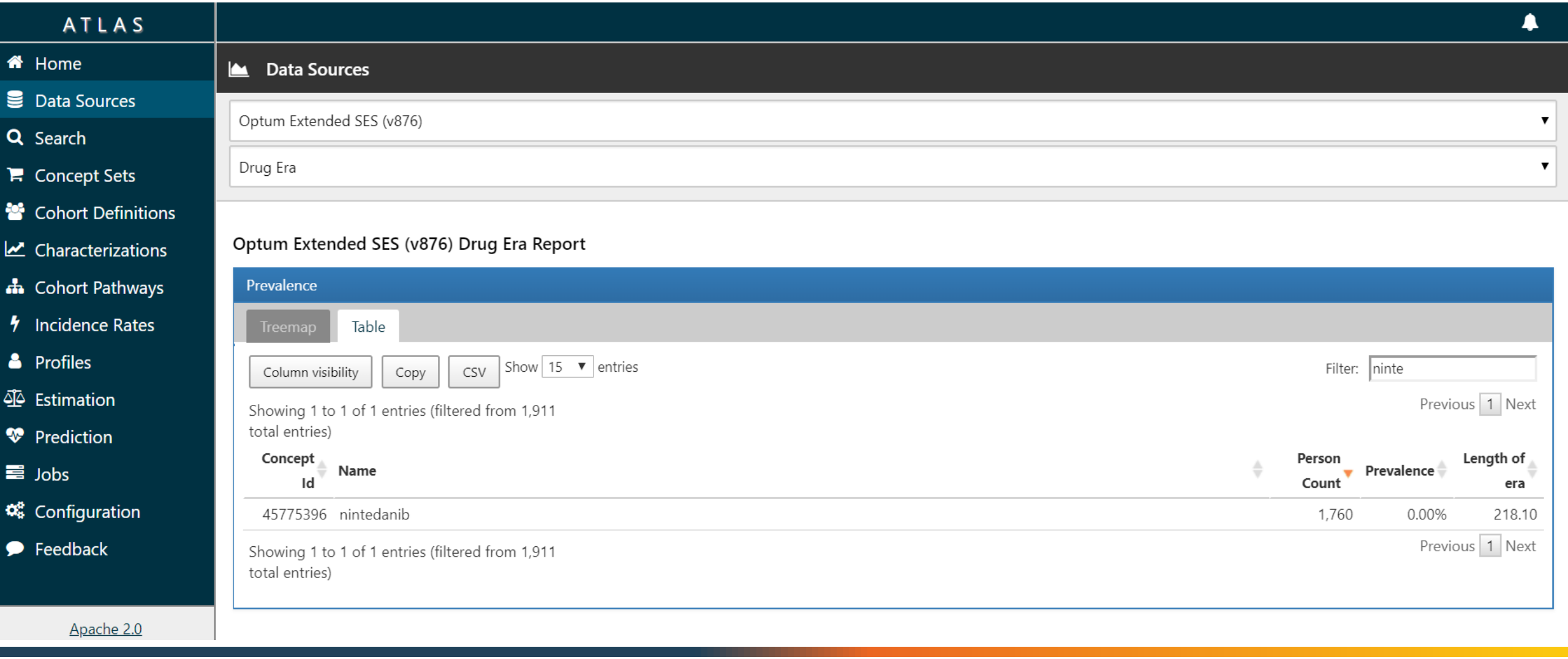
Clinical Characterization #1:
Is the drug used in the real world?



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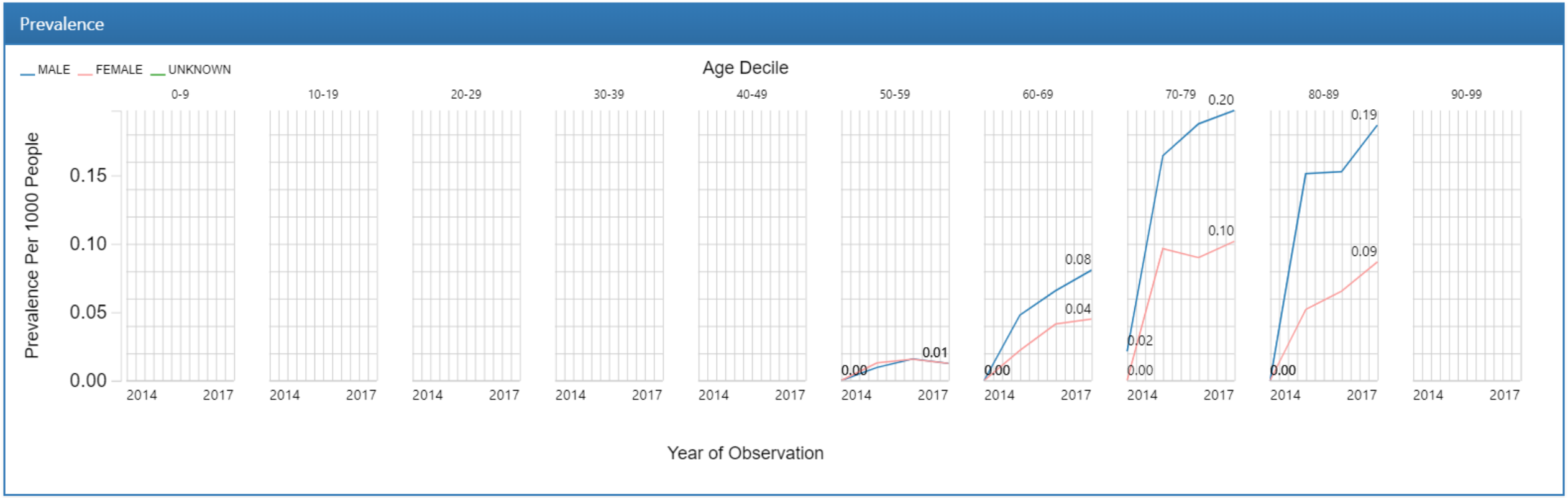
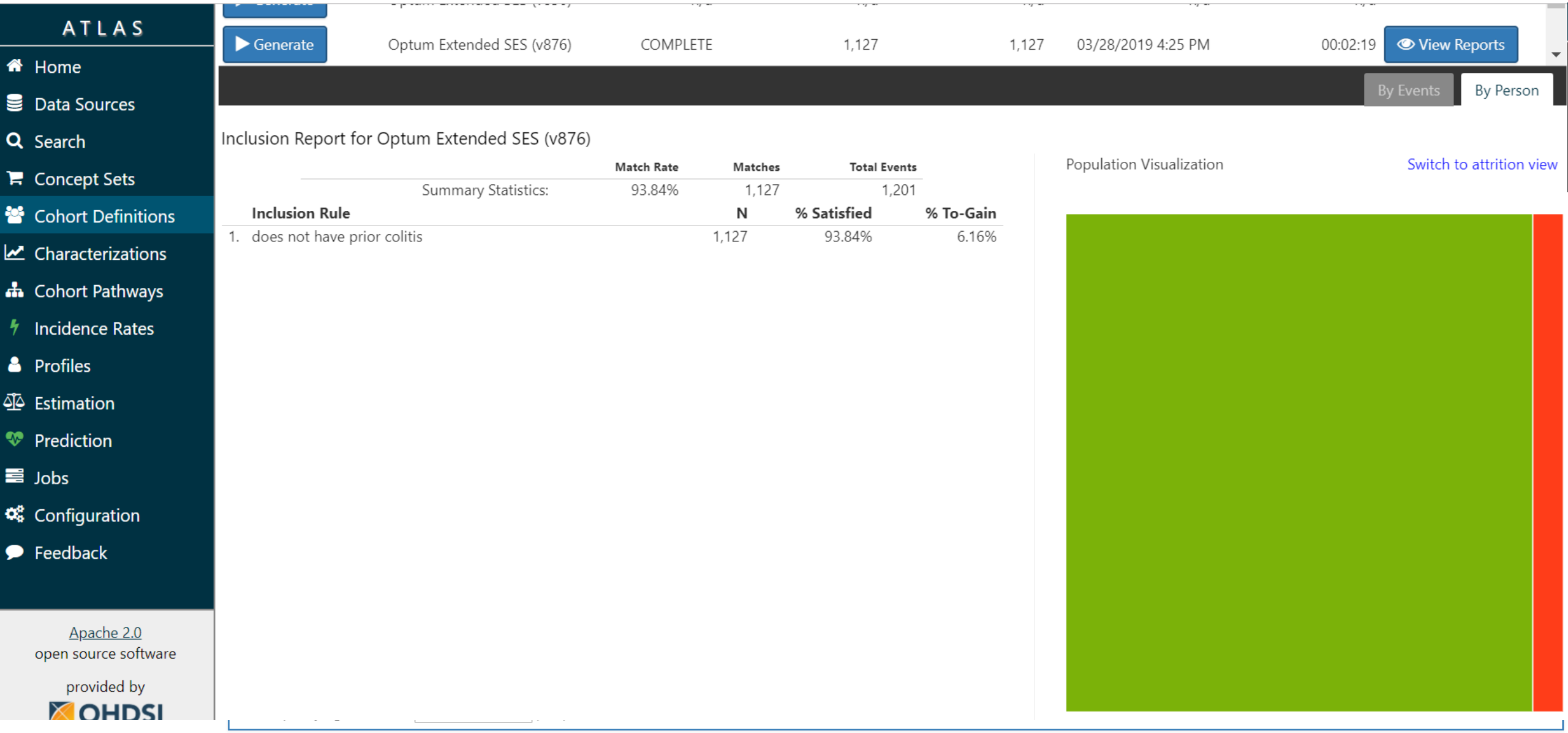
Is the drug used in the real world?

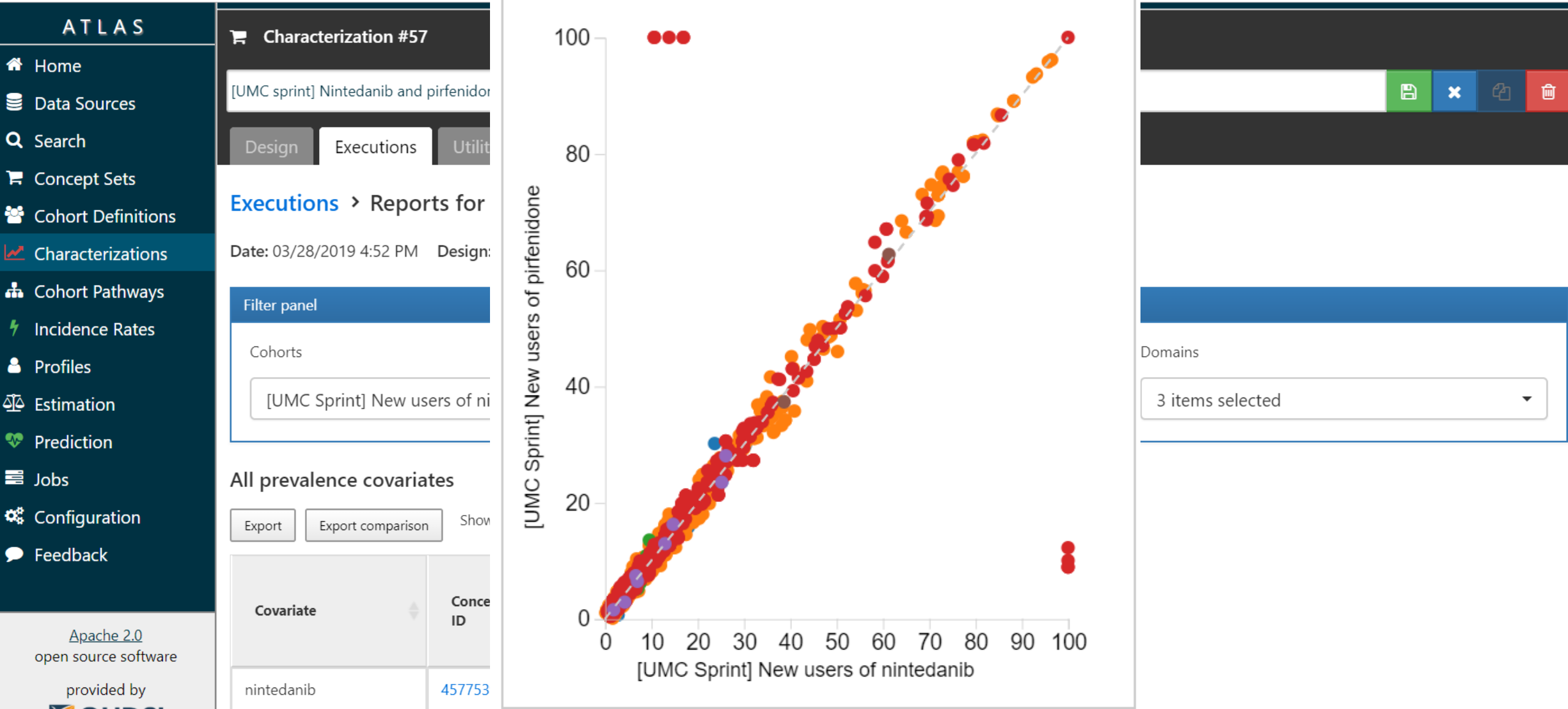
nintedanib Drilldown Report



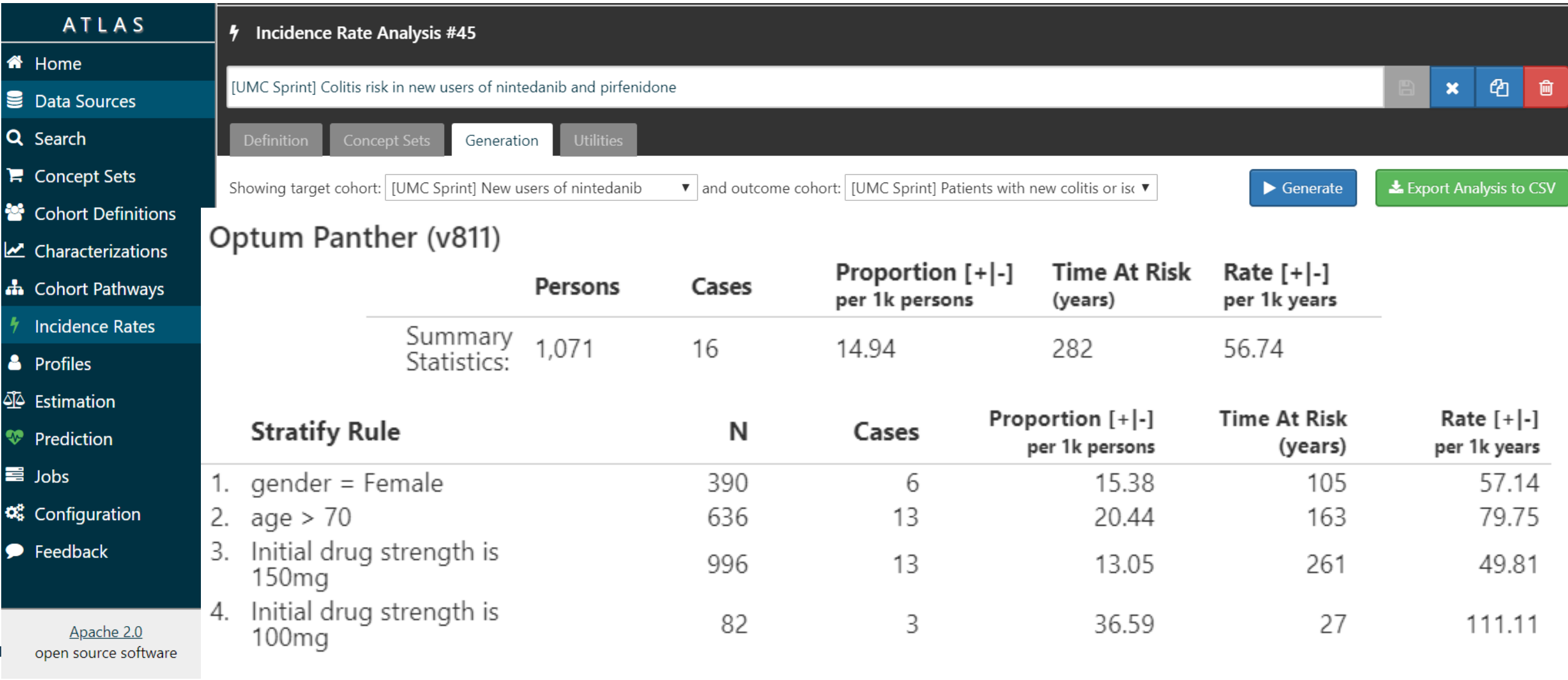
Clinical Characterization #2: How many patients are newly exposed?



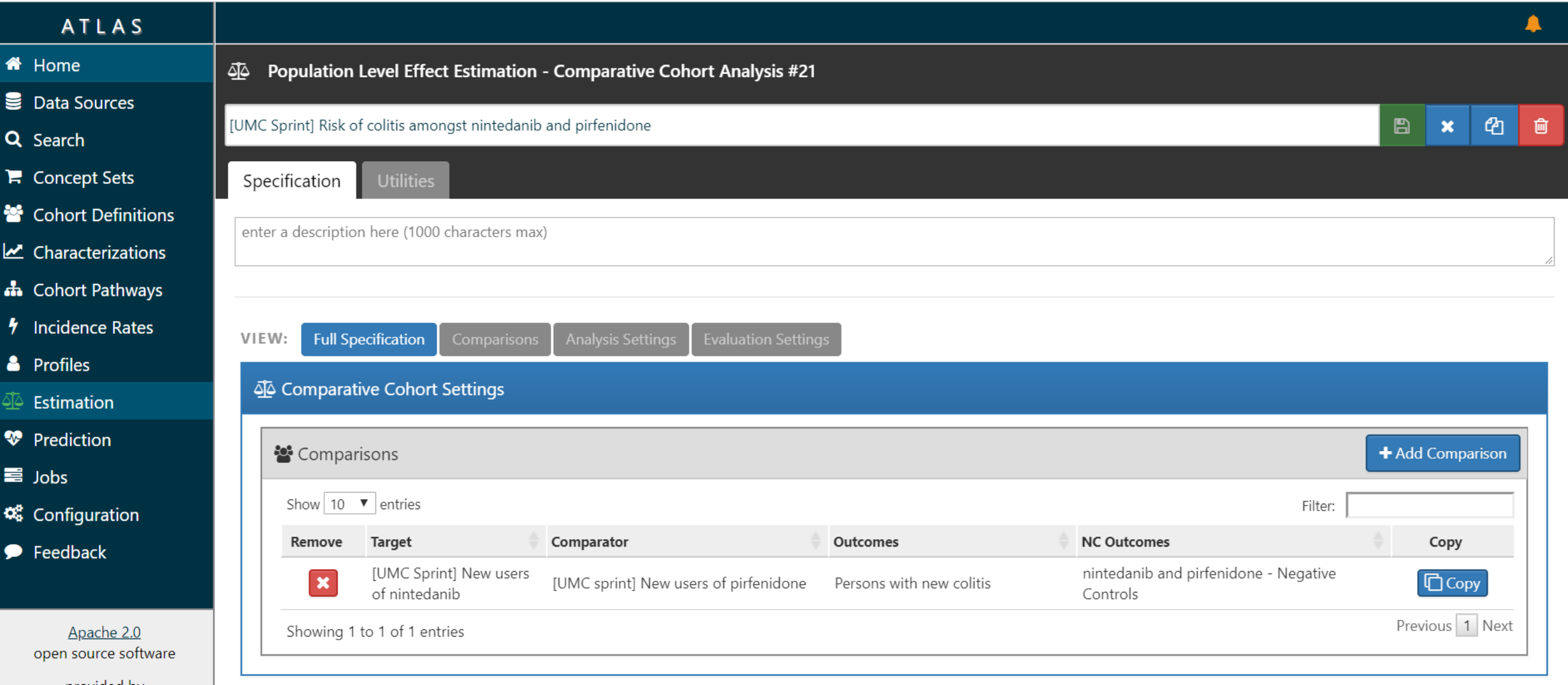
Clinical characterization #3: Who are these patients?



Clinical characterization #4: What is the incidence of the event?



Population-level effect estimation: Design a comparative cohort analysis



Population-level effect estimation: Apply multiple methods, multiple databases, and negative controls to assess consistency of results

Design	Database	Target	Comparator	Outcome	IRR	LB95	UB95
Self-controlled cohort, on-treatment	Optum	Nintenanib	Pre-exposure	Colitis	12.28	3.05	107.25

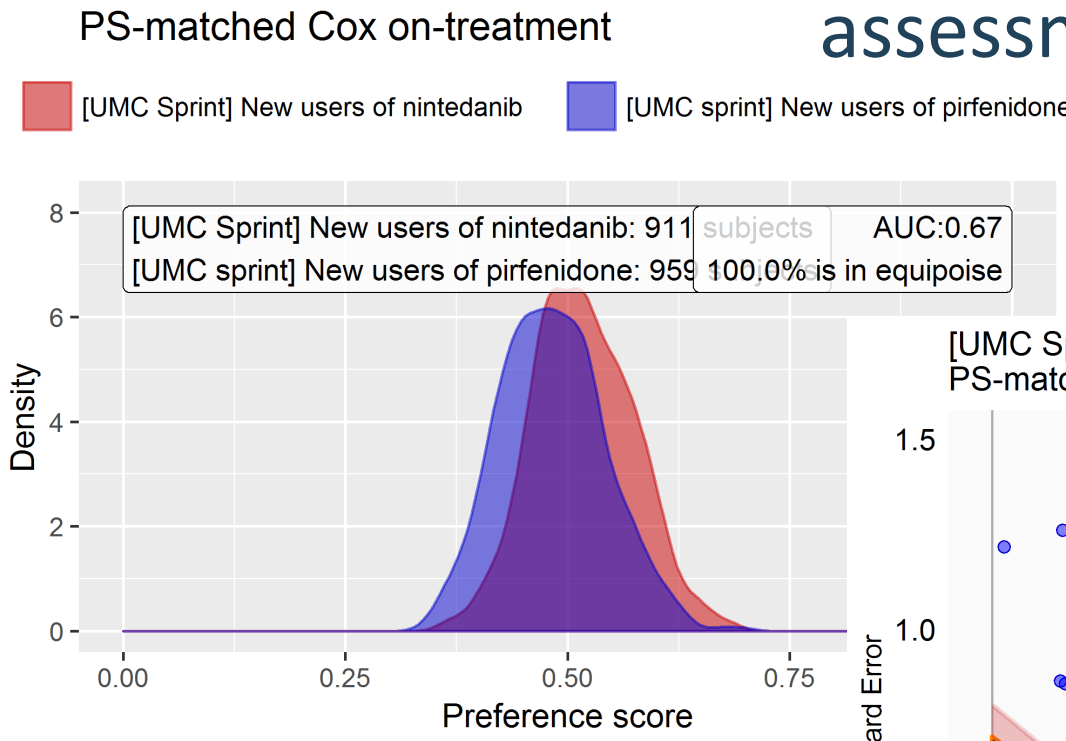
Negative control exposure?

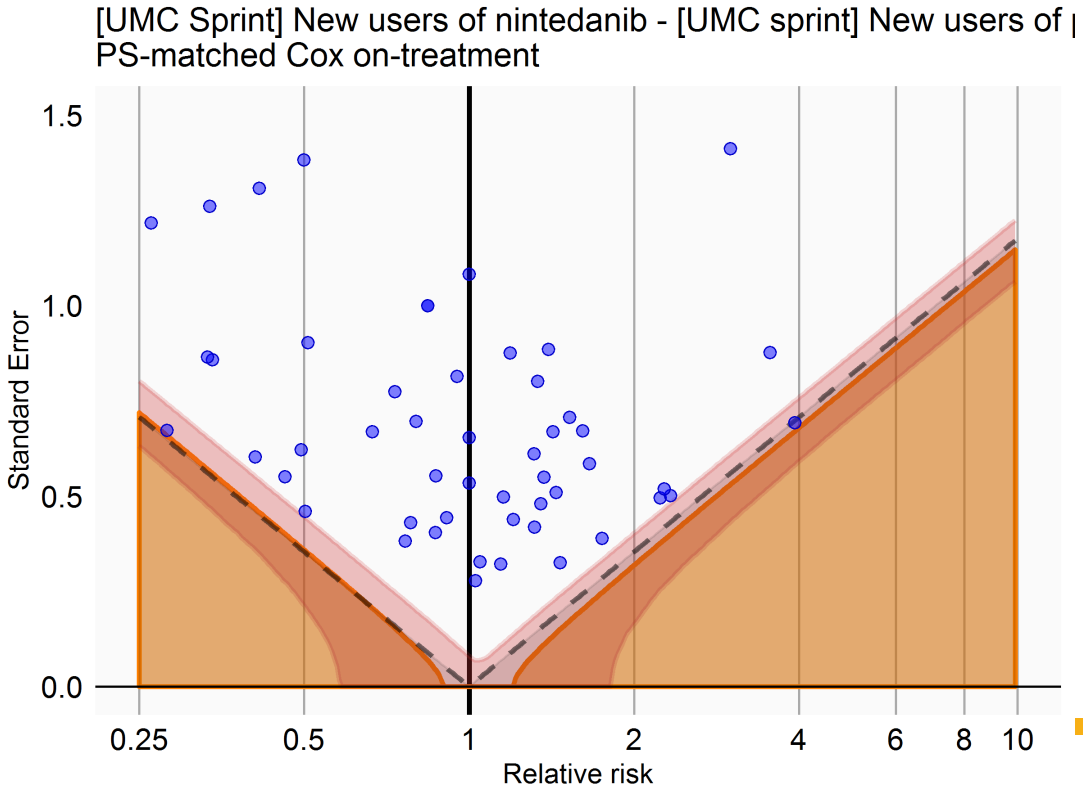
Different database?

Different analysis method?

Preliminary findings subject to review and additional analysis

Population-level estimation: following best practices for diagnostic evaluation as we should do with any protocol-based assessment





How can real world evidence help?

"What aspects of that association should we especially consider before deciding that the most likely interpretation of it is causation?"

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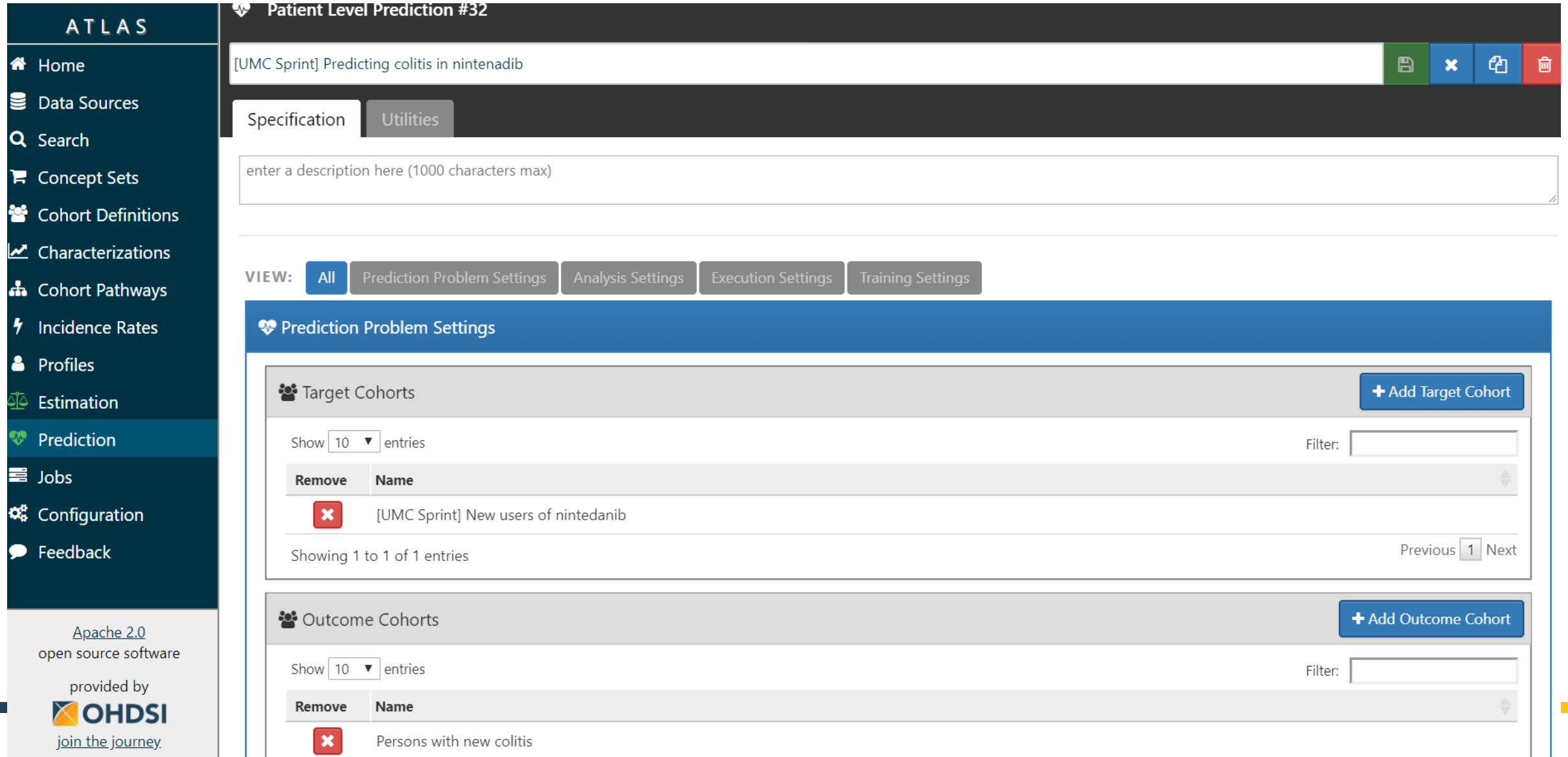
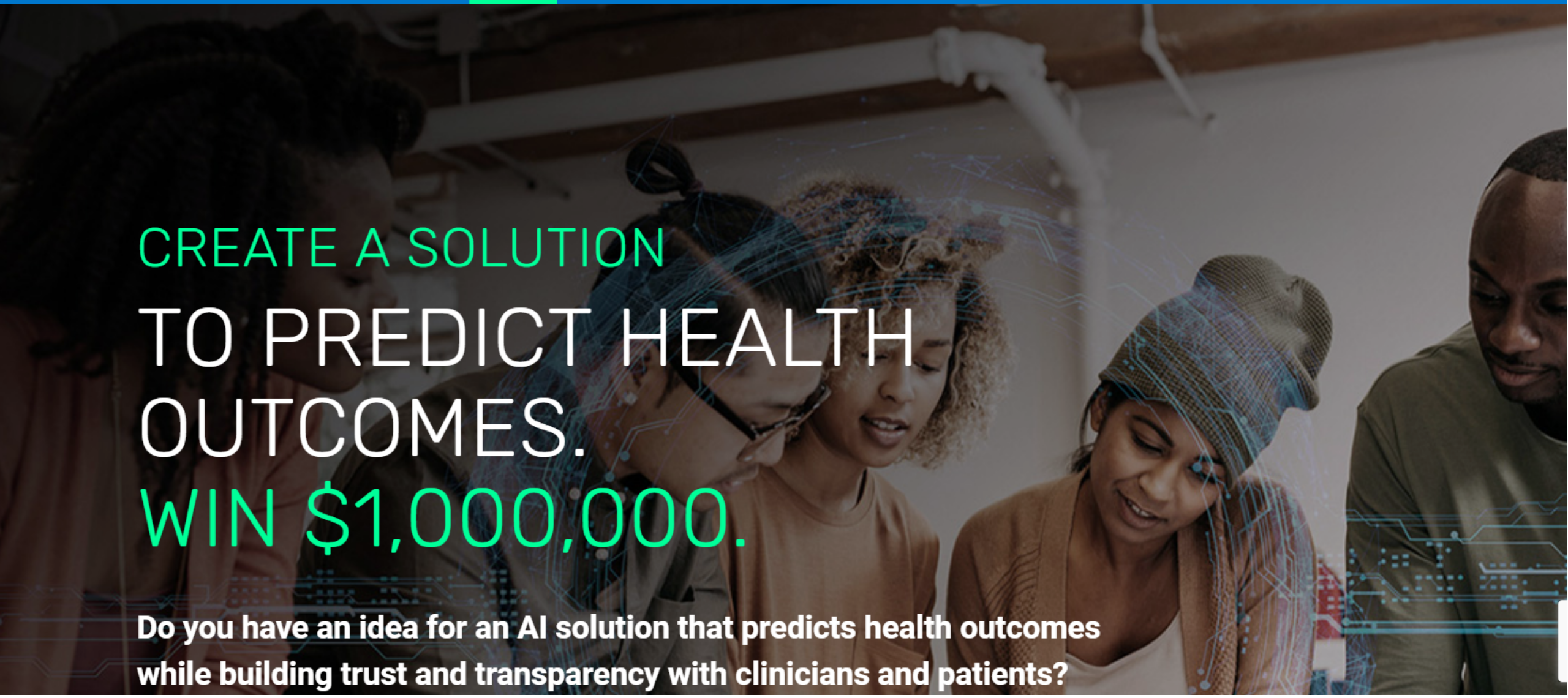
"Here then are nine different viewpoints from all of which we should study association before we cry causation. What I do not believe - and this has been suggested - is that we can usefully lay down some hard-and-fast rule of evidence that must be obeyed before we can accept cause and effect… What they can do, with greater or less strength, is to help us to make up our minds on the fundamental question - is there any other way of explaining the set of facts before us, is there any other answer equally, or more, likely than cause and effect?"

Patient-level prediction:
Which patients will experience the outcome?





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