



Data to Evidence: OHDSI in Action!

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Columbia University Medical Center



The origins of pharmacovigilance

AUG. 15, 1959

BRITISH MEDICAL JOURNAL

7



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and
sounder sleep**

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- tasteless
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- restores the natural pattern of sleep
- particularly suitable for children and the aged

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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 anti-emetic 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 fetus 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+

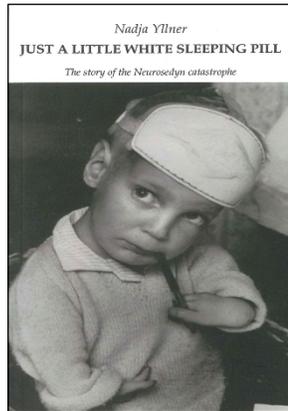
Scientists find a new clue about how thalidomide caused devastating birth defects

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)

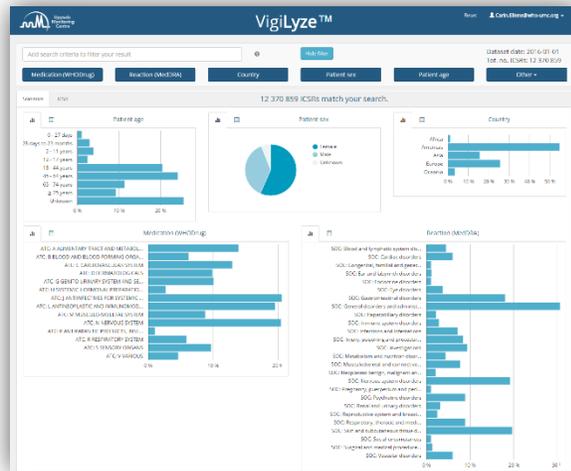
WHO Collaborating Centre for International Drug Monitoring

- 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.



UMC Uppsala Monitoring Centre Safer Use of Medicines

WHODrug portfolio

Our unique and trusted WHODrug portfolio – developed for you and with you.

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)

Report (Initials or Record #, only) Age Sex Weight Height
 [Redacted] 05 DEC 2006 55 M 80 168

Adverse Reaction Description: **DESC** Date of Onset of Reaction: 29/11/06
 Patient with a **NON ST ELEVATION MI** and diagnostic angiogram showing severe stenosis in LAD. Same day had PCI to LAD during which experienced profound and sustained hypotension NOT believed with adrenaline (several 0.5mg boluses) and 1mg of fr hydrocortisone 200mg + phenylephrine 100mg. **ALLERGIC REACTION TO CONTRAST (ISSUE 370)**

Drug Therapy Prior to Reaction (sterisk Suspected Drug(s) (please use trade names))	Daily Dosage and Route	Date Begun	Date Stopped	Reason for Use
ASPIRIN	300mg o	29/1/06	—	NSSTEMI
Clopidogrel	300mg o	29/1/06	—	NSSTEMI
TENAZEPAN	10mg o	29/1/06	—	sedation
INSULIN	IV bolus + infusion	29/1/06	29/1/06	NSSTEMI
ADRENALINE	2mg IV	29/1/06	29/1/06	sedation
HYDROCORTISONE	40mg IV	29/1/06	29/1/06	sedation
ISOSORBIDE	5mg o	29/1/06	29/1/06	sedation

Treatment (of reaction): **ADRENALINE, hydrocortisone, phenylephrine**
 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



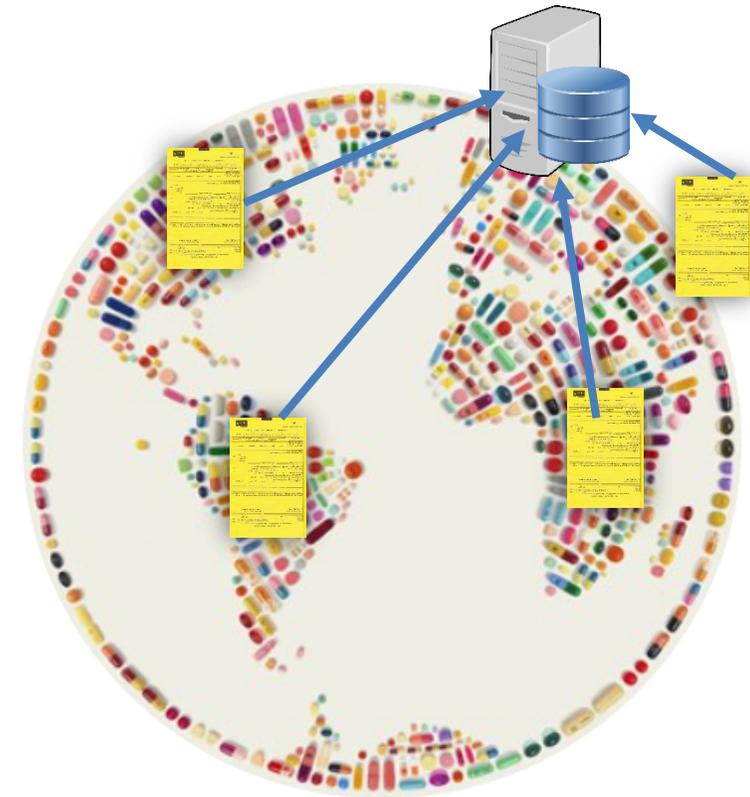
Global collection of reports

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



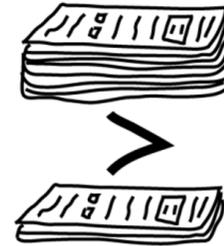
**The WHO Programme for
International Drug Monitoring**



The basis of signal detection in pharmacovigilance



Observed
vs.
Expected



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

© Springer-Verlag 1998

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

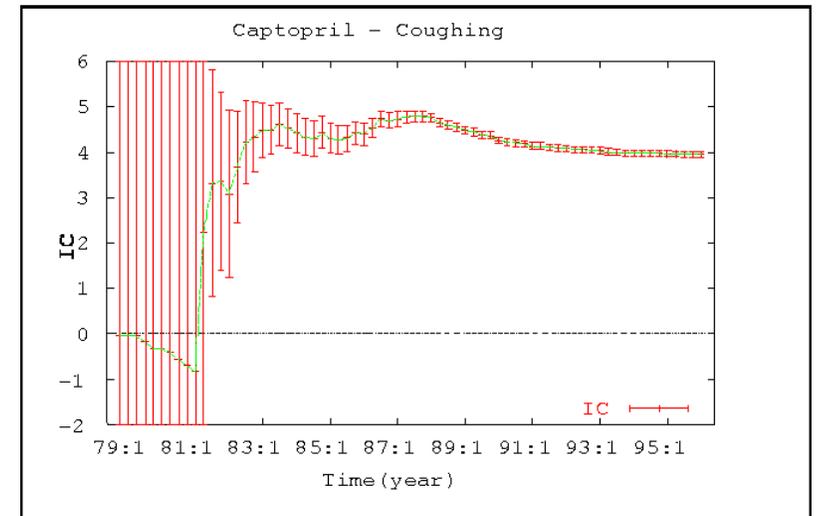
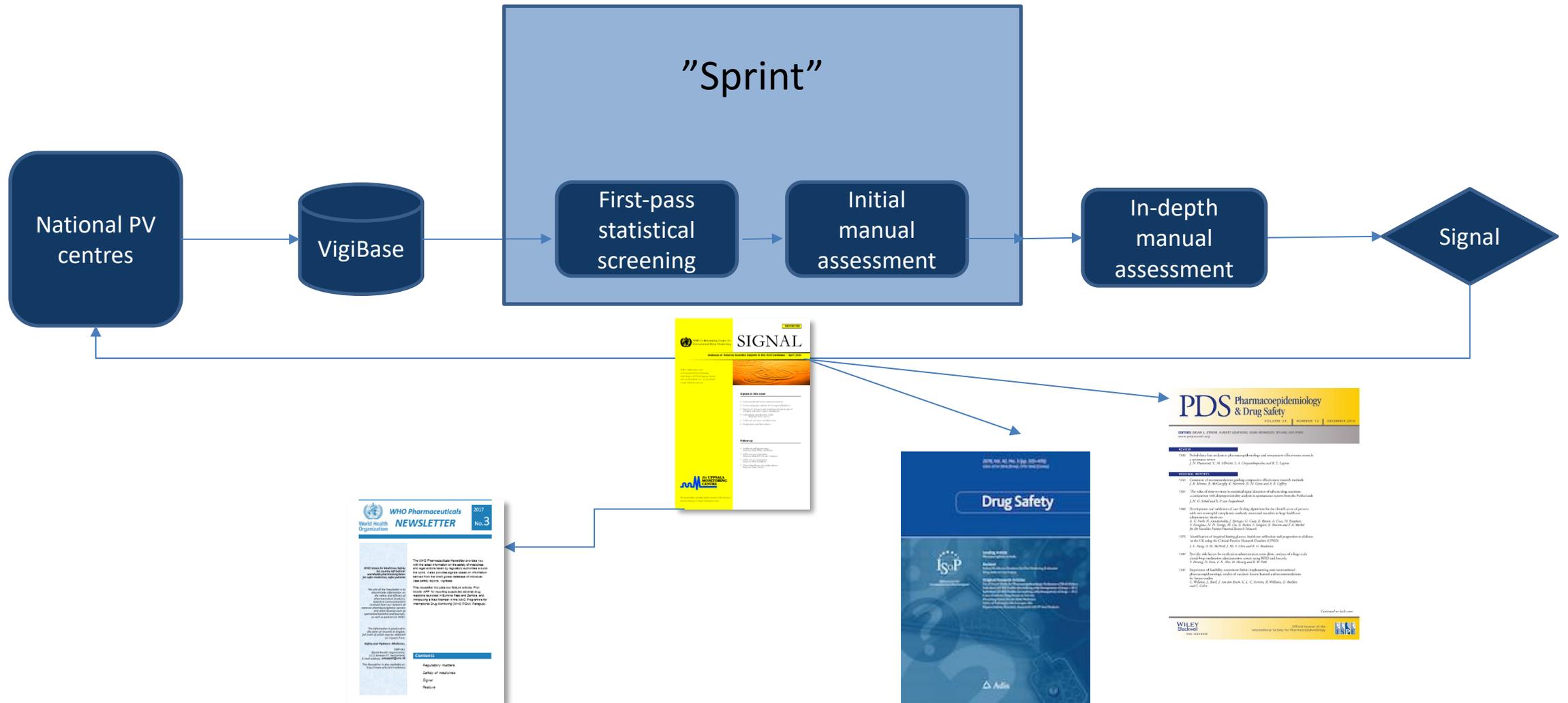


Fig. 1: Shrinkage of CI of IC over time
With increasing data, the confidence interval gets smaller. Once the value 0 is not included in the CI, a signal is flagged.
(Sten Olsson, the Uppsala Monitoring Centre, presentation, 2004)



UMC Signal detection process





Sprint





Sprint Interface

Sprint Interface

Start page

Combinations list

My combinations

Selected combination

Print selected combination

Welcome Rebecca!

Welcome to the sprint interface.

Sprint progress

3 Combinations assigned

2 Combinations finalized

1 Potential signals

Potential signals

Association id	Drug	ADR	Assessor	Medic	Finalized date
418960	Chlorambucil	Tumour lysis syndrome	RC	RC	2019-03-27

Your progress

3 Combinations assigned

2 Combinations finalized

Refresh start page



Sprint Interface

Sprint Interface ☰

Start page

Combinations list

My combinations

Selected combination

Print selected combination

Show 5 entries Search:

Actions	Association id	Drug	ADR	Assessor	Medic	Review	Finalized	vigiRank	IC	IC025	Observed	Expected	IME term	Serious	% Serious	Fatal	HLT
	1475910	Diphtheria vaccine;Hepatitis b vaccine;HIB vaccine;Pertussis vaccine;Polio vaccine;Tetanus vaccine	Meningitis haemophilus	-				0.34	4.9	4.2	19	0.1	1	Yes	100	0	Haemophilus infections,Meningeal bacterial infections
	417866	Norepinephrine	Extremity necrosis	RC	RC	N-Insufficient info	1	0.34	5.2	4.5	20	0.0	0	Yes	89	5	Peripheral vasoconstriction, necrosis and vascular insufficiency
	418960	Chlorambucil	Tumour lysis syndrome	RC	RC	Y	1	0.34	4.7	4.0	20	0.3	1	Yes	94	0	Electrolyte imbalance NEC,Oncologic complications and emergencies
	1475338	Alemtuzumab	Autoimmune hypothyroidism	-				0.34	5.2	4.5	20	0.0	1	Yes	75	0	Endocrine autoimmune disorders,Thyroid hypofunction disorders
	1475519	Sacubitril valsartan sodium hydrate	Cardiorenal syndrome	RC			0	0.34	5.0	4.3	20	0.1	1	Yes	100	7	Heart failures NEC,Renal failure and impairment

Showing 11 to 15 of 100 entries

Previous 1 2 **3** 4 5 ... 20 Next



Sprint Interface

Sprint Interface

- ▶ Start page
- ☰ Combinations list
- 📖 My combinations
- ★ Selected combination
- 🖨️ Print selected combination

Sacubitril valsartan sodium hydrate - Cardiorenal syndrome Sprint Guideline

Assessor comments

[Information](#) [Statistics](#) [Map](#) [ICSRs](#) [Label information](#) [Assessment](#) [Extra features 1](#) [Extra features 2](#)

Substance

ATCs
ANGIOTENSIN II ANTAGONISTS, COMBINATIONS

SDGs

Drug information

Not provided

Drug information (Wikipedia)
No direct entry was found for the substance

Top 10 VigiBase reported indications for the substance

	IndicationText
1	Cardiac failure

ADR

SOC
Cardiac disorders

HLTs
Heart failures NEC, Renal failure and impairment

ADR information
Not provided

ADR information (Wikipedia)
Cardiorenal syndrome (CRS) is an [umbrella term](#) used in the medical field that defines disorders of the heart and kidneys whereby “acute or chronic dysfunction in one organ may induce acute or chronic dysfunction of the other”. The heart and the kidneys are involved in maintaining hemodynamic stability and organ perfusion through an intricate network. These two organs communicate with one another through a variety of pathways in an interdependent relationship. In a 2004 report from [National Heart,](#)

Sprint Interface

Sprint Interface

- Start page
- Combinations list
- My combinations
- Selected combination**
- Print selected combination

Sacubitril valsartan sodium hydrate - Cardiorenal syndrome

Assessor comments

Edit Save Discard changes

Information **Statistics** Map ICSRs Label information Assessment Extra features 1 Extra features 2

Combination metrics		Report metrics		vigiRank metrics	
Serious	1	Observed	20	vigiRank	0.34
IC	5	Expected	0.10	Informative	6
IC025	4.3	Fatal cases	7	Narrative count	10
Drug report count	23555	Serious proportion (%)	100	Recent reports	20
ADR report count	118	Total number of countries	7	Countries with IC>0	7
First report	2016-07-11	Dechallenge	0	IC Grand	1
Last report	2018-10-27	Rechallenge	0	IC Grand reason	IC025 > 0
First report for drug	2011-10-03	Severity count	1		
		Narrative proportion (%)	50		
		Study Report proportion (%)	35		
		Single suspected	18		
		Single suspected proportion (%)	90		

Sprint Interface



Sprint Interface

- Start page
- Combinations list
- My combinations
- Selected combination
- Print selected combination

Sacubitril valsartan sodium hydrate - Cardiorenal syndrome

[Sprint Guideline](#)

Assessor comments

Information Statistics Map **ICSRs** Label information Assessment Extra features 1 Extra features 2

Patients statistics

Category	Count
Unknown	1
Female	1
Male	17

Most co-reported substances

A substance needs to be co-reported at least 3 times on the ICSRs to be in this list

Torasemide	7
Spironolactone	4
Bisoprolol	4

Most co-reported events

A reaction needs to be co-reported at least 2 times on the ICSRs to be in this list

Cardiac failure	8
Renal failure	5
Acute kidney injury	4
Blood creatinine increased	3
Hypotension	3
Glomerular filtration rate decreased	3
Blood pressure decreased	3
Dehydration	3

ICSRs list

WARNING! Do not translate this page or use Google translate on any narrative

Show entries

Search:

ReportId	Age (years)	Sex	Country	TTO	Reported Substance	Reported Reaction	Narrative
[REDACTED]		M	[REDACTED]		ENTRESTO	Cardiorenal syndrome	[REDACTED]



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



Substance	Reaction (PT)	N _{observed}	N _{expected}	IC ₀₂₅	IC
Nintedanib	Colitis	24	8.26	0.85	1.48



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 Maulif, M.Sc., Mannaig 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 BIEF 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 5 Level, South Academic Block, University Hospital Southampton NHS Foundation Trust, Tremona Rd, Southampton SO16 6YD, United Kingdom, or at lricheldi@son.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

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N ENGL J MED 370:22 NEJM.ORG MAY 29, 2014

2071

The New England Journal of Medicine

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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 sign⁵

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 diarrhea⁵

1. Supportive medications

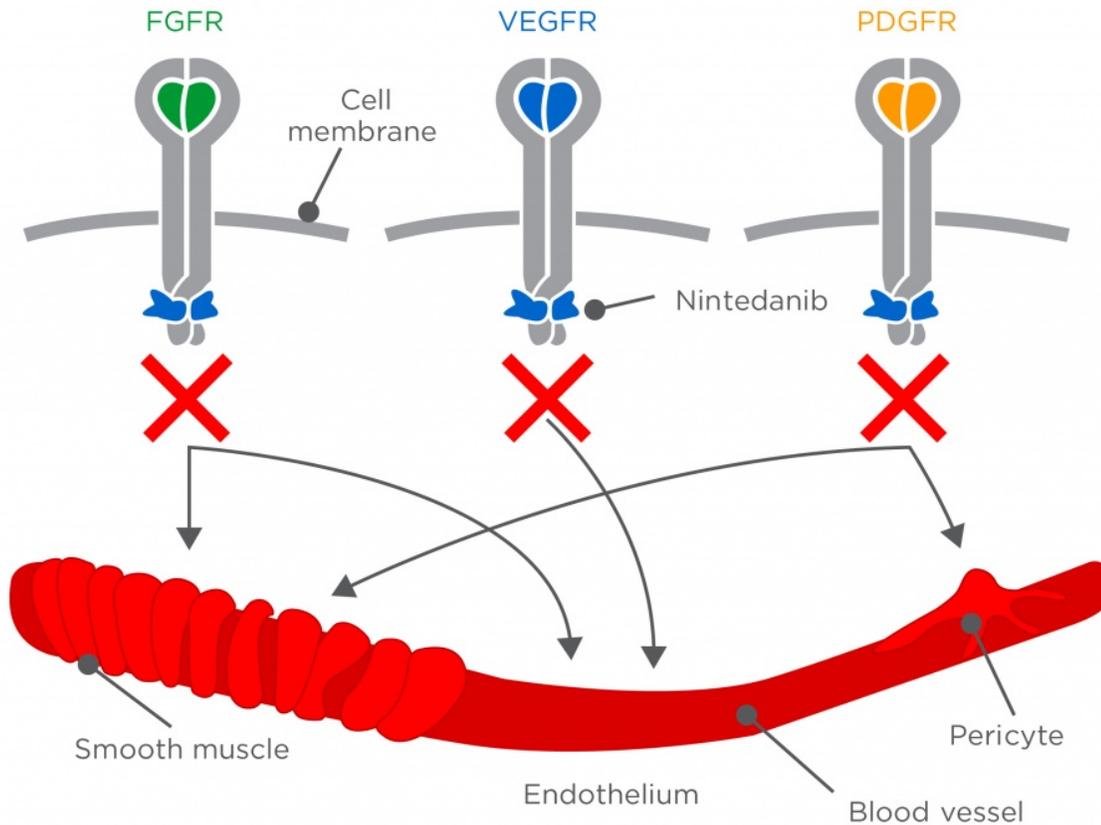
- Initiate antidiarrheals, such as loperamide

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

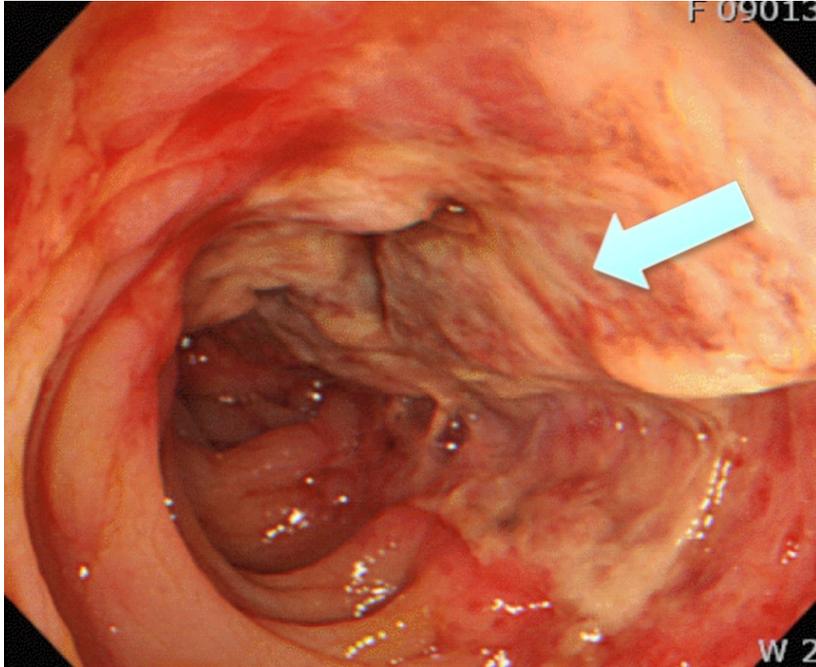
- Adequate hydration
- Avoidance of certain foods/drinks



<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 colonoscopy recommended within 48 hours of onset of symptoms
- Surgical or conservative treatment



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

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

The incidence of ischaemic colitis¹ 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,² 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. 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.⁴ 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.⁴ 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.

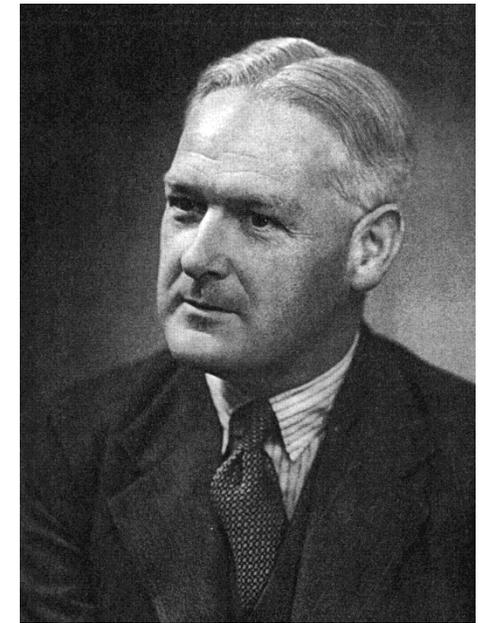
How do you diagnose ischaemic colitis?

Investigate patients with possible ischaemic colitis urgently. Computed tomography is the diagnostic investigation of choice. Guidance from the American College of Gastroenterology⁴ 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.



A question of causality



ORIGINAL RESEARCH ARTICLE

Drug Safety 2007; 30 (4): 333-346
0114-6914/07/0004-0333/\$44.50/0

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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 Voss² 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



Minireview

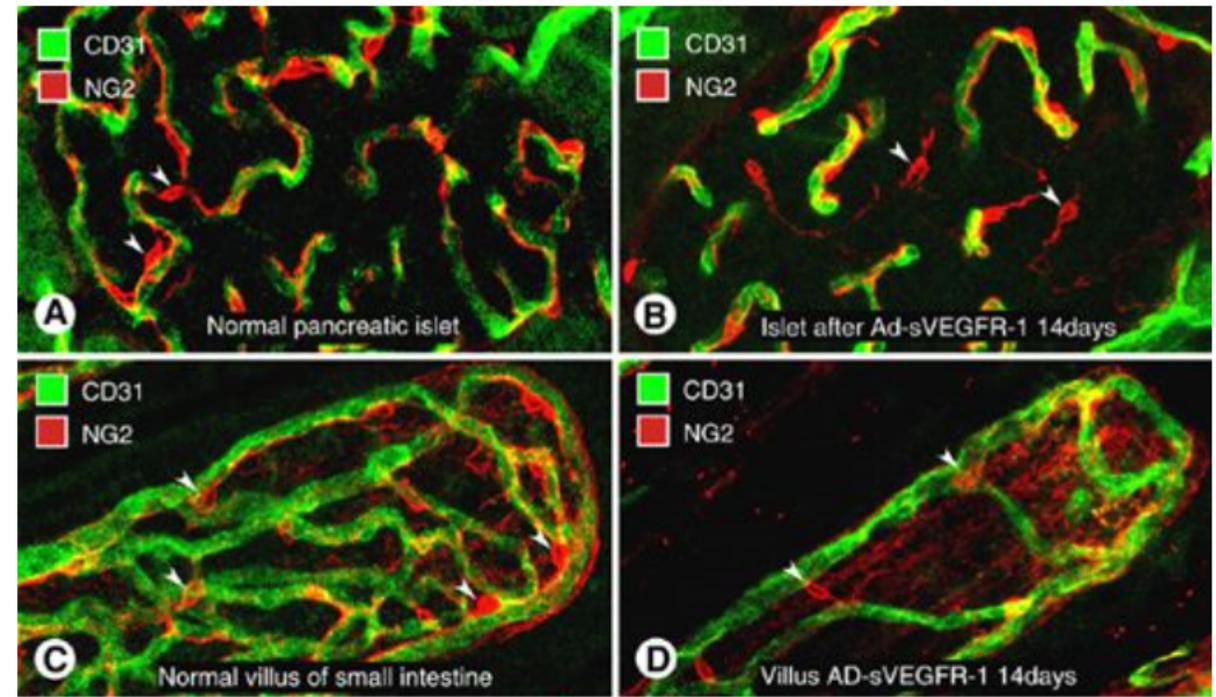
Mechanisms of adverse effects of anti-VEGF therapy for cancer

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



VigiLyze

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

All ▾ Add search criteria to filter your result ? [Hide filter](#)

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

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

Analogy



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 >](#)

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Abstract

In patients with age-related macular degeneration (AMD), the intravitreal injection of anti-vascular 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

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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 reperfomed 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.

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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

by Sir Austin Bradford Hill CBE DSC FRCP(hon) FRS
(Professor Emeritus of Medical Statistics,
University of London)

Amongst the objects of this newly-founded Section of Occupational Medicine are firstly 'to provide a means, not readily afforded elsewhere, whereby physicians and surgeons with a special knowledge of the relationship between sickness and injury and conditions of work may discuss their problems, not only with each other, but also with colleagues in other fields, by holding joint meetings with other Sections of the Society'; and, secondly, 'to make available information about the physical, chemical and psychological hazards of occupation, and in particular about those that are or not easily recognized'.

At this first meeting of the Section and before, with however laudable intentions, we set about

observed association to a verdict of causation?
Upon what basis should we proceed to do so?

I have no wish, nor the skill, to embark upon a philosophical discussion of the meaning of 'causation'. The 'cause' of illness may be immediate and direct, it may be remote and indirect underlying the observed association. But with the aims of occupational, and almost synonymously preventive, medicine in mind the decisive question is whether the frequency of the undesirable event B will be influenced by a change in the environmental feature A. How such a change exerts that influence may call for a great deal of research. However, before deducing 'causation' and taking action we shall not invariably have to sit around awaiting the results of that research. The whole chain may have to be unravelled or a few links may suffice. It will depend upon circumstances.

Disregarding then any such problem in semantics we have this situation. Our observations reveal an association between two variables

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

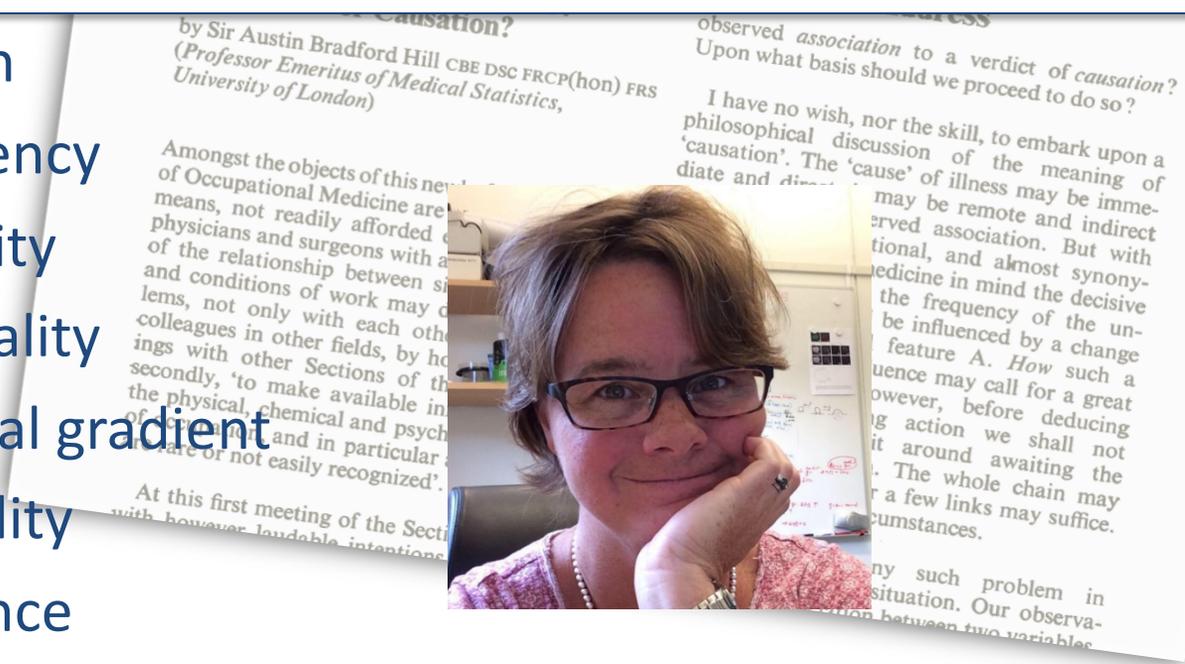


What do we have so far?

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



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



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

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

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Data Sources

Optum Extended SES (v876)

Drug Era

Optum Extended SES (v876) Drug Era Report

Prevalence

Treemap Table

Column visibility Copy CSV Show 15 entries Filter: ninte Previous 1 Next

Showing 1 to 1 of 1 entries (filtered from 1,911 total entries)

Concept Id	Name	Person Count	Prevalence	Length of era
45775396	nintedanib	1,760	0.00%	218.10

Showing 1 to 1 of 1 entries (filtered from 1,911 total entries)

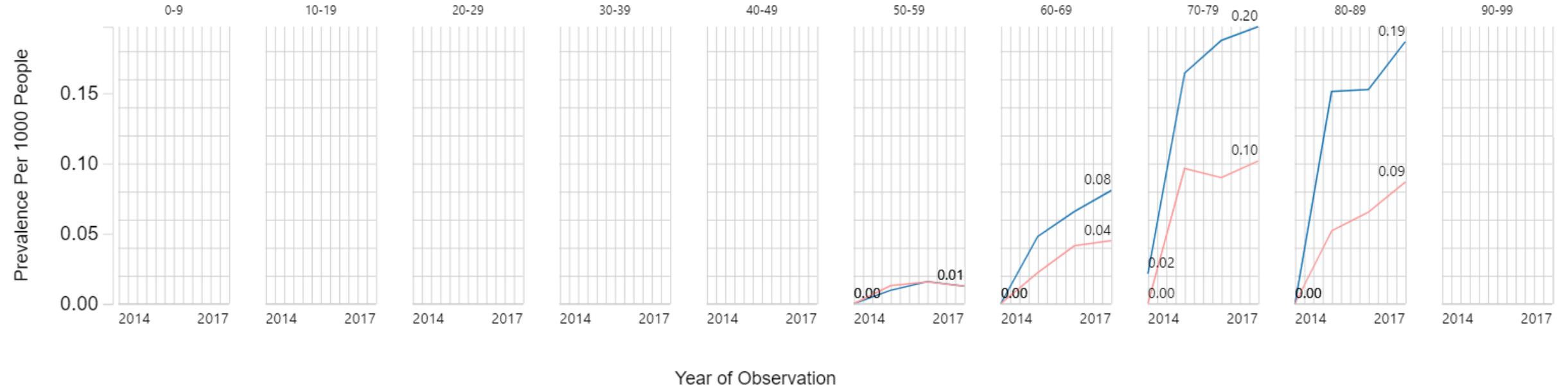


Clinical Characterization #1: Is the drug used in the real world?

nintedanib Drilldown Report

Prevalence

— MALE — FEMALE — UNKNOWN





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

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

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[Generate](#) Optum Extended SES (v876) COMPLETE 1,127 1,127 03/28/2019 4:25 PM 00:02:19 [View Reports](#)

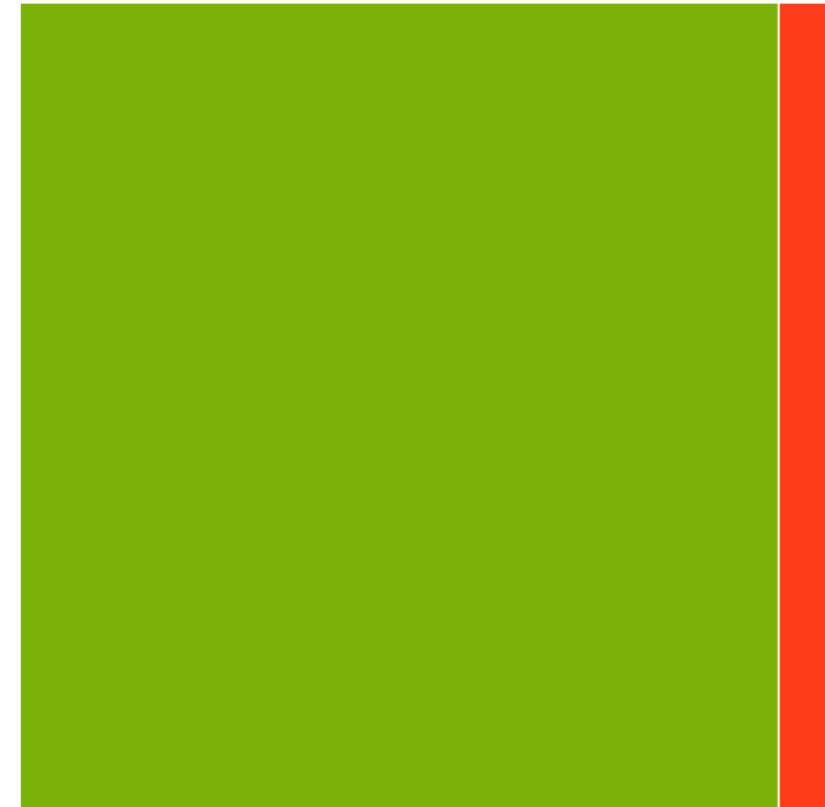
By Events **By Person**

Inclusion Report for Optum Extended SES (v876)

Inclusion Rule	Match Rate	Matches	Total Events	
		N	% Satisfied	% To-Gain
Summary Statistics:				
	93.84%	1,127		1,201
1. does not have prior colitis		1,127	93.84%	6.16%

Population Visualization

[Switch to attrition view](#)





Clinical characterization #3: Who are these patients?

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

Characterization #57

[UMC sprint] Nintedanib and pirfenidone

Design Executions Utilit

Executions > Reports for

Date: 03/28/2019 4:52 PM Design:

Filter panel

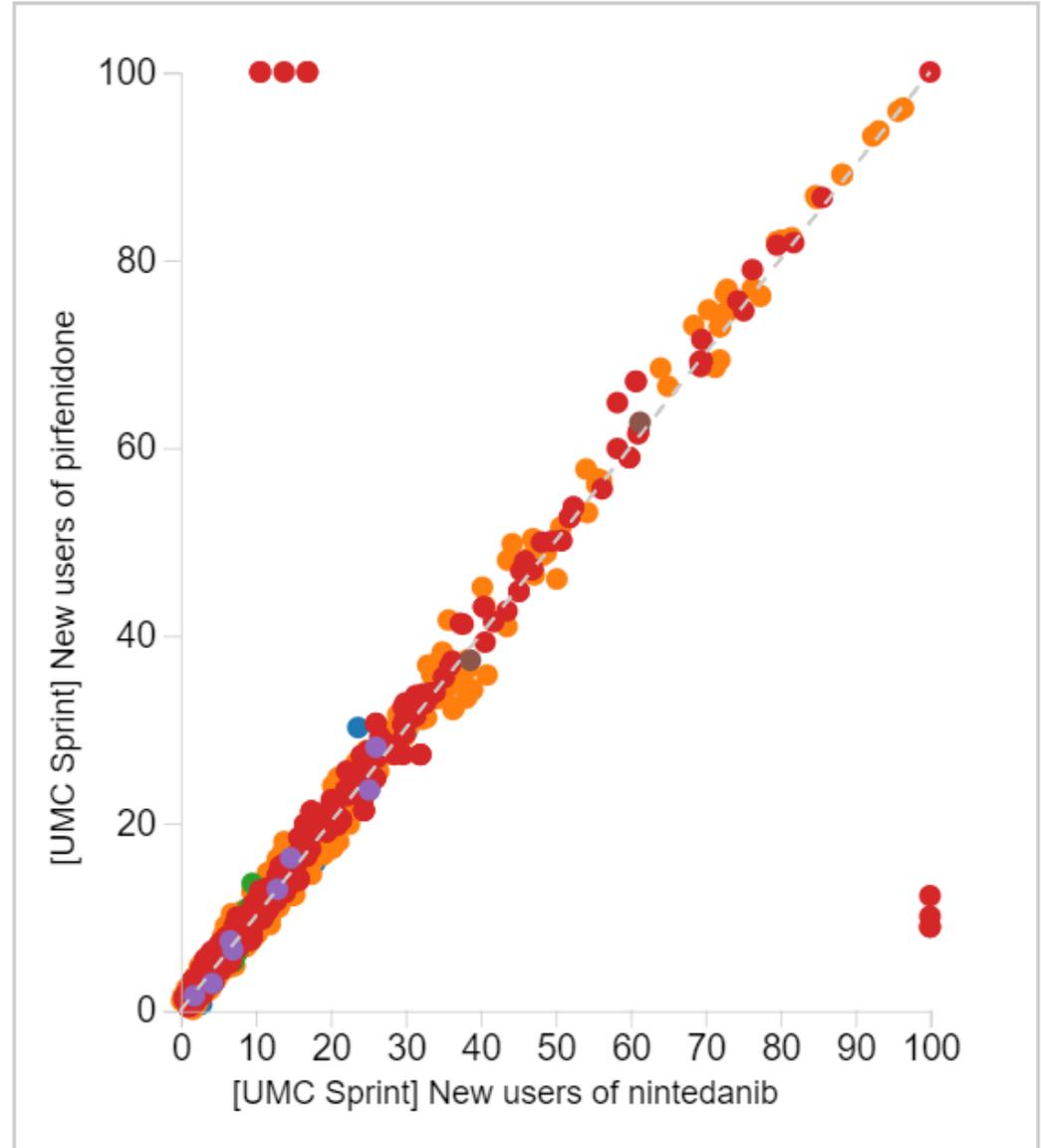
Cohorts

[UMC Sprint] New users of ni

All prevalence covariates

Export Export comparison Show

Covariate	Conce ID
nintedanib	457753



Save Close Copy Delete

Domains

3 items selected



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

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

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Incidence Rate Analysis #45

[UMC Sprint] Colitis risk in new users of nintedanib and pirfenidone

Definition | Concept Sets | **Generation** | Utilities

Showing target cohort: [UMC Sprint] New users of nintedanib and outcome cohort: [UMC Sprint] Patients with new colitis or isc

[Generate](#) [Export Analysis to CSV](#)

Optum Panther (v811)

	Persons	Cases	Proportion [+-] per 1k persons	Time At Risk (years)	Rate [+-] per 1k years
Summary Statistics:	1,071	16	14.94	282	56.74
Stratify Rule	N	Cases	Proportion [+-] per 1k persons	Time At Risk (years)	Rate [+-] per 1k years
1. gender = Female	390	6	15.38	105	57.14
2. age > 70	636	13	20.44	163	79.75
3. Initial drug strength is 150mg	996	13	13.05	261	49.81
4. Initial drug strength is 100mg	82	3	36.59	27	111.11



Population-level effect estimation: Design a comparative cohort analysis

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

Population Level Effect Estimation - Comparative Cohort Analysis #21

[UMC Sprint] Risk of colitis amongst nintedanib and pirfenidone

Specification Utilities

enter a description here (1000 characters max)

VIEW: Full Specification Comparisons Analysis Settings Evaluation Settings

Comparative Cohort Settings

Comparisons [+ Add Comparison](#)

Show 10 entries Filter:

Remove	Target	Comparator	Outcomes	NC Outcomes	Copy
	[UMC Sprint] New users of nintedanib	[UMC sprint] New users of pirfenidone	Persons with new colitis	nintedanib and pirfenidone - Negative Controls	Copy

Showing 1 to 1 of 1 entries Previous 1 Next



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?

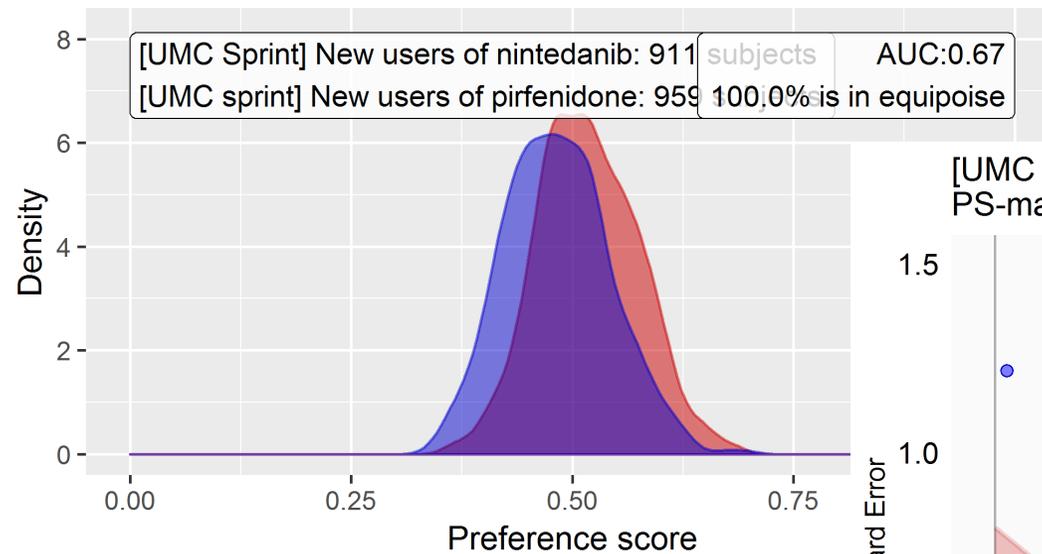
Preliminary
findings
subject to
review and
additional
analysis



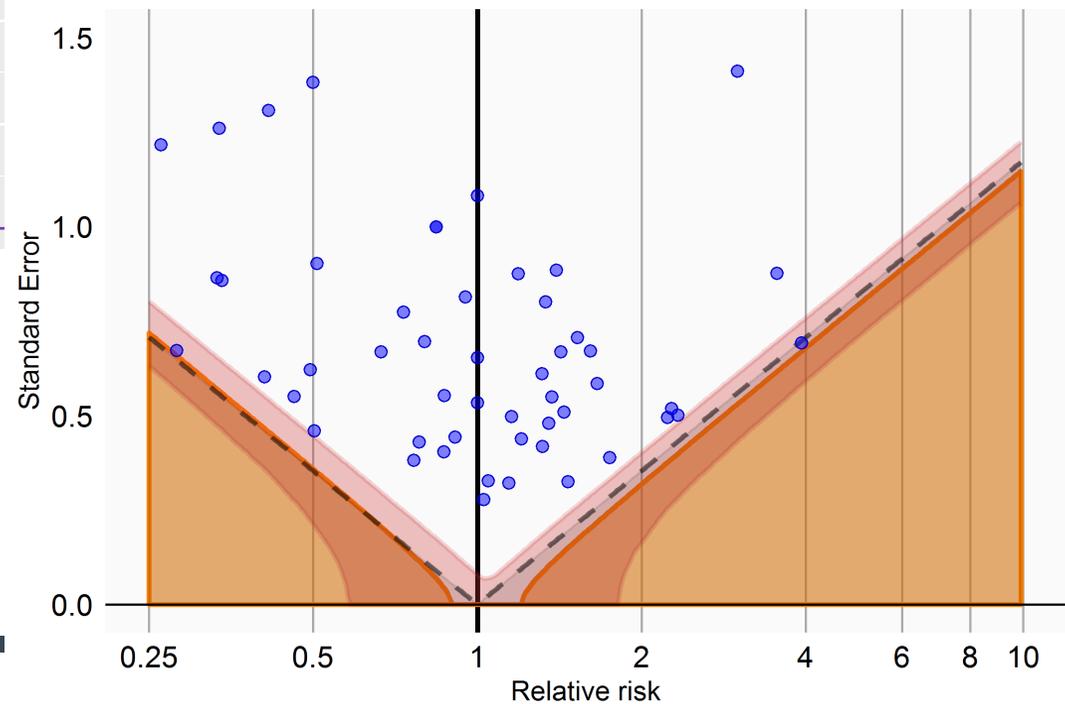
Population-level estimation: following best practices for diagnostic evaluation as we should do with any protocol-based assessment

PS-matched Cox on-treatment

[UMC Sprint] New users of nintedanib [UMC sprint] New users of pirfenidone



[UMC Sprint] New users of nintedanib - [UMC sprint] New users of | PS-matched Cox on-treatment





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

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Patient Level Prediction #32

[UMC Sprint] Predicting colitis in nintedanib

Specification Utilities

enter a description here (1000 characters max)

VIEW: All Prediction Problem Settings Analysis Settings Execution Settings Training Settings

Prediction Problem Settings

Target Cohorts [+ Add Target Cohort](#)

Show 10 entries Filter:

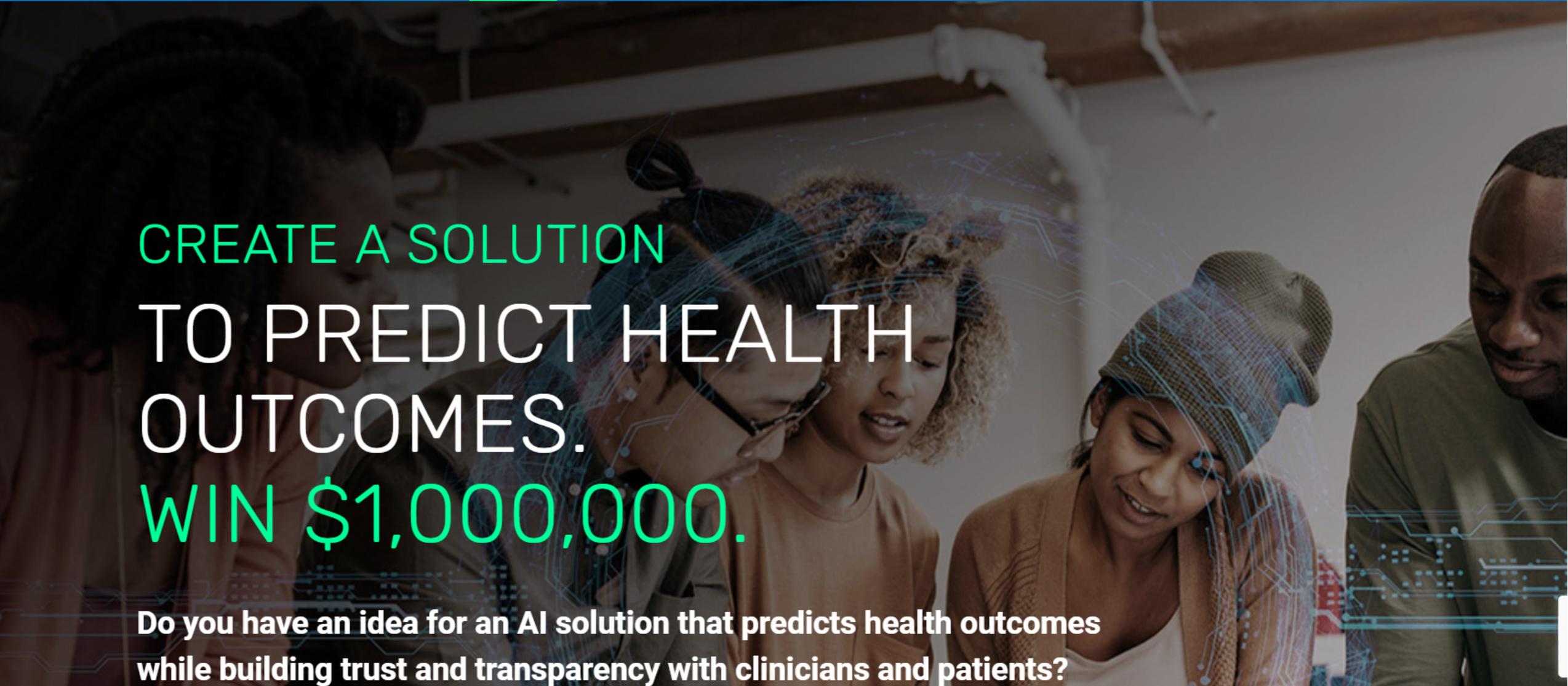
Remove	Name
	[UMC Sprint] New users of nintedanib

Showing 1 to 1 of 1 entries Previous 1 Next

Outcome Cohorts [+ Add Outcome Cohort](#)

Show 10 entries Filter:

Remove	Name
	Persons with new colitis



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