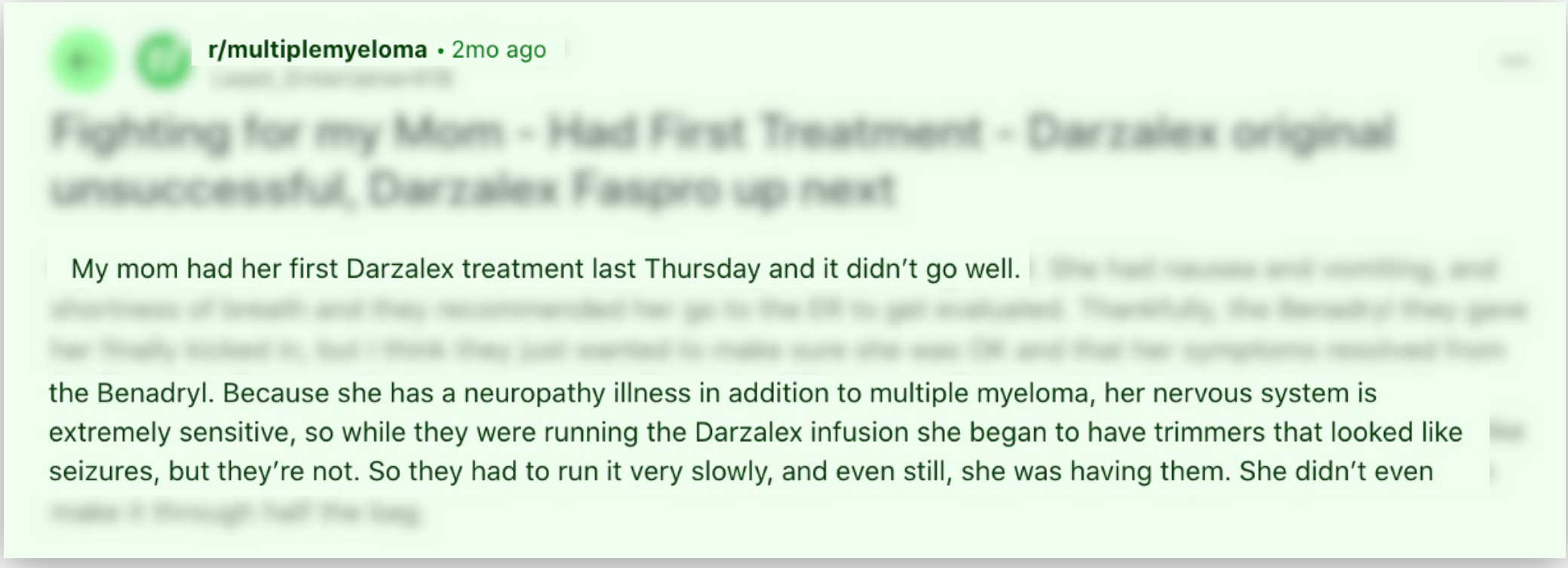
Echo: A multi-agent system for patient-centered pharmacovigalence

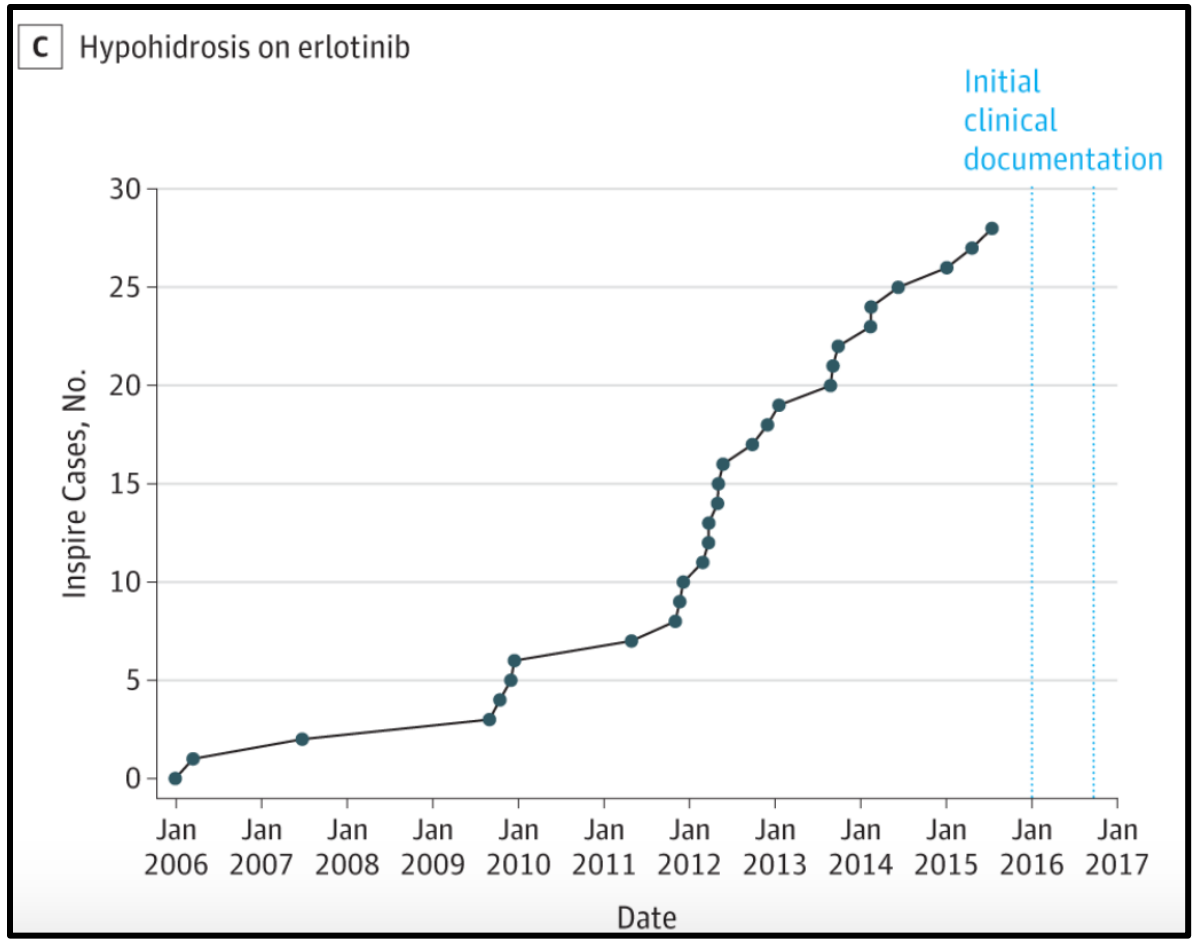
Claude Sonnet 3.5 (Anthropic) and Megha Srivastava (Stanford)

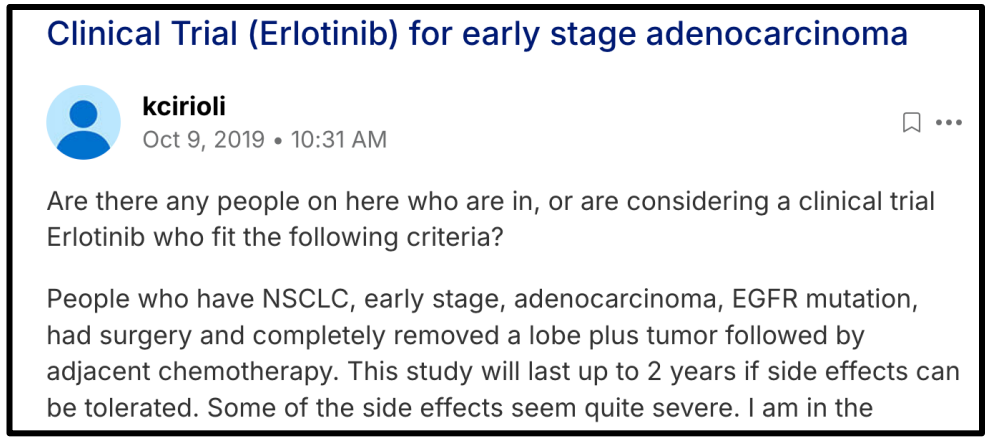
Contact: megha@cs.stanford.edu



Oncology patients report complex drug-side effects interactions months (or years!) before official recognition – *how can we detect these signals earlier?*

Prior work on Inspire community forum





- Research team new what drug-symptom associations to search for (e.g. hypohidrosis)
- Focused only on skin-related side effects
- Required manual labeling to train DeepHealthMiner to detect posts related to side-effects

[Ransohoff et. al., 2018]

Overview of Echo

Explorer

reddit

I can't say for sure **it's the Gleevec or it's the overlap of the two chemos**, but I can say that I would not be at all surprised if it was the Gleevec...for the first month I had **sort of a strange smell in my nose, if that makes sense. Kind of a dank, wet dog kind of smell**

be patient with yourself...i second the Zofran recommendation with Gleevec because **smell was potent**

patients discuss affected smells with imatinib (pre-2018)

drug: gleevec
drug_canonical: imatinib
side effect: parosmia
temporal weight: 1.0
confidence:0.9
community support:0.6
confounders: [chemotherapy]

Analyzer

U.S. FOOD & DRUG ADMINISTRATION
openFDA
Dataset that supplies data to openFDA
FDA Adverse Event Reporting System

Imatinib
nausea, 28.6
fatigue,24.4
rash, 20.0

verifier score: 0.0
Novel Association!

Verifier

Proposer

1st Hypothesis: Tyrosine Kinase Pathway Disruption in Olfactory Processing
Imatinib's inhibition of multiple tyrosine kinases (ABL, c-Kit, PDGFR) may disrupt cellular signaling pathways critical for olfactory neuron function.

2nd Hypothesis: Shared Gustatory-Olfactory Dysfunction
Parosmia may represent the olfactory component of a broader chemosensory disruption, given that imatinib already causes documented dysgeusia in 3-13% of patients (van der Werf et al., 2017).

J Clin Med. 2022 Aug 9;11(16):4641. doi: 10.3390/jcm11164641

Drug-Associated Parosmia: New Perspectives from the WHO Safety Database

Diane Merino [1,2], Alexandre Olivier Gérard [2,3], Susanne Thümmler [4,5], Nouha Ben Othman [2], Delphine Viard [2], Fanny Rocher [2], Alexandre Destere [2], Elise Katheryne Van Obberghen [6], Milou-Daniel Drici [2,*]

Editor: Christian A Mueller

Parasmia still not formally associated with imatinib (2022)

Explorer Agent

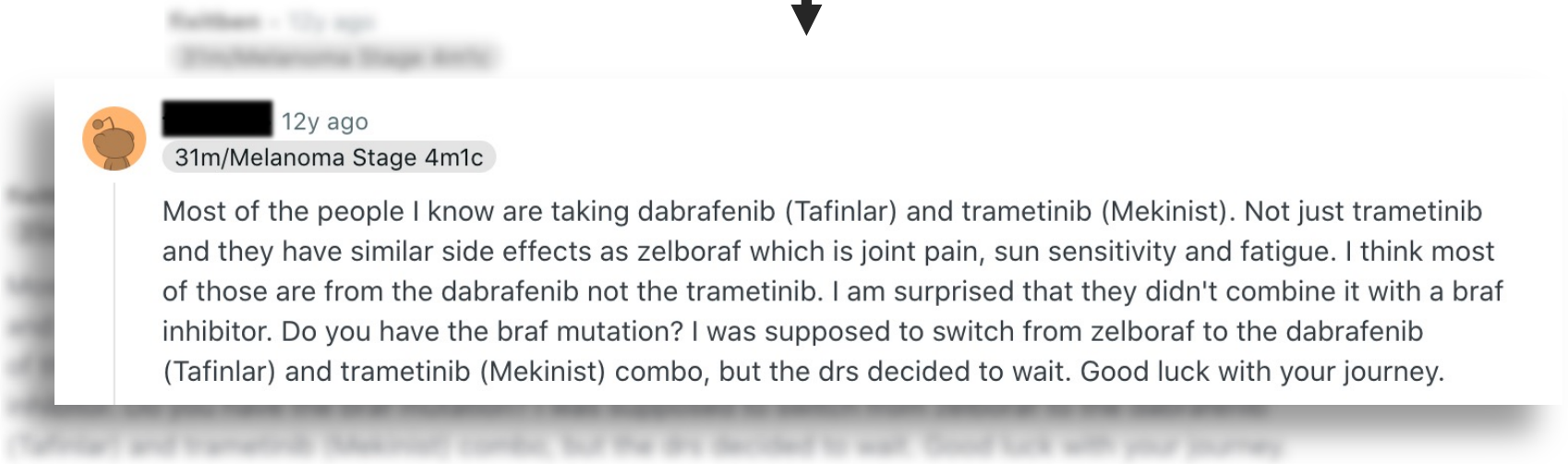
reddit

r/AskDocs

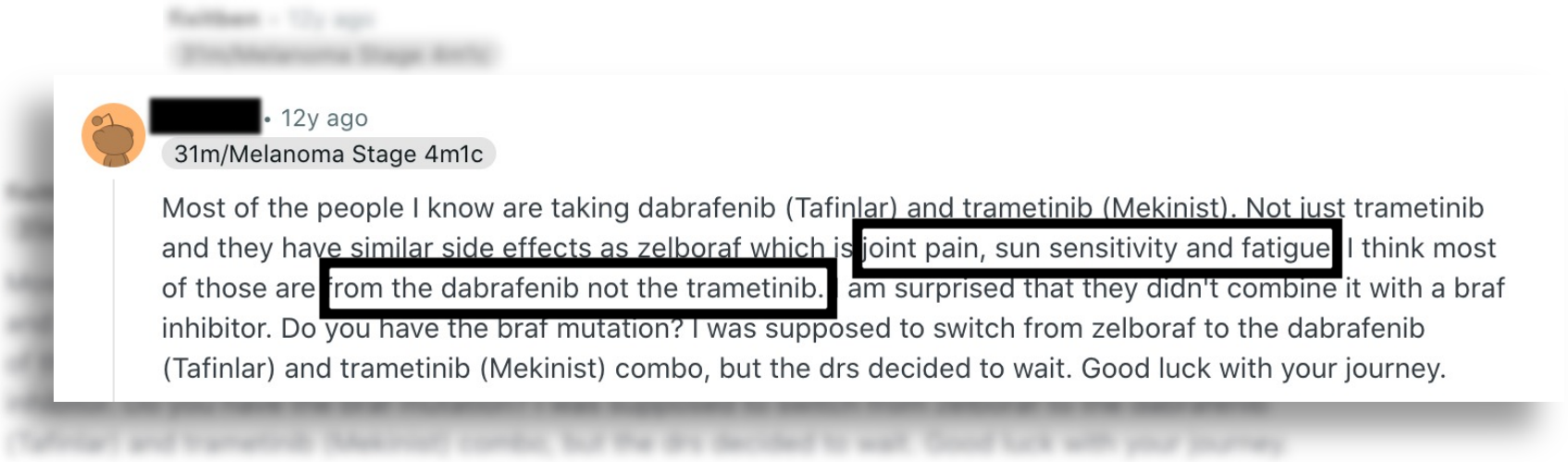
r/cancer

r/immunotherapy

...

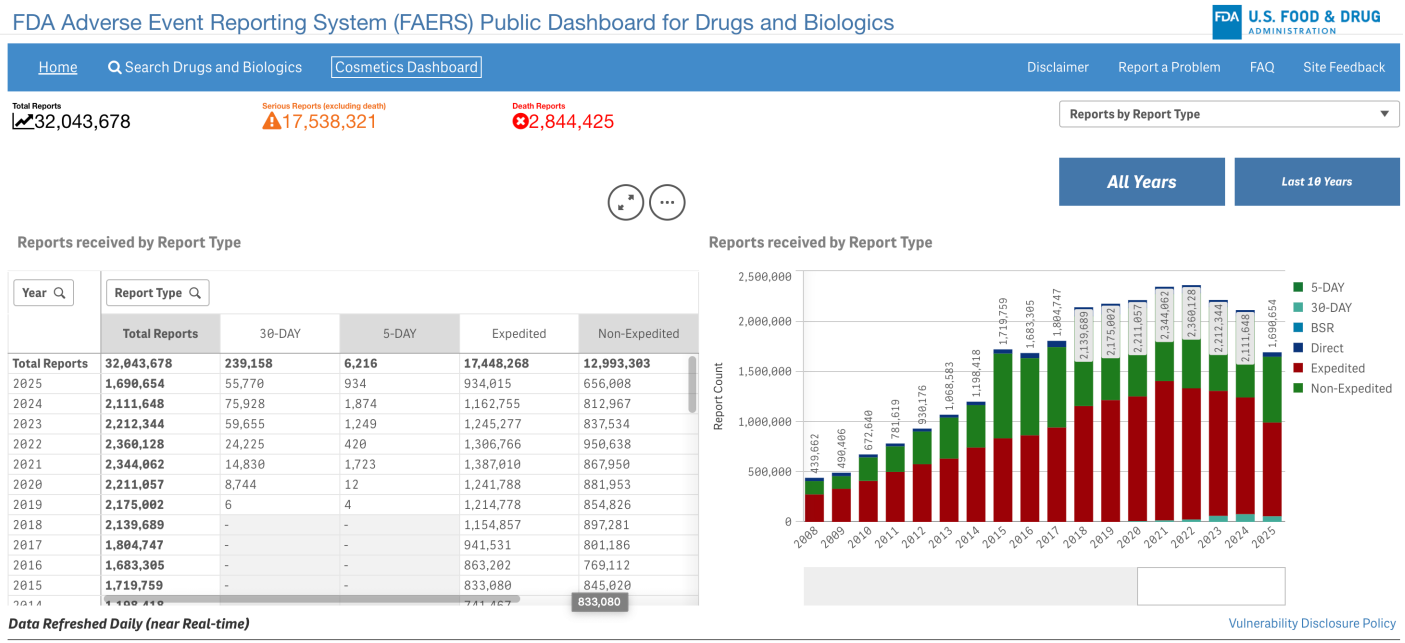


Analyzer Agent




```
"dabrafenib": [
{
”year”:2013,
“symptom”:”sun sensitivity",
“symptom_official:”photosensitivity",
“confounders”:[”trametinib”],
“temporal_weight”:1.0,
“strength”:0.6,
“community”:0.0
}...]
```

Verifier Agent




```
"dabrafenib": [
{
"year":2013,
"symptom":"sun sensitivity",
"symptom_official:"photosensitivity",
"confounders":["trametinib"],
"temporal_weight":1.0,
"strength":0.6,
"community":0.0
}...]
```

→

```
VISUAL IMPAIRMENT  score=11.49  (FAERS n=483)
VISION BLURRED  score=9.49  (FAERS n=323)
HYPERSENSITIVITY  score=5.82  (FAERS n=113)
```

No photosensitivity → score = 0

Novel Association??

January - March 2023 | Potential Signals of Serious Risks/New Safety Information Identified by the FDA Adverse Event Reporting System (FAERS)

Product Name: Trade (Active Ingredient) or Product Class	Potential Signal of a Serious Risk / New Safety Information	Additional Information (as of June 16, 2023)
Biktarvy (bictegravir, emtricitabine, and tenofovir alafenamide)	Weight increased	FDA is evaluating the need for regulatory action.
Braftovi (encorafenib) Tafinlar (dabrafenib)	Photosensitivity reaction	FDA is evaluating the need for regulatory action.

New safety information re: photosensitivity added 10 years later!

Proposer Agent


```
"dabrafenib": [
{
"year":2013,
"symptom":"sun sensitivity",
"symptom_official":"photosensitivity",
"confounders":["trametinib"],
"temporal_weight":1.0,
"strength":0.6,
"community":0.0
}...]
```

Photoproduct Formation Hypothesis: Dabrafenib may form UVA-absorbing photoproducts when exposed to ultraviolet radiation, similar to the mechanism established for vemurafenib [Eberlein et. al., 2020].

Test this by exposing dabrafenib to UVA radiation in vitro and measuring spectrofluorometric changes, then applying the drug and irradiated metabolites to cultured keratinocytes to assess cytotoxicity differences.

Result 1: Comparing Explorer Agents

Agent for **Explorer**	Keyword Baseline	Claude 3.5 Haiku	Claude 3.5 Sonnet
Total Drugs	40	141	131
Total (Drug, ADR) Associations	378	288	640
Recall (Restricted Set)	0.22	0.08	0.27

- Smaller LMs underperform simple baseline in symptom extraction
- General low recall → patient bias to discuss rare symptoms on forums

Result 2: Novel Associations

Association	Temporal	Confidence	Community	Verifier	Patient Quote
Pembrolizumab → Daytime somnolence	10/10	10/10	10/10	0.0	asleep at my desk mid-afternoon
Paclitaxel → Laryngeal edema	10/10	10/10	10/10	0.0	my throat was closing up
Nivolumab → Pericardial effusion	10/10	10/10	8/10	0.0	two emergency pericardial windows
Fluorouracil → Abdominal bloating	8/10	8/10	10/10	0.0	she feels bloated especially after food
Oxaliplatin → Social withdrawal	8/10	8/10	8/10	0.0	I've withdrawn from all social interactions

Result 2: Novel Associations

Association	Proposer Report
Pembrolizumab → Daytime somnolence	Primary Hypothesis: Immune-Mediated Sleep-Wake Cycle Disruption. Pembrolizumab's PD-1 checkpoint inhibition may trigger excessive immune activation that disrupts hypothalamic sleep-wake regulatory circuits[Krueger et al., 2016, Imeri and Opp, 2009]...
Paclitaxel → Laryngeal edema	Primary Hypothesis: Hypersensitivity-Mediated Laryngeal Inflammation. Paclitaxel is formulated with Cremophor EL (polyoxyethylated castor oil), a known histamine liberator that can cause immediate hypersensitivity reactions in 2–4% of patients [Weiss et al., 1990]...
Nivolumab → Pericardial effusion	Primary Hypothesis: Immune-Related Adverse Event (irAE) via T-cell Hyperactivation. Nivolumab's blockade of the PD-1/PD-L1 checkpoint pathway removes critical immune tolerance mechanisms, potentially triggering autoimmune-mediated pericarditis...
Fluorouracil → Abdominal bloating	Primary Hypothesis: Gastrointestinal Microbiome Disruption and Dysbiosis. Fluorouracil's cytotoxic mechanism through thymidylate synthase inhibition may significantly alter the intestinal microbiome composition. This microbial imbalance could result in increased intestinal gas production and impaired gas clearance, manifesting as abdominal bloating...
Oxaliplatin → Social withdrawal	Primary Hypothesis: Platinum-Induced Neuroinflammation and Limbic System Dysfunction. Oxaliplatin's platinum compounds may accumulate in brain regions critical for social cognition, particularly the prefrontal cortex and limbic system.

Result 3: Confounding Variables

Confounding variable	Example (Drug, ADR)
surgical menopause	(letrozole, weight loss), (zoledronicacid, cognitive impairment), (tamoxifen, depression)
multiple myeloma	(daratumumab, nausea and vomiting), (dexamethasone, renal failure), (lenalidomide, general malaise)
recent surgery	(bevacizumab, impaired wound healing), (pegfilgrastim, sepsis), (pembrolizumab, pain)
male	(cabozantinib, hypertension), (oxaliplatin, social withdrawal), (ciltacabtageneautoleucel, CD4 lymphopenia)
young age	(bleomycin, alopecia), (etoposide, fatigue), (epcoritamab, serious infections)

4 case studies showing "early warning"

pre-2017

- *"I developed pneumonitis and had to be hospitalized for 5 days, which is also why i haven't resumed treatment "* (nivolumab, r/cancer)
- *"My aunt finished chemo and keytruda but developed severe pneumonitis adverse event from keytruda..."* (pembrolizumab, r/cancer)
- *"I had a 3 week fever, it was pretty awful. But got through it..."* (nivolumab, r/cancer)

2018

In this issue of the *Journal of Thoracic Oncology*, Suresh et al.[6] address the incidence and risk factors associated with CIP in a retrospective cohort of 205 advanced NSCLC patients treated over a 10-year period in an academic center. Notably, all cases of CIP were determined by multidisciplinary team consensus as to exclude patients with disease progression or infection. No consistent radiological pattern of CIP was identified in this series. Within this cohort, consisting of both trial and nontrial patients, CIP incidence was 19% (n = 39), much higher than previously reported in clinical trials. Most cases of CIP occurred within 6 months of treatment initiation, with greater than 50% of cases graded as severe (grade 3-5). Squamous histology was significantly associated with higher rates of CIP (incidence rate ratio: 2.29, 95% CI: 1.08–4.83) whereas female sex and use of combination checkpoint inhibitors showed a nonsignificant trend towards higher CIP incidence. All patients received first-line

Echo: A multi-agent AI system for patient-centered pharmacovigilance

Discovering unreported oncology drug side effects from Reddit discussions

Load JSON Data | Search: mus | Clear | ng 10 of 631 as

Drug	Symptom	Temporal	Confidence	Community	Novelty Score	Analyze	Propos
dexamethasone	muscle cramps	0.800	0.800	0.800	0.800	Analysis	Rep
lenalidomide	muscle cramps	0.800	0.867	0.667	0.778	Analysis	Rep
chemotherapy	muscle wasting	0.800	0.800	0.600	0.733	Analysis	Rep
bendamustine	toxicity	0.600	0.600	0.800	0.667	Analysis	Rep
everolimus	lack of therapeutic	0.800	1.000	0.000	0.600	Analysis	Rep
lomustine	quality of life impa	0.800	1.000	0.000	0.600	Analysis	Rep
lomustine	fertility impairment	0.800	0.800	0.000	0.533	Analysis	Rep
pomalidomide	muscle cramps	0.800	0.800	0.000	0.533	Analysis	Rep
nivolumab	muscle weakness	0.800	0.800	0.000	0.533	Analysis	Rep
chemotherapy	muscle weakness	0.600	0.600	0.000	0.400	Analysis	Rep

Echo: A multi-agent AI system for patient-centered pharmacovigilance

Analyzer Report - pembrolizumab / dermatitis

pembrolizumab → dermatitis

Analysis Metrics

Temporal Weight: 0.700
Confidence Score: 0.600
Community Metric: 0.700
Novelty Score: 0.667
Number of Reports: 2

Identified Confounders

- stage 3A Melanoma

Supporting Evidence

Quote 1:
Hopefully this is a chemo rash or some sort of Keytruda side effect

Quote 2:
After the second treatment I experienced a rash and intense itching

Takeaways

1. Today's language models can better understand subtleties in patient experiences
2. Social media can be more timely than trial data / EHRs!
3. Future work: expand to more patient discussion forums and non-oncology drugs
   - *What happens when Reddit/other forums get filled with AI-generated content?*