Results | Of the 283,502 patients initiating treatment with infused chemotherapy between 2004 and 2014, patients receiving care in physician offices were older compared with those receiving care in HOPDs (mean, 54 vs 51 years; P < .001) and they had a statistically, but not clinically meaningful, lower comorbidity (comorbidity score of zero: 95% in offices vs 94% in HOPDs; P < .001). The rate of commercially insured patients receiving infused chemotherapy in HOPDs increased from 6% of infusions in 2004 to 43% in 2014 (Figure 1).

Spending at the drug level was significantly lower in offices vs in HOPDs ($1446; 95% CI, $1457-$1474 vs $3799; 95% CI, $3761-$3836; P < .001). Day-level spending was lower for patients treated in offices ($3502; 95% CI, $3490-$3515 vs $7973; 95% CI, $7927-$8019; P < .001). Total reimbursement during the 6-month treatment–episode was also lower in offices ($43700; 95% CI, $42885-$44517 vs $84660; 95% CI, $82969-$86352; P < .001) (Figure 2). Sensitivity analysis on breast cancer patients found similar results.

Discussion | Shifting the provision of infused chemotherapy from physician offices to HOPDs is increasing and is associated with increased spending for chemotherapy services. The study’s main limitation is the inability to identify whether the cost differential between physician offices and HOPDs is driven by facility fees. Owing to the limitation of claims data, we were not able to assess the stage or grade of the cancer diagnosis or to examine if the stage or grade of the cancer varies between sites. This study was not able to measure quality of care, which may vary by site of care. Potential targets for reduction of excess spending and creation of a more efficient health care system can come from private insurers following Medicare’s lead, which has started to equalize payments across sites of care.6

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Detecting Chemotherapeutic Skin Adverse Reactions in Social Health Networks Using Deep Learning

Adverse drug reactions (ADRs) occur in nearly all patients undergoing anticancer therapy, contributing to morbidity, therapy disruptions, and rising health care costs.1 Their identification and characterization are hampered by clinical trials that are underpowered to detect rare events, the division of patients across institutions, patient exclusion from trials, publication editorial delays, and lack of participation and planning in oncology clinical trials of medical disciplines outside of oncology.

Table. Automated Deep Learning Pipeline for Skin Adverse Effects to EGFR and PD-1 Inhibitors in Social Health Networks at Frequencies Comparable With Those in the Literature*

<table>
<thead>
<tr>
<th>ADRs</th>
<th>Literature Rank</th>
<th>Forum Frequency</th>
<th>PRR</th>
</tr>
</thead>
<tbody>
<tr>
<td>With erlotinib (Tarceva; Genentech)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Erythematous eruption or acne</td>
<td>Most common</td>
<td>1649</td>
<td>7.59</td>
</tr>
<tr>
<td>Acne</td>
<td></td>
<td>391</td>
<td>12.68</td>
</tr>
<tr>
<td>Pruritus</td>
<td></td>
<td>424</td>
<td>2.96</td>
</tr>
<tr>
<td>Xerosis</td>
<td></td>
<td>466</td>
<td>10.75</td>
</tr>
<tr>
<td>Paronychia, nail changes</td>
<td>Least common</td>
<td>167</td>
<td>7.53</td>
</tr>
<tr>
<td>Bullous eruption</td>
<td></td>
<td>86</td>
<td>1.37</td>
</tr>
<tr>
<td>Hypohipidrosis</td>
<td>Not reported</td>
<td>33</td>
<td>1.90</td>
</tr>
<tr>
<td>Psoriasis</td>
<td>Not reported</td>
<td>2</td>
<td>0.12</td>
</tr>
</tbody>
</table>

With nivolumab (Keytruda; Merck) and pembrolizumab (Opdivo; Bristol-Myers Squibb)

| Erythematos us eruption            | Reported        | 159             | 1.31|
| Pruritus                           | Reported        | 82              | 1.34|
| Xerosis                            | Reported        | 18              | 0.62|
| Psoriasis                          | Rare            | 6               | 1.04|
| Bullous eruption                   | Rare            | 8               | 0.33|
| Paronychia, nail changes           | Rare            | 5               | 0.36|
| Hypohipidrosis                     | Not reported    | 5               | 0.73|
| Acne                               | Not reported    | 12              | 0.53|

Abbreviations: ADR, adverse drug reactions; EGFR, epidermal growth factor receptor; PD-1, programmed cell death-1; PRR, proportional reporting ratio.

* The PRR calculated for each drug-ADR pair was compared against PRRs for drug-ADR pairs with no known associations. Rank order of ADRs associated with erlotinib and PD-1 inhibitors, demonstrating high concordance between forum reports and PRR for each ADR and published literature.
Postmarket drug surveillance platforms, such as US Food and Drug Administration (FDA) monitoring rely on voluntary, spontaneous reporting and lack temporal advantage over literature. Early recognition of ADRs could substantially improve health outcomes and decrease societal costs. Internet community health forums provide a mechanism for several hundred million individuals to discuss current health concerns and may serve as a resource for computational detection of ADRs. However, the language in social media is highly informal, and expressed medical concepts are often nontechnical, descriptive, and challenging to extract using dictionary-based methods.

Herein, we demonstrate proof-of-principle early detection of chemotherapeutic-associated skin ADRs from social health networks using a deep learning-based signal generation pipeline to capture how patients describe cutaneous eruptions in their own words and use statistical methods to quantify the association strength of our target drug-ADR pairs.

Methods We extracted mentions of common and rare cutaneous ADRs from 8 million posts in the Inspire health forum (https://www.inspire.com/) related to the epidermal growth factor inhibitor (EGFRi)–associated reactions and for autoimmune blistering reactions and psoriasis flares on programmed cell death-1 inhibitor treatment. Inspire forum posts describing these ADRs preceded initial case reports by an average of 7 months (range, 3-9 months). C, Twenty-three distinct users described hypohidrosis in a causal relationship with erlotinib as early as 2006, with a significantly enriched proportional reporting ratio (1.90), implicating hypohidrosis as a novel, missed, rare ADR. The line at January 2017 indicates the initial clinical documentation. The vertical line at 2016 shows the last analyzed Inspire content.

Figure. Cutaneous Adverse Drug Reactions (ADRs) Identified by DeepHealthMiner in Inspire Forums Preceding Initial Published Clinical Reports

A Erythematous eruption on erlotinib

B Nail changes on erlotinib

C Hypohidrosis on erlotinib

Plots show cumulative post count (y-axis) at each date (x-axis) for time-to-detection analysis. A and B, Papulopustular (acneiform) eruption and nail and finger changes were first described in association with erlotinib (Tarceva; Genentech) in case reports published in September 2005 and September 2006, respectively. Inspire posts for these reactions appeared 5 and 3 months in advance of publication, respectively. Collectively, for these epidermal growth factor inhibitor (EGFRi)-associated reactions and for autoimmune blistering reactions and psoriasis flares on programmed cell death-1 inhibitor treatment, Inspire forum posts describing these ADRs preceded initial case reports by an average of 7 months (range, 3-9 months). C, Twenty-three distinct users described hypohidrosis in a causal relationship with erlotinib as early as 2006, with a significantly enriched proportional reporting ratio (1.90), implicating hypohidrosis as a novel, missed, rare ADR. The line at January 2017 indicates the initial clinical documentation. The vertical line at 2016 shows the last analyzed Inspire content.
strength, a proportional reporting ratio (PRR) was calculated and compared with drug-ADR pairs with no known associations to calibrate the threshold at which the PRR represents true ADR signal. To establish time-to-detection comparisons against literature, we reviewed exclusions, excluding noncausal drug-ADR mentions, and compared the frequency and timing of these detections against published clinical reports. An institutional review board protocol was not required by Stanford University.

Results | Our system achieved a microaverage precision of 0.90 for named entity recognition of our target ADRs by manual validation. We report the PRR for each target drug-ADR pair and the distribution of the PRR values for 81 drug-ADR pairs with negative associations (median, 0.12; mean, 0.2; maximum, 1.4), which served as experimental negative controls. The PRR for more than 95% of negative drug-ADR pairs is less than 0.82; thus, a drug-ADR pair with PRR greater than 1 is likely to be a true-positive.

To temporally benchmark Inspire content against publications and clinical presentations, we compared causal drug-ADR mentions of erythematous eruption and nail changes with erlotinib, and psoriasis flares and blistering reactions with immune checkpoint inhibitors in the Inspire database with first-published clinical reports. Known ADRs were reported at frequencies comparable with those of published reports but with significantly enriched PRR scores (Table) and an average lead time of 7 months in advance of literature reporting (range, 3-9 months) (Figure, A and B). In addition, we detected 23 novel cases of hypohidrosis in patients receiving erlotinib (Figure, C) with an enriched PRR score of 1.90, which may represent a rare, missed ADR that has been present in online discussion for more than 11 years. EGFR is expressed in sweat glands and is involved in the hypohidrotic ectodermal dysplasia phenotype, suggesting a mechanism by which EGFR inhibition can produce hypohidrosis.

Discussion | Several hundred million individuals discuss health-related issues in online forums, offering a robust resource for drug safety surveillance. Our deep learning pipeline extracts mentions of cutaneous ADRs with high precision from the highly informal text in social health networks, detecting ADRs with an average 7-month lead-time from clinical reports. In addition, it uncovered a novel cutaneous ADR, not previously reported. We demonstrate the capacity of deep learning-based methods to detect ADRs from online health forums, offering the potential for real-time pharmacosurveillance with rapid discovery of ADRs preceding FDA detection and published clinical reports.

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Reurrence in Resected Gastroenteropancreatic Neuroendocrine Tumors

Gastroenteropancreatic neuroendocrine tumors (GEP-NETs) are widely heterogeneous malignant abnormalities. Their natural history is poorly described, with little understanding of recurrence patterns. Surveillance for resected GEP-NETs may include clinical review, laboratory tests, and numerous medical and nuclear imaging modalities. These modalities can increase patient anxiety, may be associated with potential harm (eg, exposure to ionizing radiation), and have not been shown to improve outcomes. Current guidelines vary widely in recommendations, reflecting the lack of data.

Information on the natural history and recurrence of the disease may improve patient-centered follow-up of this population. We hypoth-