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 cutaneous 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 1) 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 at 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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Accepted for Publication: December 13, 2017.

Published Online: March 1, 2018. doi:10.1001/jamaoncol.2017.5688

Author Contributions: Drs Sarin and Shah had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Ransohoff, Nikfarjam, Kwong, Sarin, Shah. Acquisition, analysis, or interpretation of data: All authors. Drafting of the manuscript: Ransohoff, Nikfarjam, Sarin. Critical revision of the manuscript for important intellectual content: All authors. Statistical analysis: Ransohoff, Nikfarjam, Jones, Shah. Obtained funding: Shah. Administrative, technical, or material support: Nikfarjam, Loew. Study supervision: Nikfarjam, Kwong, Sarin, Shah.

Conflict of Interest Disclosures: None reported.

Funding/Support: This work was partially supported by National Institutes of Health grant No. 5R01GM101430-05.

Role of the Funder/Sponsor: The funding source had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Additional Information: Ms Ransohoff and Dr Nikfarjam are co-first authors. Drs Kwong, Sarin, and Shah are senior authors.

Additional Contributions: We thank the Inspire team for making this dataset available to us for analysis: Peter Hartzler, AB, chief technical officer; Jeff Terekowitiz, BA, senior director of product; and Kathryn Ticnkor, MA, senior manager, research and insights. They were not compensated for their assistance.


Recurrence 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-
The predominant tumor site was small intestine (43 [46.6%]), and 480 (51.3%) were women. Median follow-up was 46.8 months. Age at diagnosis was 60 years (interquartile range, 48-70 years), and diagnosis was approved by the institutional review board at Sunnybrook Health Sciences Centre, which granted a waiver of consent.

This is the largest known series examining outcomes of patients with fully resected GEP-NETs. Disease recurrence occurs much later than most other gastrointestinal tract cancers, and patients with pNETs recur earlier than those with SI-NETs. The observed patterns of imaging are inconsistent with the observed timeframe of recurrence, particularly in the first 3 years where only one-third of cancers recur. These data are limited by the lack of detailed pathologic data, particularly Ki-67 index and lymph node status.

Future research should focus on the cost-effectiveness of surveillance and its impact on patient outcomes. These data can inform guidelines for surveillance in this population that accounts for the natural history of this disease.

Table. Overall Survival and Cumulative Incidence of Recurrence Among 936 Patients With Resected Gastroenteropancreatic Neuroendocrine Tumors

<table>
<thead>
<tr>
<th>Time, y</th>
<th>Overall Survival, % (95% CI)</th>
<th>Cumulative Incidence of Recurrence, % (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All NETs</td>
<td>Small Intestinal NETs</td>
</tr>
<tr>
<td>3</td>
<td>92.2 (90.3-93.8)</td>
<td>93.9 (91.0-95.7)</td>
</tr>
<tr>
<td>5</td>
<td>85.4 (82.8-87.6)</td>
<td>86.5 (82.7-89.6)</td>
</tr>
<tr>
<td>10</td>
<td>68.1 (64.1-71.7)</td>
<td>66.9 (60.8-72.3)</td>
</tr>
<tr>
<td>15</td>
<td>54.6 (49.2-59.7)</td>
<td>49.1 (40.8-56.9)</td>
</tr>
</tbody>
</table>

The number of imaging tests declined over time since neuroendocrine tumor (NET) diagnosis, from 1.04 investigations per 100 patient-days in months 1 to 3 to 0.29 in months 25 to 36, and 0.18 in months 109 to 120.

The Kaplan-Meier method; and the cumulative probability of recurrence was estimated using the cumulative incidence function (CIF), accounting for death as a competing risk. Use of imaging tests was presented descriptively. Statistical analyses were performed with SAS statistical software (version 9.4; SAS Institute, Inc). This study was approved by the institutional review board at Sunnybrook Health Sciences Centre, which granted a waiver of consent owing to the deidentification of data used.

Results | Of the 936 patients included in the analysis, the median age at diagnosis was 60 years (interquartile range, 48-70 years), 480 (51.3%) were women. Median follow-up was 46.8 months. The predominant tumor site was small intestine (43 [46.6%]), and pancreatic NETs accounted for 187 (20.0%). The OS was 92.2% at 3 years, 85.4% at 5 years, and 68.1% at 10 years among all patients (Table), with significant difference across the sites of origin (log-rank P = .04). The cumulative incidence of recurrence was 23.3% at 3 years, 33.5% at 5 years, and 48.5% at 10 years, with recurrence occurring earliest among patients with pancreatic NETs (Gray's test for equality of CIF P < .001) (Table) (Figure).

Discussion | This is the largest known series examining outcomes of patients with fully resected GEP-NETs. Disease recurrence occurs much later than most other gastrointestinal tract cancers, and patients with pNETs recur earlier than those with SI-NETs. The observed patterns of imaging are incongruent with the observed timeframe of recurrence, particularly in the first 3 years where only one-third of cancers recur. These data are limited by the lack of detailed pathologic data, particularly Ki-67 index and lymph node status.

Future research should focus on the cost-effectiveness of surveillance and its impact on patient outcomes. These data can inform guidelines for surveillance in this population that accounts for the natural history of this disease.
The presence of competing risks.

129-140.

Other clinically meaningful alternatives, such as time to a clinical event as an endpoint for a noninferiority study, using hazard ratio as a comparison metric may not be appropriate.2 Other clinically meaningful alternatives, such as the restricted mean event-free time, have been discussed extensively in the literature.3 From Figure 2 in Hortobagyi et al,1 the mean SRE-free time up to 1 year for 12W zoledronic acid (the area under the Kaplan-Meier curve) is 316 days.2-4 That is, for future patients receiving 12W zoledronic acid up to 1-year follow-up, they will be event-free for 316 days. The difference between the 2 groups (4W minus 12W) is ~2 days, with the upper bound of the 95% CI being 18 days. That is, for SRE-free time, the worst case for 12W would be 18 days shorter than 4W of having an SRE, which is only 5% of the 365-day follow-up time. This empirical quantification has a much clearer clinical, heuristic interpretation than the hazard ratio to justify whether 12W zoledronic acid is noninferior to 4W zoledronic acid with respect to treatment efficacy.

Takahiro Hasegawa, DPH
Lee-Jen Wei, PhD

Zoledronic Acid Dosing in Patients With Metastatic Breast Cancer

To the Editor Hortobagyi et al1 conducted a noninferiority study for zoledronic acid dosing every 12 weeks (12W), comparing it with its counterpart of dosing every 4 weeks (4W) in women with breast cancer metastatic to bone. The primary endpoint was whether the patient had at least 1 debilitating skeletal-related event (SRE) by 12 months. The SREs occurred in 44 patients (22.0%) in the 4W zoledronic acid group and 47 patients (23.2%) in the 12W zoledronic acid group. The treatment difference (12W minus 4W) is 1.2%, with the upper bound of the I-sided 97.5% confidence interval (CI) being 9.8%, barely within the prespecified noninferiority margin of 10%. That is, potentially, 12W zoledronic acid can be 9.8% worse than 4W zoledronic acid with respect to the SRE rate. Using such a large observed noninferiority margin to claim that 12W is as good as 4W is debatable.

The aforementioned end point did not reflect the temporal treatment effect profile. Therefore, one of the key secondary study end points was time to first SRE. The resulting hazard ratio (12W vs 4W) is 1.06 (95% CI, 0.70-1.60). Because the upper bound of the CI is 1.60, it is not clear that a possible 60% increase of hazard from 12W over 4W would be acceptable clinically to make a noninferiority claim for 12W zoledronic acid. With the time to a clinical event as an end point for a noninferiority study, using hazard ratio as a comparison metric may not be appropriate.2 Other clinically meaningful alternatives, such as the restricted mean event-free time, have been discussed extensively in the literature.3 From Figure 2 in Hortobagyi et al,1 the mean SRE-free time up to 1 year for 12W zoledronic acid (the area under the Kaplan-Meier curve) is 316 days.2-4 That is, for future patients receiving 12W zoledronic acid up to 1-year follow-up, they will be event-free for 316 days. The difference between the 2 groups (4W minus 12W) is ~2 days, with the upper bound of the 95% CI being 18 days. That is, for SRE-free time, the worst case for 12W would be 18 days shorter than 4W of having an SRE, which is only 5% of the 365-day follow-up time. This empirical quantification has a much clearer clinical, heuristic interpretation than the hazard ratio to justify whether 12W zoledronic acid is noninferior to 4W zoledronic acid with respect to treatment efficacy.

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Conflict of Interest Disclosures: None reported.

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Published Online: November 30, 2017. doi:10.1001/jamaoncol.2017.0487

To the Editor We read the results of the Optimize-2 trial by Hortobagyi et al1 with keen interest. After 9 or more doses of monthly zoledronic acid or pamidronate, 416 women with breast cancer with bone metastases were randomized to receive zoledronic acid once every 4 weeks (4W) or zoledronic acid once every 12 weeks (12W) for 1 year. The results showed that the 12W zoledronic acid was noninferior to 4W zoledronic acid dosing. The results in the Optimize-2 are strikingly similar to recently published CALGB/Alliance trial 70604 by Himelstein et al.2 More than 1880 patients (breast cancer n = 855, prostate cancer n = 689, multiple myelomas n = 278) were randomized to receive 4W or 12W zoledronic acid starting with the first dose of randomization. In trial 70604, 12W zoledronic acid was noninferior to 4W zoledronic acid in the entire population and by a priori subset analysis in the breast cancer population. In Optimize-2 and trial 70604, there were no statistically significant differences in the frequency of skeletal-related events, time to first skeletal-related event, skeletal morbidity rate, and brief pain inventory.

Trial 70604 enrolled more than double the number the women as OPTIMIZE-2, and given the reduced costs, 12W dosing would be considered if noninferiority has been established by future trials.