Discovery of Noncancer Drug Effects on Survival in Electronic Health Records of Patients With Cancer: A New Paradigm for Drug Repurposing

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PURPOSE Drug development is becoming increasingly expensive and time consuming. Drug repurposing is one potential solution to accelerate drug discovery. However, limited research exists on the use of electronic health record (EHR) data for drug repurposing, and most published studies have been conducted in a hypothesis-driven manner that requires a predefined hypothesis about drugs and new indications. Whether EHRs can be used to detect drug repurposing signals is not clear. We want to demonstrate the feasibility of mining large, longitudinal EHRs for drug repurposing by detecting candidate noncancer drugs that can potentially be used for the treatment of cancer.

PATIENTS AND METHODS By linking cancer registry data to EHRs, we identified 43,310 patients with cancer treated at Vanderbilt University Medical Center (VUMC) and 98,366 treated at the Mayo Clinic. We assessed the effect of 146 noncancer drugs on cancer survival using VUMC EHR data and sought to replicate significant associations (false discovery rate < .1) using the identical approach with Mayo Clinic EHR data. To evaluate replicated signals further, we reviewed the biomedical literature and clinical trials on cancers for corroborating evidence.

RESULTS We identified 22 drugs from six drug classes (statins, proton pump inhibitors, angiotensin-converting enzyme inhibitors, β-blockers, nonsteroidal anti-inflammatory drugs, and α-1 blockers) associated with improved overall cancer survival (false discovery rate < .1) from VUMC; nine of the 22 drug associations were replicated at the Mayo Clinic. Literature and cancer clinical trial evaluations also showed very strong evidence to support the repurposing signals from EHRs.

CONCLUSION Mining of EHRs for drug exposure–mediated survival signals is feasible and identifies potential candidates for antineoplastic repurposing. This study sets up a new model of mining EHRs for drug repurposing signals.

INTRODUCTION Cancer drug development is increasingly expensive and time consuming. The development of a new drug is estimated to cost $648 million1 to $2.5 billion2 and takes an average of 9 to 12 years before market availability.3 The drug development success rate is less than 8% because of lack of efficacy, excess toxicity, declining research and development, cost of commercialization, and payer influence.4 Cancer drugs are now the top sellers among all Food and Drug Administration–approved therapies.5 Although many new cancer therapeutics are in development, new methods to accelerate drug discovery are needed. Drug repurposing has received great attention6–7 in recent years as one potential solution. A recent study reported that the discovery of new indications of existing drugs accounts for 20% of new drug products.8

Electronic health records (EHRs) could be an important source for drug repurposing discovery, but EHRs, which are now present in 96% of health care systems,9 have not been extensively leveraged for drug repurposing studies. Recent studies have demonstrated that EHR data can be used as an efficient, low-cost resource to validate drug repurposing signals detected from other sources.10,11 Currently, limited research exists on using EHR data for drug repurposing, and most published studies have been conducted in a manner that requires predefined hypotheses. For example, recent evidence has suggested that metformin improves cancer survival12,13 and decreases cancer risk in patients with diabetes,14 which suggests clinical promise as an antineoplastic agent. We previously found in a retrospective EHR-based study that metformin is associated with superior
This study demonstrated that mining of EHRs for drug exposure–mediated survival signals is feasible and identifies potential candidates for antineoplastic repurposing. It sets up a new model of mining EHRs for drug repurposing signals.
drug exposure with overall survival (ie, time from cancer diagnosis to death) or last medical record date in the EHR (censored). Study covariates were patient demographics (age, biologic sex, race); tumor information (type, stage); diseases with International Classification of Diseases, Ninth Revision, Clinical Modification, codes grouped into phenome-wide association study\textsuperscript{17} phenotypes; and normalized drugs. Because the dimensionality of covariates was high, we conducted variable screening using a univariable Cox model for each disease-related covariate and kept those with $P < .3$. Other variables were directly used without any filtering. We assessed mortality using a multivariable Cox proportional hazards regression model that adjusted for all the selected covariates and reported the $P$ values, HRs, and 95% CIs. We used a cutoff FDR-adjusted\textsuperscript{18} $P < .1$ to select the top-ranked drugs associated with cancer survival; this cutoff was chosen to minimize the risk of excessive false negatives at this hypothesis-generating stage.\textsuperscript{19} All analyses were conducted using R 3.1 with the survival, Hmisc, and rms packages (http://www.r-project.org).

**RESULTS**

**Drug Repurposing Signals Detected From the VUMC EHR**

At VUMC, we identified 43,310 patients with cancer diagnosed at age 18 years or older between January 1, 1995, and December 31, 2010. Patients were a median age of 57 years at diagnosis, 57% were male, and 93% were white. The major cancer types were prostate (5,673; approximately 13%), breast (3,968; approximately 9%), lung (3,346; approximately 8%), and colorectal (2,537; approximately 6%). We collected 2,630 variables for each individual, including three patient demographics (age, biologic sex, race), two tumor information (type, stage), 1,279 of 100%, 20%, or 10% if the total number of publications was fewer than 20, 21 to 200, or more than 200, respectively. If necessary, the body of available publications also was reviewed. After review, each publication was labeled as one of three categories: evidence to support an antineoplastic effect wherein the drug, alone or in combination, has a cytotoxic effect on cancer cells in vitro or in vivo; evidence to support a carcinogenic effect wherein the drug, alone or in combination, has a proliferative effect on cancer cells in vitro or in vivo; and inconclusive wherein no conclusion can be made about the drug’s cytotoxic or proliferative effect in vitro or in nonrandomized in vivo studies, or the drug failed to demonstrate statistical superiority in a randomized in vivo trial.

**Search of human interventional cancer trials for supporting evidence.** In a previous study, 25,530 cancer treatment trials were collected from ClinicalTrials.gov.\textsuperscript{20} Among them, we identified 1,068 cancer trials associated with the 146 noncancer drugs used in this study. This subset was manually reviewed and categorized as follows: Category A, the intended primary outcome is survival or a surrogate of survival, including direct effects on a tumor (eg, changes in proliferation indices), solely from the candidate drug (primary effect); category B, the intended primary outcome is survival or surrogate of survival (as in category A) on the basis of synergy between the candidate drug and one or more known antineoplastics (additive effect, including radiotherapy given with the candidate drug); category C, the candidate drug is being used for supportive care purposes or to counter adverse effects of other interventions; and category D, false positives. Of the trials identified as category A or B, we also required that the study be in patients with a current or former diagnosis of cancer; chemoprevention trials were excluded. We also tested whether our signal detection method is significantly different from random selection of drug candidates by using permutation analysis. Additional details are available in the Data Supplement.
survival (Table 1). Among the 22 initially detected drugs from the VUMC EHR, nine were replicated (Table 1). Figure 1 compares the HRs and 95% CIs for the nine replicated drugs. The Data Supplement shows the unadjusted Kaplan-Meier survival curves and associated 95% CIs for the nine drugs detected from both EHRs.

Validation Using Biomedical Literature
For each of the nine potential drugs detected from VUMC and found in the Mayo Clinic analysis, we searched PubMed for corroborating evidence. A total of 1,348 relevant biomedical publications were found for all nine drugs. As listed in Table 2, all nine drugs have at least one publication that supported an antineoplastic effect, whereas five of them have at least one publication that reported a carcinogenic effect. For all nine drugs, there are more publications that supported their antineoplastic effect compared with their carcinogenic effect. Two drugs, simvastatin and metformin, have a substantial number of publications (20 and 57, respectively). Eighteen of 20

**TABLE 1. Noncancer Drugs Associated With Improved Cancer Survival From the VUMC and Mayo Clinic EHRs**

| Drug Name | VUMC HR (95% CI) | FDR-Adjusted P | Mayo Clinic HR (95% CI) | FDR-Adjusted P |
|-----------|-----------------|----------------|------------------------|----------------|
| Rosuvastatin* | 0.81 (0.69 to 0.95) | .0691 | 0.68 (0.50 to 0.92) | .0846 |
| Simvastatin* | 0.84 (0.79 to 0.90) | <.001 | 0.82 (0.76 to 0.87) | <.001 |
| Amlodipine* | 0.84 (0.79 to 0.90) | <.001 | 0.85 (0.78 to 0.93) | .0054 |
| Tamsulosin* | 0.87 (0.80 to 0.96) | .0435 | 0.71 (0.59 to 0.85) | .0061 |
| Metformin* | 0.88 (0.80 to 0.97) | .0571 | 0.87 (0.80 to 0.95) | .0173 |
| Omeprazole* | 0.89 (0.84 to 0.94) | .0006 | 0.90 (0.85 to 0.96) | .0120 |
| Warfarin* | 0.90 (0.85 to 0.96) | .0084 | 0.90 (0.84 to 0.96) | .0174 |
| Lisinopril* | 0.91 (0.86 to 0.97) | .0328 | 0.93 (0.89 to 0.97) | .0173 |
| Metoprolol* | 0.92 (0.86 to 0.98) | .0519 | 0.69 (0.61 to 0.77) | <.001 |
| Olmesartan | 0.72 (0.59 to 0.89) | .0200 | 0.90 (0.56 to 1.4) | .8827 |
| Sildenafil* | 0.73 (0.65 to 0.82) | <.001 | 1.0 (0.74 to 1.4) | .9683 |
| Phenobarbital* | 0.77 (0.63 to 0.94) | .0603 | 0.83 (0.60 to 1.2) | .5775 |
| Carvedilol* | 0.78 (0.68 to 0.90) | .0090 | 0.96 (0.83 to 1.1) | .8763 |
| Diclofenac* | 0.81 (0.69 to 0.96) | .0945 | 0.73 (0.55 to 0.98) | .1794 |
| Carbamazepine* | 0.84 (0.73 to 0.97) | .0981 | 1.0 (0.82 to 1.3) | .9415 |
| Ramipril* | 0.85 (0.76 to 0.95) | .0451 | 0.99 (0.81 to 1.2) | .9785 |
| Epoetin* | 0.85 (0.79 to 0.93) | .0023 | 1.7 (0.98 to 2.8) | .2429 |
| Olanzapine* | 0.85 (0.75 to 0.97) | .0981 | 1.1 (0.83 to 1.6) | .7084 |
| Atorvastatin* | 0.86 (0.80 to 0.93) | .0018 | 0.92 (0.83 to 1.0) | .3921 |
| Esomeprazole* | 0.89 (0.84 to 0.95) | .0040 | 0.88 (0.69 to 1.1) | .5669 |
| Celecoxib* | 0.91 (0.84 to 0.98) | .0944 | 0.68 (0.48 to 0.96) | .1441 |
| Lansoprazole* | 0.92 (0.86 to 0.98) | .0771 | 0.91 (0.80 to 1.0) | .4002 |
| Midazolam | 1.0 (0.94 to 1.0) | .9964 | 0.43 (0.27 to 0.67) | .053 |
| Pravastatin | 0.87 (0.76 to 1.0) | .2091 | 0.64 (0.54 to 0.75) | <.001 |
| Venlafaxine | 0.95 (0.84 to 1.1) | .6654 | 0.69 (0.54 to 0.87) | .0190 |
| Oxybutynin | 1.0 (0.70 to 0.91) | .8439 | 0.79 (0.68 to 0.91) | .0174 |
| Lovastatin | 0.92 (0.81 to 1.0) | .4504 | 0.81 (0.72 to 0.92) | .0173 |
| Captopril | 0.99 (0.86 to 1.1) | .9057 | 0.85 (0.75 to 0.96) | .0488 |
| Hydrochlorothiazide | 0.99 (0.93 to 1.1) | .8307 | 0.92 (0.87 to 0.96) | .0054 |

NOTE. Study covariates were patient demographics (age, biologic sex, race), tumor information (type, stage), diseases, and medications. Abbreviations: EHR, electronic health record; FDR, false discovery rate; HR, hazard ratio; VUMC, Vanderbilt University Medical Center.
In this study, we mined large-scale EHR data to detect drug repurposing signals with potential cancer treatment implications. We found strong associations with improved overall cancer survival for statins, proton pump inhibitors, angiotensin-converting enzyme inhibitors, β-blockers, NSAIDs, and α-1 blockers in two EHR systems. We also found evidence for these effects in the biomedical literature and clinical trials. Manual review of the biomedical literature and permutation analysis of cancer clinical trials also show that our proposed method generates potentially valid drug repurposing signals. These findings indicate that the use of EHRs is feasible as a new resource for drug repurposing signal detection. We believe that this study will set up a new model for drug repurposing signal detection using EHRs and thus complement existing methods for drug repurposing studies. For example, scientists have developed computational methods to detect new treatment signals for existing drugs, including structure-based screening, adverse effect networks analysis, genomic and gene expression analysis, and biomedical literature mining. Various data sources from genomics, drug chemical structure, and phenotypic information have been explored.

This study is different from previous EHR-based drug repurposing studies. Most previous studies were conducted with a predefined hypothesis about drug and indication. These approaches highly depend on domain experts to define hypotheses and select relevant variables, which could be time consuming if we examine a large number of drugs. In this study, we have taken a data-driven approach that aimed to generate hypotheses. Instead of limited variables defined by domain experts, we included all available information (e.g., patient demographics, diseases, drugs) as variables in the analysis. Of course, some important variables likely are not recorded in EHRs and thus not included in the analysis. For example, sociobehavioral determinants of health, including healthy behaviors, are rarely recorded in the current generation of EHRs.

Some noncancer drugs identified in our study have strong evidence for cancer treatment from studies using other data sources. For example, many recent retrospective studies reported metformin associations with improved cancer survival and a chemoprevention trial in colorectal adenoma was positive. We identified 64 ongoing or completed clinical trials studying metformin alone or in combination, whose anticancer effect could be related to mammalian target of rapamycin inhibition. Ongoing cancer trials also are evaluating statins for cancer treatment (e.g., a trial to assess the efficacy of simvastatin and capecitabine in locally advanced rectal cancer [ClinicalTrials.gov identifier: NCT02161822]). Recent studies...
have reported that NSAIDs reduce the risk of a wide range of cancers (colon cancer,37 oral cancer,38 breast cancer,39 melanoma40) through blocking cellular proliferation and by promoting apoptosis.37 Of note, celecoxib (an NSAID) was identified as being the most heavily studied, with 92 ongoing or completed clinical trials,41 but the signal for improved survival at VUMC did not replicate at the Mayo Clinic.

Repurposing signals have been found in population-based cohort studies, such as the signal for increased cancer survival in patients who take statins.42-44 A smaller number of prospective repurposing trials have reported successes, such as a randomized trial of estradiol therapy of hormone receptor–positive, aromatase inhibitor-resistant advanced breast cancer45; a phase II study of pioglitazone in patients with stage IA to IIIA non–small-cell lung cancer (ClinicalTrials.gov identifier: NCT01342770); and an n-of-1 trial that combined metformin with trametinib in a patient with advanced ovarian cancer.46 Although some repurposing trials, such as pravastatin added to standard chemotherapy for small-cell lung cancer, have been negative,47 increasingly granular phenotyping efforts will lead to refined patient selection. In particular, the advent of routine germline sequencing, somatic tumor profiling, and immunophenotyping will allow for precise patient selection, as in the NCI-MATCH (National Cancer Institute Molecular Analysis for Therapy Choice) trial.48 Currently, some drugs have no evidence, or sometimes conflicting findings, about their effects on treating cancer according to existing literature. For example, one study examined captopril and found no clear association between the use of antihypertensive drugs and prostate cancer.49 However, another study that focused on users of captopril showed a lower risk of subsequent prostate cancer.50 Our literature review was based on a sampling strategy and may have overlooked human trials with strong evidence for antineoplastic effects. Of note, given that this is a repurposing study for candidate drugs not clearly known to have antineoplastic properties, much of the discovered literature was based on cell lines or was retrospective in nature. In addition, the well-known bias to selectively report positive results likely extends to a bias toward reporting antineoplastic results (eg, approximately 350,000 results were found using the medical subject headings term, antineoplastic agents, and only approximately 47,500 for the term carcinogens), which may have affected our findings. Five drugs, including amlodipine,51 tamsulosin,52 metformin,53 warfarin,54 and lisinopril55 have published results that report an increased risk of cancer. These unsupported signals could be either false positive or novel findings. Additional research with more careful study designs or in-depth mechanism experiments is required to validate or reject these hypotheses.

This study has limitations. Similar to other epidemiologic studies using observational data, our study may suffer from incomplete information and/or unmeasured confounder effects. It is possible, although unlikely because of the time frame of the analysis, that certain clinicians were aware of the potential anticancer effects of some of the study drugs and were intentionally prescribing them for cancer treatment; temporal resolution of self-administered drug exposures is a difficult and as-yet unsolved problem in clinical data extraction.56,57 To accommodate the large-scale analysis, our study design is relatively simple: Comparison groups were defined on the basis of mentions of the study drug only without considering the actual exposure details (timing of the drug exposure and drug doses administered) and other potential bias; overall survival, not cancer-specific survival, was used because there were no cancer-specific survival

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**TABLE 2. Results of Literature Search for Corroborating Evidence for Drugs Associated With Improved Cancer Survival From Both VUMC and Mayo Clinic Cohorts**

| Drug Name | Reviewed Cancer-Relevant Studies | Antineoplastic Effect | Carcinogenic Effect | Inconclusive |
|-----------|----------------------------------|-----------------------|---------------------|--------------|
| Rosuvastatin | 9 | 7 (5, 1, 1 [R, 1]) | 0 | 2 (1, 0, 1 [R, 1]) |
| Simvastatin | 20 | 18 (15, 1, 3 [R, 3])** | 0 | 2 (0, 0, 2 [RCT, 2]) |
| Amlodipine | 6 | 5 (3, 2, 0) | 1 (0, 0, 1 [R, 1]) | 0 |
| Tamsulosin | 5 | 0 | 0 | 5 (0, 0) |
| Metformin | 57 | 40 (15, 8, 17 [R, 15; NR, 3; RCT, 1]) | 2 (0, 0, 2 [R, 1; NR, 1]) | 13 (1, 0, 12 [R, 11; RCT, 1]) |
| Omeprazole | 10 | 8 (4, 0, 4 [NR, 3; RCT, 1]) | 2 (0, 1, 1 [R, 1]) | 0 |
| Warfarin | 17 | 5 (2, 1, 2 [R, 1; NR, 1; RCT, 1]) | 1 (0, 0, 1 [NR, 1]) | 11 (0, 1, 9 [R, 3; NR, 3, RCT, 3]) |
| Lisinopril | 7 | 2 (1, 1, 0) | 1 (0, 0, 1 [NR, 1]) | 4 (0, 0, 4 [R, 1; NR, 2; RCT, 1]) |
| Metoprolol | 3 | 0 | 0 | 3 (2, 0, 1 [R, 1]) |

Abbreviations: NR, nonrandomized; R, retrospective; RCT, randomized controlled trial.

*Total is > 100% because one trial reported both cell line and human results.
data. However, because the goal of this study was to generate hypotheses, we expect that more carefully designed studies would evaluate such findings in functional models and/or randomized controlled trials. Furthermore, the survival model only examined each drug without considering the combinations of variables. Therefore, our method cannot be used to identify the effect of combinations of drugs.

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**EQUAL CONTRIBUTION**

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**AUTHORS’ DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST**

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