Validating drug repurposing signals using electronic health records: a case study of metformin associated with reduced cancer mortality

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The Issue of Drug Discovery

- Developing a new drug will take:
  - $800 million
  - 10 – 17 years
  - 10% success rate
- A productivity problem of pharmaceutical industry

Reichert JM. Trends in development and approval times for new therapeutics in the US. *Nature reviews. Drug discovery.* 2003;2(9):695-702.

Drug Repurposing

- Drug repurposing (repositioning or re-profiling) – find new indications of existing drugs
  - Find new uses of FDA-approved drugs
  - Rescue drugs previously failed in clinical trials
- Advantages: known pharmacokinetic, pharmacodynamic, and toxicity profiles
  - Lower risk
  - Lower cost
  - Less time

Computational Approaches to Drug Repurposing

- Large-scale compound databases containing structure, bioassay, and genomic information, e.g., NIH's Molecular Libraries Initiative
- Computational approaches
  - Structured-based virtual screening (Ma DL et al, *Chem Soc Rev,* 2013)
  - Analysis of side effect profiles (Campillos M, *Science*, 2008; Lounkine E et al, *Nature*, 2012)
  - Genomic and gene expression data (Wang and Zhang, *Nat Biotechnol*, 2013)
  - Biomedical literature mining (Andronis C et al, *Brief Bioinfom*, 2011)
- Electronic health records (EHRs)

EHRs Data

- Large EHRs – millions of records for more than a decade
- By 2014, all US hospitals will implement EHRs systems
- Types of data in EHRs
  - Structured
    - Administrative data
    - Billing codes: ICD9, CPT, …
    - Lab tests
    - Computerized orders
    - …..
  - Unstructured
    - Admission notes
    - Discharge summaries
    - Clinic visit notes
    - Pathology notes
    - ……

EHRs for Drug Studies

- EHRs data
  - Rich treatment and outcome information
  - Longitudinal practice-based data
- Different types of drug studies
  - Pharmacoepidemiology
  - Pharmacoeconomics
  - Pharmacovigillance
  - Pharmacogenomics (with Biobanks)

Challenges for using EHR Data

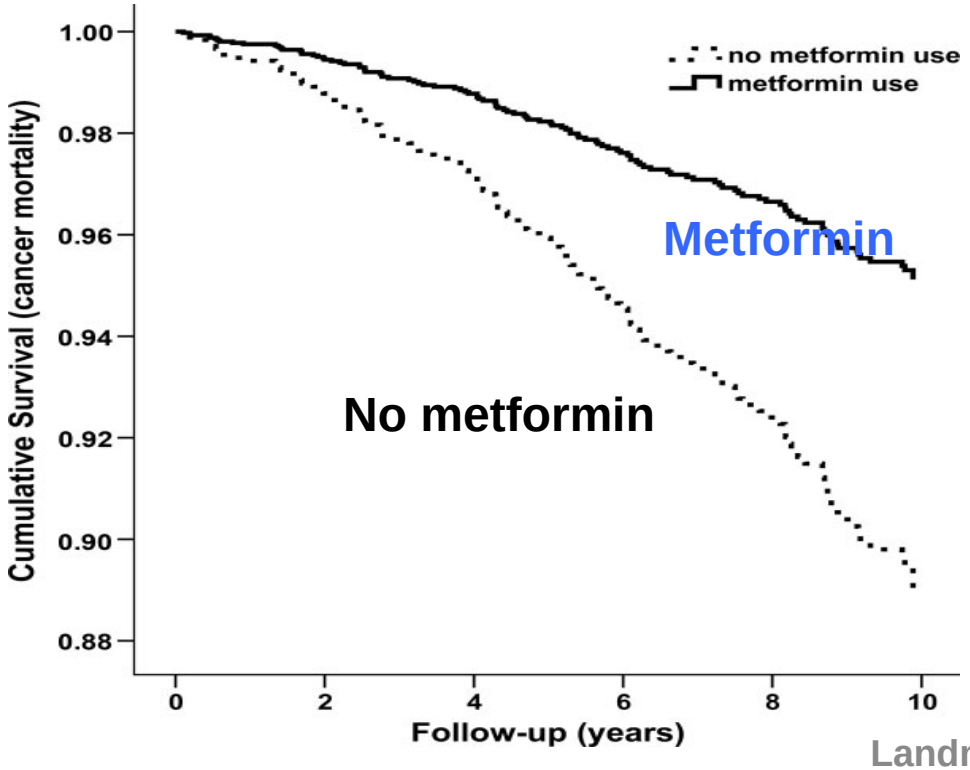
- Data extraction
  - Much of detailed information is embedded in narrative text
  - Heterogeneous data sources, e.g., different terminologies
- Data abstraction and analysis
  - Discrepancy
  - Missing data
  - Confounding
- The need for informatics approaches

A study of metformin and cancer mortality using EHR and informatics

- We want to answer two questions:
  - Can EHR data be used to find new indications of existing drugs?
  - What is the role of informatics in this type of research?
- Specific aim – validate the association between metformin and improved cancer survival rate using EHR data

Metformin and cancer survival

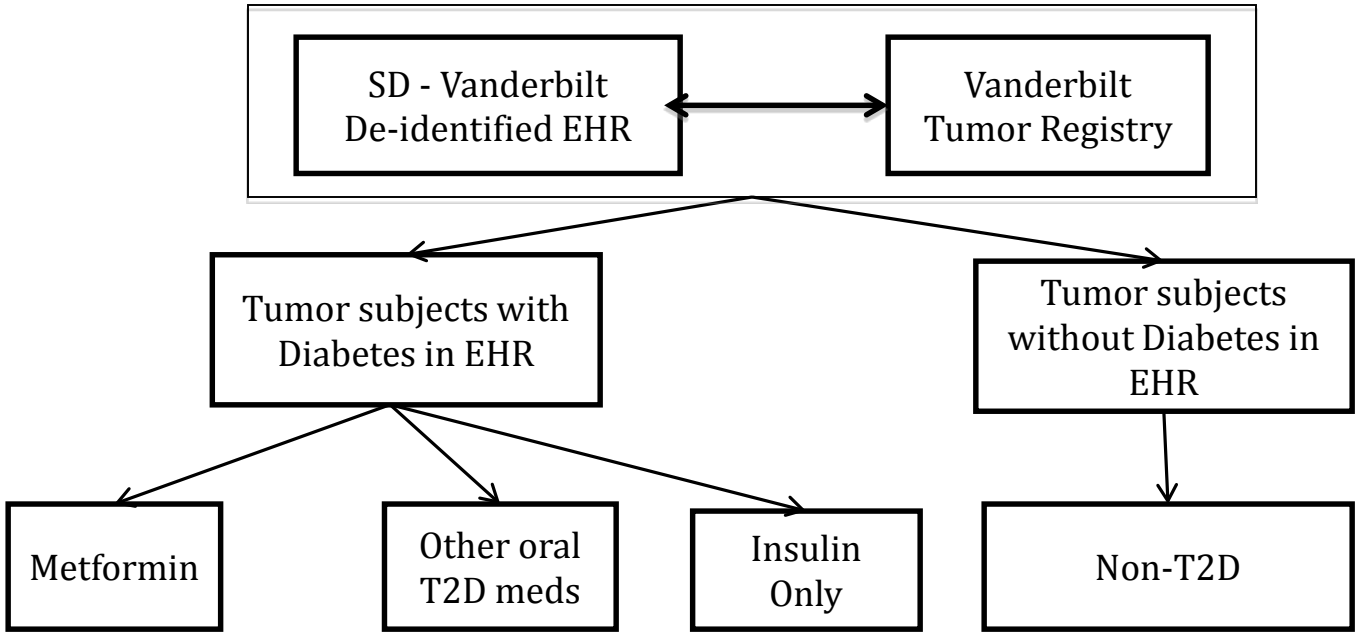
- Reduced Cancer Mortality with Metformin Use Among Diabetics



Landman Diab Care 2010

Study Design

- Primary analysis – Vanderbilt



- Replication – Mayo Clinic

The Use of Informatics

- Cohort Identification
  - Type 2 Diabetes algorithm developed by eMERGE
  - MedEx for determining medication exposure

- Covariates extraction
  - Smoking status
  - Height and weight

Informatics – Cohort Identification

- Type 2 Diabetes algorithm developed by eMERGE
  - ICD9 codes
  - Medications
  - Lab test
- Evaluated at Vanderbilt and other sites, high performance (PPV>95%)

Informatics – Medication Exposure

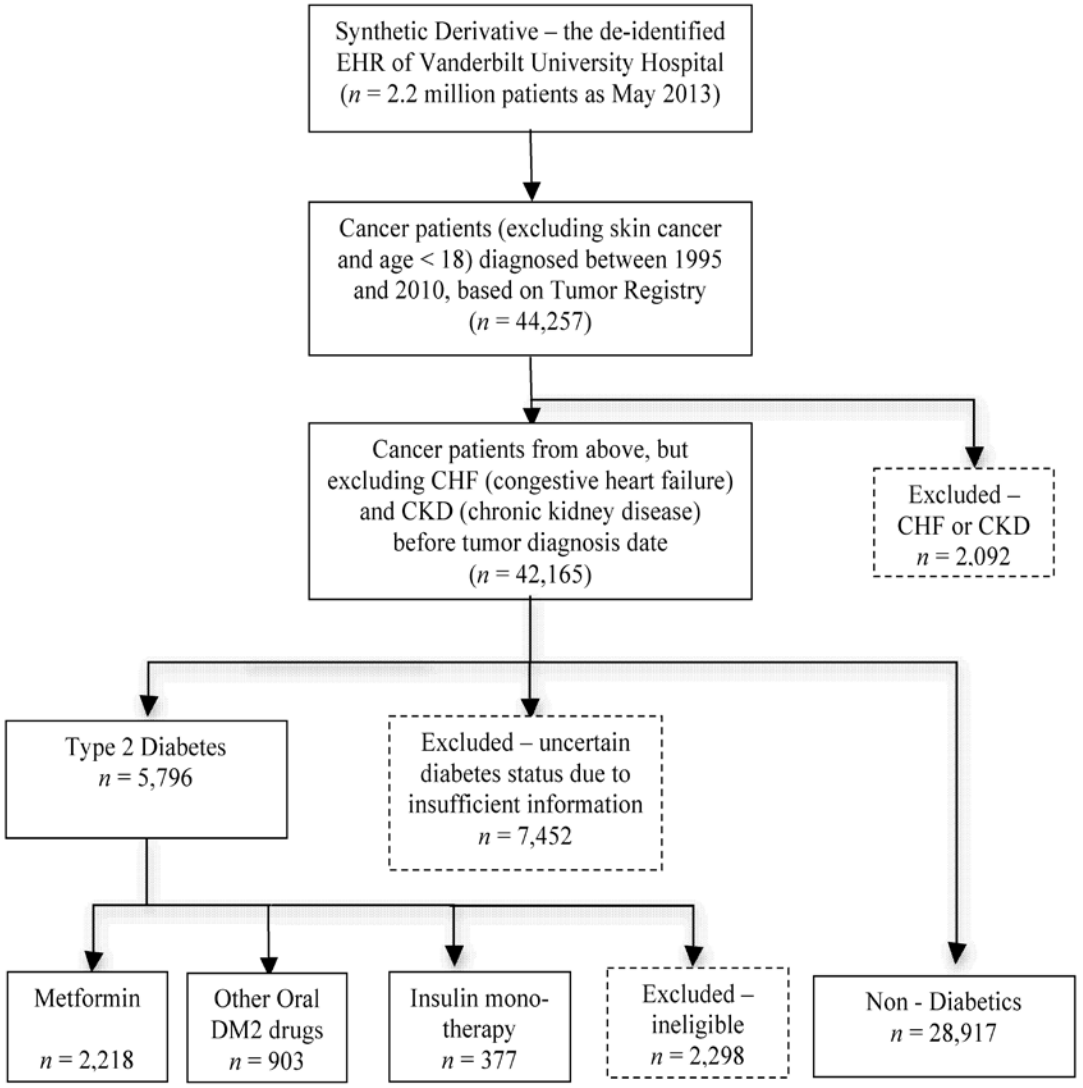
- MedEx
  - Identify drug name and signature information
  - Identify other T2D drugs
  - Determine metformin and its daily dose
  - Available at http://code.google.com/p/medex-uima/

- Heuristic rules for drug exposure

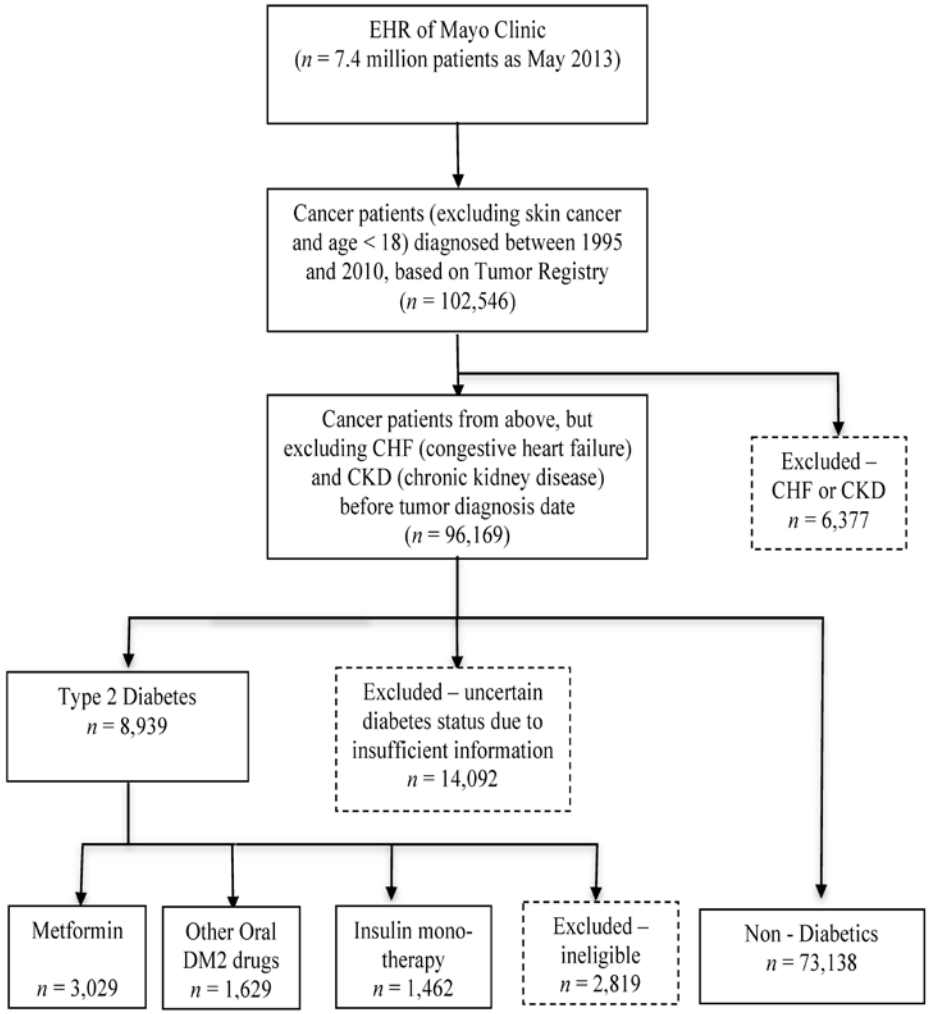
Informatics – covariate extraction

- Smoking status
  - The default cTAKES smoking status module did not work well on Vanderbilt text
  - Customized to Vanderbilt narratives – a 93% PPV for smoking status
- Height and weight
  - Structured fields - 42% height and 36% weight were missing
  - A simple regular expression program reduced missing rate to 33% and 16% for height and weight respectively

Data Extraction Workflow - Vanderbilt



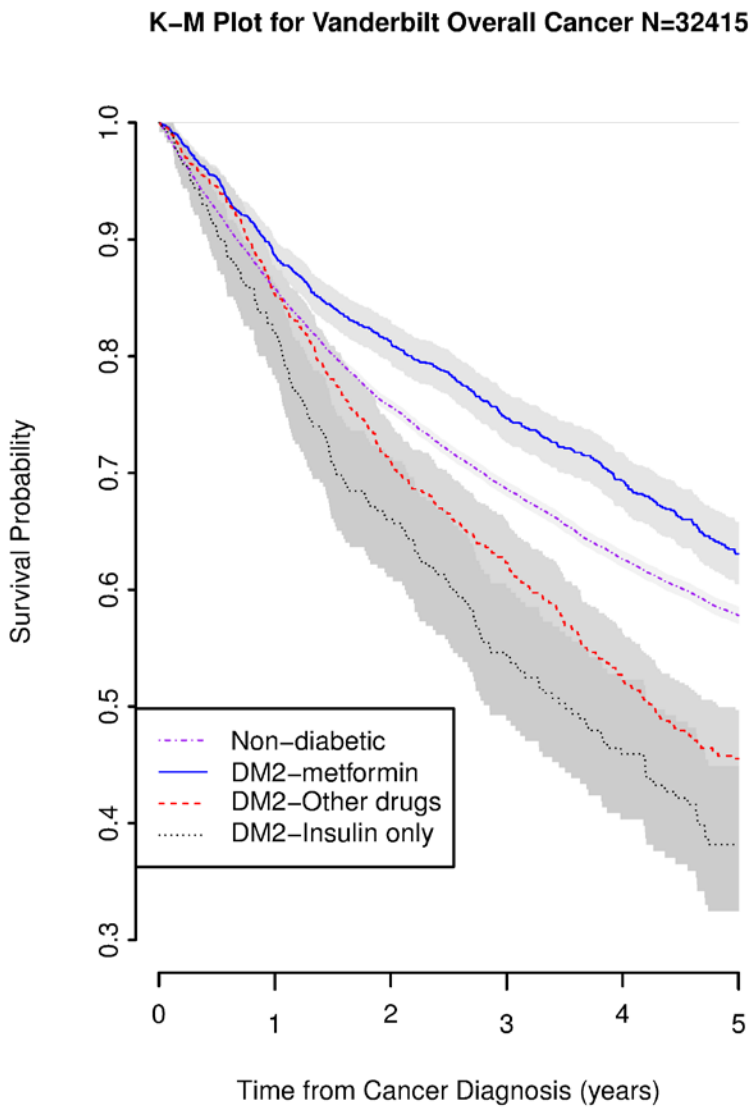
Data Extraction Workflow - Mayo

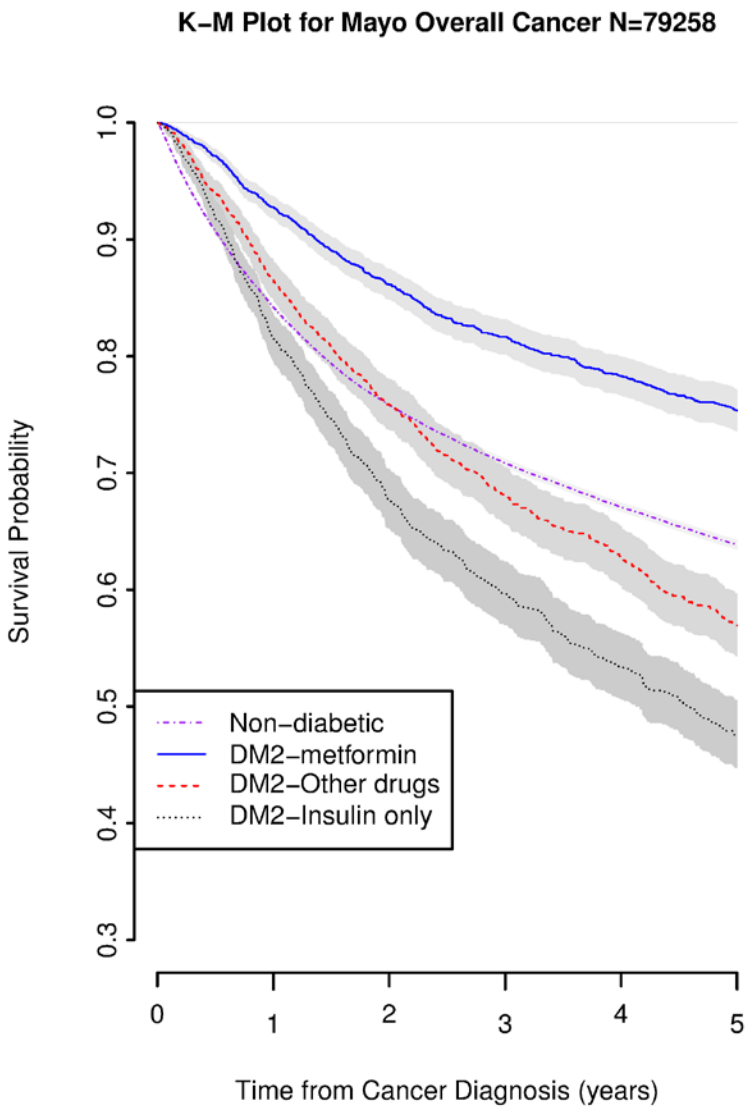


Data Set Statistics - Vanderbilt

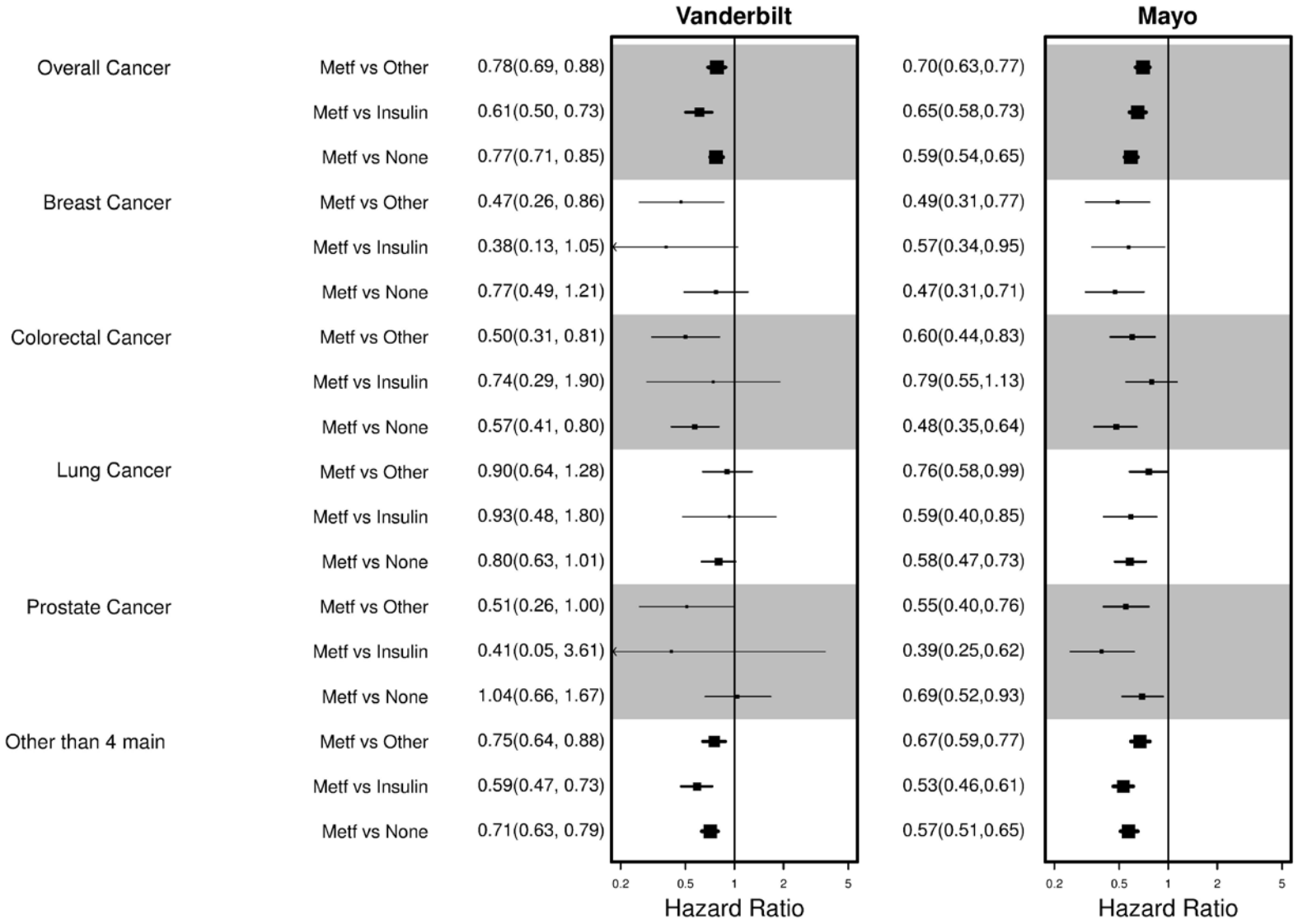
	Type 2 Diabetics (T2D)			Non- T2D
	Metformin	Other oral meds	Insulin	
# of patients	2218	903	337	28917
Age	62	64	59	58
Female (%)	42%	39%	42%	43%
Race (W/B)	88% / 12%	90% / 10%	88% / 12%	93% / 7%
BMI	31	31	29	27
A1C	7.5	7.5	7.6	N/A
…..				
% of died	30% (658)	49%(442)	59%(406)	33%(9449)

Survival Analysis – all cancers





Cox proportional hazards model – all and four individual cancers



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Limitations

- Incomplete medication exposure information
- Imperfect phenotyping algorithms
- Did not adjust for cancer treatment regimens
- Limited sample size for individual cancers

Conclusion

- Large EHRs are valuable sources for drug repurposing studies
- Informatics is the key to speed up this type of research
- A new drug repurposing model for using EHRs and informatics
  - Rapid pilot studies for hypothesis generation
  - Quick replications of known signals
  - New knowledge discovery (with solid study design and data extraction methods)

Future work

- More drugs – screening hundreds of other drugs
- More data sources – EHRs, claims, disease registries …
- More NLP tools for clinical phenotyping – customizable, high-performance, user-friendly
- More analysis methods – missing data, confounder identification, bias correction …

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Thank you!

Questions?

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