# Leveraging Real World Data to Characterize Immune Related Adverse Events

Addressing Resistance in the Development of Cancer Immune Modulator Therapeutics
A National Academies of Sciences, Engineering, and Medicine Workshop

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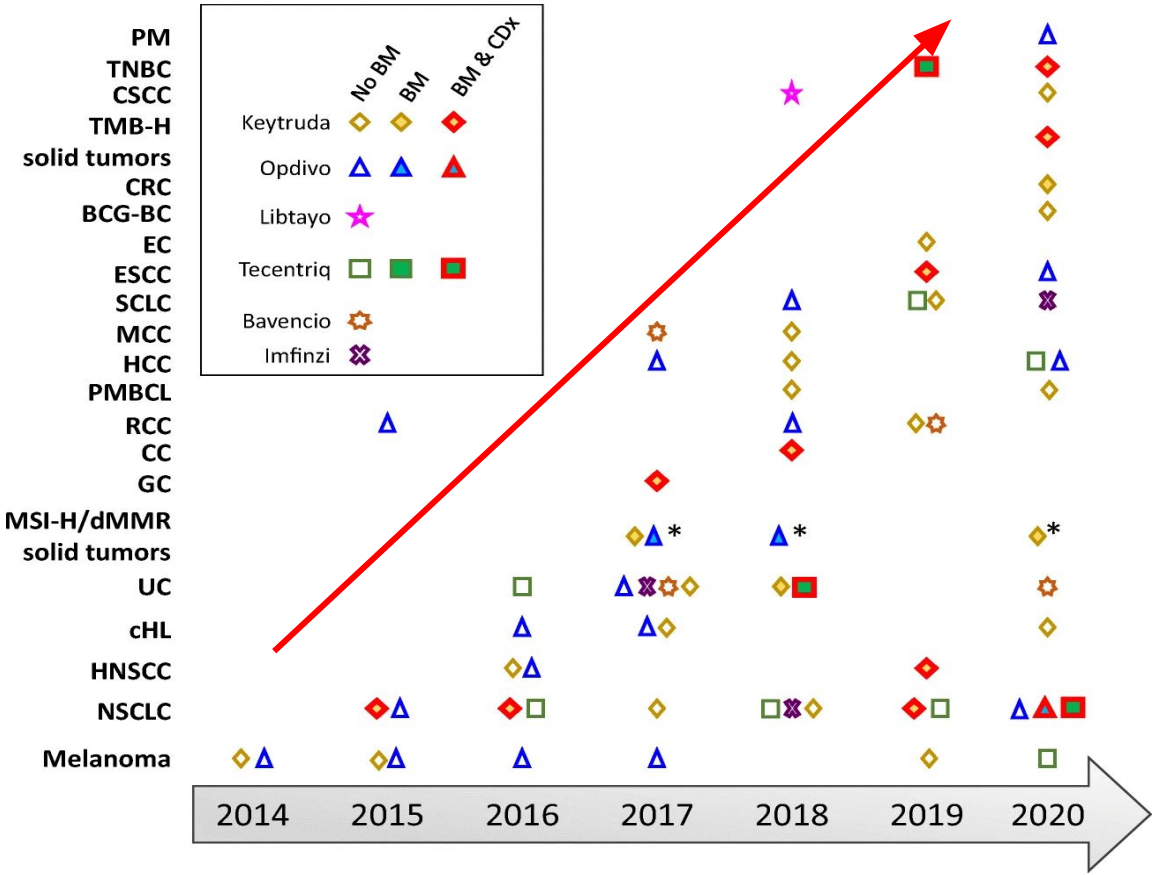
# Disclosures

*Dr. Yerram reports employment at Flatiron Health, Inc., which is an independent subsidiary of the Roche Group.*

*Dr. Yerram reports stock ownership in Roche.*

# Increasing FDA Approvals of Immune Checkpoint Inhibitors (ICI)

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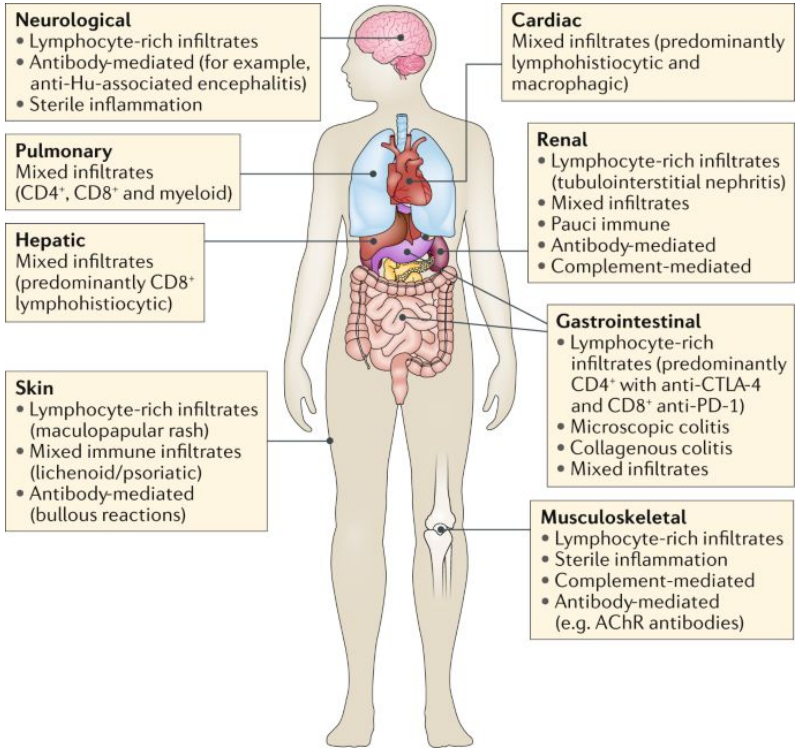
Twomey JD et al. AAPS J . 2021;23(2):39.

# Immune Related Adverse Events (irAEs)

- Experienced by vast majority of patients
  - Risk of ICI affecting any organ is up to 86% with CTLA-4 inhibitors and 82% with anti-PD(L)1 agents
- Can lead to discontinuation, permanent organ damage, fatal outcomes
- Comprehensive understanding of irAEs needed to understand risk-benefit of ICI in larger groups of patients
- Need to to improve detection, diagnosis, management of clinically significant irAEs with increasing utilization of ICI




Esfahani et al. Nat Rev Clin Oncol. 2020;17(8):504-515

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# Real World Data (RWD) for irAEs

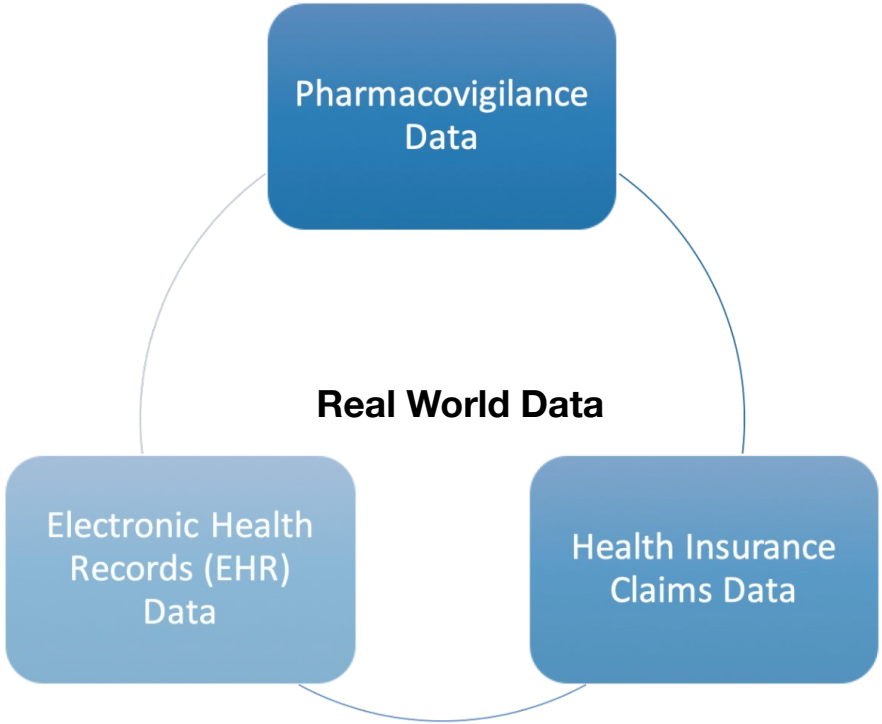
**Strengths**

- Often more diverse populations than those in clinical trials (i.e autoimmune diseases, organ dysfunction)
- Study irAEs that occur outside of clinical trial study period

**Challenges**

- Missingness & Incomplete data
- Data quality issues
- No standardized reporting for AEs
  - Difficult to categorize severity/grade of AE
- Difficult to understand causality

# Real World Data (RWD) Sources to Study irAEs




**Ideal Real World Data (RWD) Source**

- Large sample sizes
- Ease of case finding
- Rich clinical details
- Ability to understand incidence rates
- Standardized reporting

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# Data Source Considerations

## Pharmacovigilance Data

- Spontaneous adverse event reporting
- FAERS & VigiBase
- Voluntary reporting by heterogeneous sources
- Unable to determine incidence
- Capture of more severe or rare irAEs
- May lack clinical details

## Health Insurance Claims Data

- Breadth and variety of data
- Lacks certain clinical details
- Includes only insured patient populations
- Differences in billing practices
- Primary purpose of data is reimbursement

## EHR Data

- Includes only patients in EHR network
- Rich with clinical information
- Varying rates of missingness
- Time and resource intensive to categorize unstructured data

# Further applications of RWD for irAEs

1. Characterizing demographic factors and biomarkers related to irAE risk
2. Further characterize rare irAEs
3. Evaluations of irAEs and ICI efficacy
4. Evaluate ICI re-challenge for lower risk to severe irAEs

# Case Study

Question:  Which baseline factors in patients with cancer receiving ICI therapies are associated with the risk of irAE development?

# Case Study: Pharmacovigilance Data

## Age-Associated Changes in Adverse Events Arising From Anti-PD-(L)1 Therapy

*Xinyi Huang[1,2,3], Tiantian Tian[2,3], Yan Zhang[2,3], Shengjian Zhou[4], Pingping Hu[2,3*†] and Jiandong Zhang[2,3*†]*

**Table 2 (adapted): Multivariate logistic regression of odds ratio for different irAEs controlling for multiple conditions (including age)**

| | | |
|---|---|---|
| **Pulmonary Toxicity** | | |
| | Adjusted OR | P value |
| 65≤age<75 | 1.270 | <0.001 |
| Age ≥75 | 1.380 | <0.001 |
| **Hepatitis** | | |
| | Adjusted OR | P value |
| 65≤age<75 | 0.614 | 0.012 |
| Age ≥75 | 0.504 | 0.014 |
| **Myasthenia gravis; Colitis; Hypophysitis; Skin reaction; Thyroid toxicity; Neurologic toxicity; GI toxicity; Adrenal insufficiency; Myocarditis; Myositis; Encephalitis; Diabetes; Hematologic toxicity** | | |
| | P value | |
| 65≤age<75 | Not significant | |
| Age ≥75 | Not significant | |

### Study Highlights

- 17006 patients treated with PD-(L)1 therapies for lung cancer selected from US FDA Adverse Event Reporting System (FAERS) database
- 96% of all AEs studied were serious
- Elderly patients exhibited higher rates of pulmonary toxicity while younger patients had increased hepatotoxicity

### Strengths

- Large sample size of patients with irAEs

### Limitations

- Information based on spontaneous reporting (reporting bias)
- Limited clinical details
- Majority of irAEs were serious in nature
- Unable to understand causal relationship of irAE to ICI



Huang X et al. Front Oncol . 2021;11:619385.

# Case Study: Healthcare Claims Data

## A Population-based Study of Immunotherapy-related Toxicities in Lung Cancer

Elizabeth J. Cathcart-Rake,[1] Lindsey R. Sangaralingham,[2,3] Henry J. Henk,[2] Nilay D. Shah,[2,3,4] Irbaz Bin Riaz,[1] Aaron S. Mansfield[1]

**Table 4** Associations Between Baseline Variables and irAEs

| Parameter | *P* Value | HazardRatio | Parameter | *P* Value | HazardRatio |
|---|---|---|---|---|---|
| Year | .58 | 1.02 | Race (ref = White) | | |
| Gender, male vs. female | .42 | 1.05 | Asian | .60 | 1.11 |
| Age group, y (ref = 18-49) | | | Black | .16 | 1.13 |
| 50-64 | .18 | 1.23 | Hispanic | .03 | 1.30 |
| 65-74 | .11 | 1.28 | Unknown | .29 | 1.09 |
| 75+ | .14 | 1.26 | I/O (ref = atezolizumab) | | |
| Line of treatment (ref = first) | | | | | |
| Second+ | <.0001 | 0.77 | | | |
| Census region (ref = Midwest) | | | | | |
| Northeast | .21 | 1.11 | | | |
| South | .57 | 1.04 | | | |
| West | .57 | 1.06 | | | |

## Study Highlights

- 3164 patients with NSCLC who received PD-(L)1 inhibitors from commercial insurance claims database (OptumLabs) with cumulative irAE incidence of 52.5%
- No associations seen with age, gender, or region and frequencies of irAEs in any tissue
- Patients who received ICI in later lines had higher risk of irAEs

## Strengths

- Large sample size and broad view of irAEs in ICI therapies

## Limitations

- Unable to understand causality
- Lack of disease information (histology, stage)
- Reporting frequency may vary based on how a clinician bills
- ICD codes may overcapture

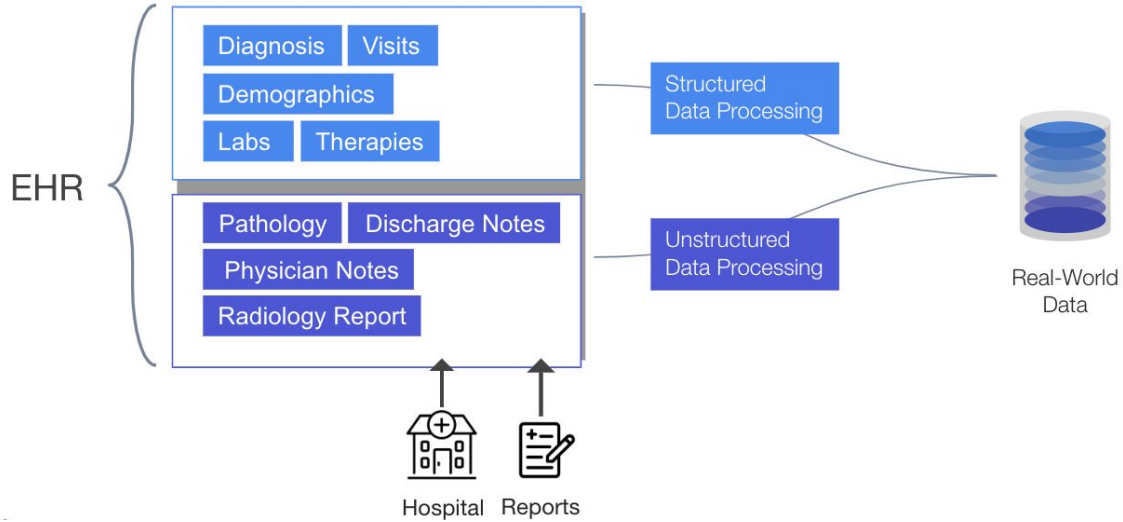
Cathcart-Rake EJ et al. Clin Lung Cancer . 2020;21(5):421-427.e2.

# Case Study: Oncology EHR Data

Are baseline factors in patients with cancer receiving ICI therapies associated with the risk of irAE development?

- Pharmacovigilance  & healthcare claims data
  - **Strengths**: Large sample sizes; readily available and utilized RWD
  - **Limitations**: Limited clinical details; more likely to capture severe irAEs
- Account for known risk factors (i.e autoimmune comorbidities, steroid utilization)
- Understand if AE was a result of immunotherapy or other factors (i.e radiation pneumonitis vs immune related pneumonitis)
- Characterize mild to moderate irAEs and severity of irAEs

# EHR Data Components




## Considerations

- Rich clinical data
- Time and resource intensive (unstructured data)
- Sample sizes

# How do irAE data get abstracted from EHR?

1

Capture new or worsening AEs of interest during treatment interval

2

Capture attribution and outcomes related to the AE

**Treatment Interval**: Durvalumab 01/01/2018 - 01/01/2020

***Clinic Visit Date: 05/01/19***

**History of Present Illness**

**CT chest reviewed with Dr. [ ] and patient today.**
**It shows concern for pneumonitis**

**Plan**

**Pneumonitis due to durvalumab on CT scan and c/w clinical picture.**
**Will have him Start prednisone taper, written instructions given to pt today**

**CHEMOTHERAPY:**
Durvalumab [ ]/18 - [ ]/19
Treatment held 2/21/19 to present due to pneumonitis.

**AE of Interest:**
*Pneumonitis*

**Onset Date:**
05/01/2019

**Attribution:**
*Directly attributed*

**Outcomes:**
*Therapy Held*
*Treatment for the AE*

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# Example: EHR irAE Data Model

**Autoimmune Comorbidities** (at baseline):

Y/N for the following:

- Prior irARE
- Behcet's syndrome
- Celiac disease
- Chronic lymphocytic thyroiditis
- Crohn's disease
- Graves thyroiditis
- Idiopathic thrombocytopenic purpura
- Inflammatory arthritis
- Multiple sclerosis
- Myasthenia gravis
- Myositis
- Polymyalgia rheumatica
- Psoriasis
- Reiter's disease
- Sarcoidosis
- Sjogren's syndrome
- Spondyloarthropathy
- Systemic lupus erythematosus
- Transverse myelitis
- Type 1 diabetes
- Ulcerative colitis
- Vitiligo
- Other

+

**irAEs and Associated Outcomes**:

- AE name
  - irColitis
  - irHepatitis
  - irHypophysitis
  - irNephritis
  - irPneumonitis
  - irRash
  - irAE, other
- Onset date
- Attribution (Direct attribution, Possible attribution, Not attributed, Not documented)
- Therapy-related outcomes
  - Dose or schedule change (Y/N)
  - Therapy hold (Y/N)
  - Therapy discontinuation (Y/N)
- Other outcomes
  - Other Treatment for the AE
  - Hospitalization (Y/N) + dates for each hospitalization
  - Death (Y/N)

# Current Challenges & Future Directions

## Challenges

**Case finding**

- Time and resource intensive process to identify irAE cases

**Limited sample sizes**

**Standardized reporting for irAEs**

## Future Directions

**Machine learning (ML) and Natural language processing (NLP) to identify irAEs**

- Can we use ML to predict the frequency of rare irAEs? Which patients will develop irAEs? When will they develop irAEs?

**Integrated data sources**

- Claims & EHR data
- Utilize real world data & clinical trials

**Need to optimize irAE reporting**

- Standardized definitions for rare irAEs
- Encourage routine reporting of serious and unexpected AEs to FAERs or drug manufacturers by clinicians
- Integration within EHR systems

# Key Takeaways

- There is growing need to better characterize immune related adverse events
- Real world data sources - including pharmacovigilance, health insurance claims, and EHR data -  can provide opportunities to study questions related to irAEs
- Consider the advantages and disadvantages of each data source when utilizing RWD to characterize irAEs

# Thank You

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