Towards a Structured Classification of Immune-Related Adverse Events to Inform a Clinical Decision Support System for Early Recognition in Cancer Patients on Immune Checkpoint Inhibitors

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Introduction

- Immune Checkpoint Inhibitors (ICIs) have revolutionized cancer treatment in the past decade, especially in non-small cell lung, melanoma and renal cancers.[1]
- However, ICIs can cause debilitating side effects known as immune-related adverse events (irAEs)[2] in the skin, endocrine system, liver, gastrointestinal system, lungs, muscle, neurological system, kidneys, heart, and eyes.[2]
- IrAE severity ranges from mild (e.g., skin rashes) to life threatening (e.g., encephalitis) and is graded 1-5 (mild, moderate, severe, life-threatening or death) according to the Common Terminology Criteria for Adverse Events (CTCAE)
- Prior work has identified irAEs and common ICI side effects,[3] developed ICI patient-reported outcome (PRO) scales,[4] and published machine learning algorithms to predict irAEs.[4] These have seen limited clinical use due to poor integration with clinical informatics solutions.
- We aim to develop a clinical decision support (CDS) system to facilitate early recognition of irAEs, using PROs and machine learning to inform timely recognition of irAEs and reduce high-grade irAEs.
- As a first step to developing the CDS, using National Comprehensive Cancer Network (NCCN)[3] evidence, which maps irAEs with their associated symptoms, we conducted a review of existing terminologies used for irAEs.

Overview of Proposed Clinical Decision Support System

- The CDS system will entail collection of patient-reported data (PROs) to regularly track and report PROs that are indicative of potential irAEs.
- Questions will be organized by bodily system **(Figure 1)**.
- Data will be sent to a provider-facing clinical decision support (CDS) tool to inform early detection and proper management of irAEs.

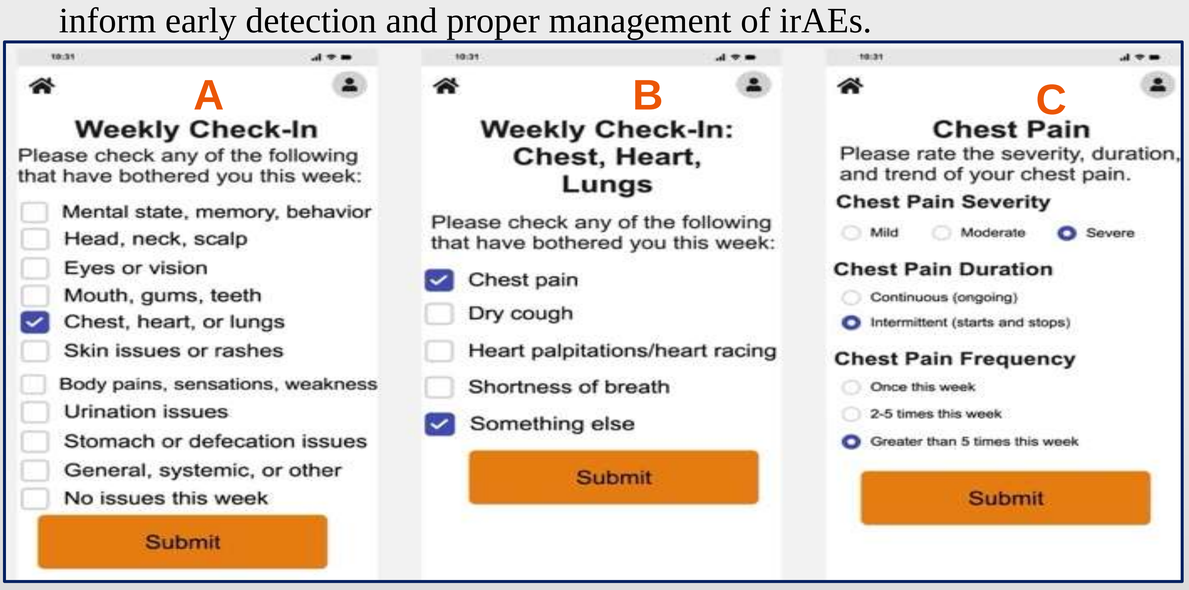

Figure 1. Example of PROs app; screen C shows only if a relevant item in B is selected; screen B only if a relevant item in A is selected; co-design to be conducted to improve appearance vis-a-vis user preferences

Mapping Symptoms to irAEs Based on NCCN Guidelines

1. Conditions to irAE Type: E.g., Pneumonitis is a Pulmonary irAE; Myocarditis is a Cardiac irAE

irAE types: *Cardiac, Dermatologic, Endocrine, Gastrointestinal, Musculoskeletal, Nervous, Ocular, Pulmonary, and Renal.*[3]

2. Symptoms to associated irAEs: e.g., Chest pain is associated with Pneumonitis; Chest pain is associated with Myocarditis (chest pain is a symptom of both myocarditis and pneumonitis)

irAEs: *Myocarditis, Bullous dermatitis, Maculopapular rash, Pruritus, SJS, Lichen planus, Psoriasis, Oral mucosa inflammation, Sicca syndrome, Oral Dysesthesia, Hyperglycemia related Diabetic Ketoacidosis, Overt and Central Hypothyroidism, Thyrotoxicosis, Hypophysitis, Primary adrenal insufficiency, Colitis, Transaminitis, Cholestasis, Pancreatitis, Inflammatory arthritis, Myositis, Polymyalgia rheumatica, Giant cell arteritis, Aseptic meningitis, Encephalitis, Guillain-Barre syndrome, Myasthenia gravis, Peripheral neuropathy, Acute demyelinating encephalomyelitis, Optic neuritis, Transverse myelitis, Ocular changes, Pneumonitis, and Acute kidney injury.*[3]

		irAE Type	
Body System	**Symptoms**	**Cardio**	**Nervous System**
Chest	Chest pain	X	
Chest	Dry cough		
Chest	Heart palpitations	X	
Eye	Changes in color vision		X

		Endocrine irAE Type	
Location	**Symptom**	**Hyperglycemic-related Diabetic Ketoacidosis (DKA)**	**Overt Hypothyroidism**
Chest	Heart Palpitations	X	
Eye	Sensitivity to light		
GI	Constipation		X

Figure 2. Sample of symptom-irAE-body system mapping

3. Symptoms to body system (to categorize in patient-friendly groupings): e.g., Chest pain has Finding Site Chest

Symptoms: *73 symptoms indicative of one or more irAEs.*[3] *Examples: chest pain, heart palpitations, eye pain or tenderness, dry mouth, and generalized weakness*

Body Systems: *Chest, eye, gastrointestinal, head, mental state, sensation, skin, systemic symptoms, urogenital*

Review of irAE and irAE Symptom Terminologies

- **Terminologies examined:** ICD-9, ICD-10, LOINC, SNOMED-CT, MeSH

irAE Symptom	SNOMED	LONIC	ICD10CM	ICD9CM	MeSH Code
Chest pain	Chest pain 29857009; acute chest pain 102587001	Chest pain (Clinical observation) 58259-3	Chest pain, unspecified: R07.9; Other chest pain: R07.8; Other chest pain: R07.89	Chest pain, unspecified: 786.50; Chest pain: 786.5; Other chest pain: 786.59	Chest pain-D002637
Dry cough	Dry cough 11833005; Episodic dry cough 810511000000109; Cough 49727002; Persistent cough 284523002; Decreased coughing 52673003; No cough 139177007; Dry cough 139179005; Increasing frequency of cough 62731002	64145-6-Do you usually have a cough, (Clinical observation), LP116178-7-In the last 12 months, have you had a dry cough at night, apart from a cough associated with a cold or chest infection(Component)	Cough: R05	Cough: 786.2	D003371-Cough

Figure 3. Sample of documentation of irAE symptoms in terminologies reviewed

- **Surveys**
  - General PRO scales**:** PRO-CTCAE, EORTC QLQ-C30, EQ-5D, SDS, SF-36,Fact-G Fact-BL, FACT-L, FACT-M, FKSI-DRS, FSKI-19, QLQ-LC13, QLQ-H&N35, LCSS, FACT-Fatigue, Brief Fatigue Inventory.
  - ICI PRO Scales: Azuma et al, FACT-ICM, Kaiku, Ronin Symptom Scale, Zhang et al.

irAE Symptom	Azuma et al.	FACT ICM	Kaiku	Ronin Symptom Monitoring	Zhang et al
Chest Pain	not in measure	not in measure	chest pain	not in measure	cardiac discomfort, pain in the precordial region
Dry cough	Do you have a dry cough without sputum?	I have been Coughing	cough	not in measure	cough, respiratory discomfort
Heart palpitations	Do/did you feel palpitations	not in measure	not in measure	palpitations, pounding or racing heartbeat	cardiac discomfort, palpitations

Figure 4. Sample of documentation of irAE symptoms in PRO surveys

Conclusion

- 73 symptoms of irAEs mapped onto 9 body systems, 35 of irAEs and 9 irAE types
- 21 surveys and 5 terminologies examined
- No existing PRO survey is inclusive of all potential irAE symptoms
- We did not examine irAE signs (e.g., lab values) since this is intended to develop a PRO scale to drive the CDS
- Future work: Examining additional terminologies, ontologies

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