# Management of Immune Related Adverse Events

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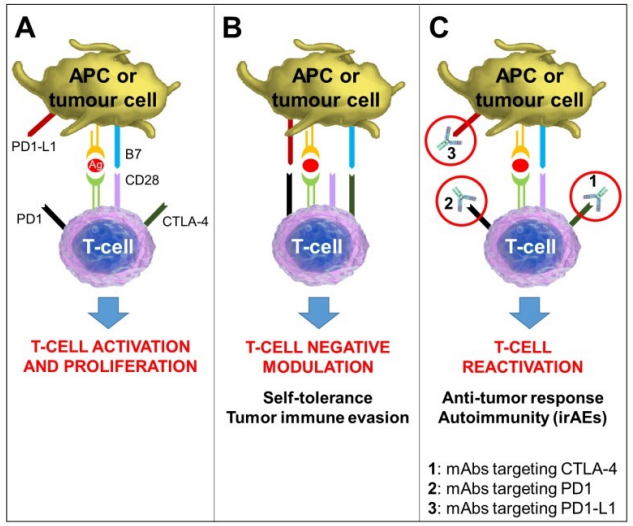
# Objectives

- Review overall goals of Immune Checkpoint Inhibitors (ICPs)
- Discuss common toxicities of ICPs, highlighting common and most dangerous.
- Demonstrate basic foundational treatment approaches using a case study.
- Review resources for the clinician.

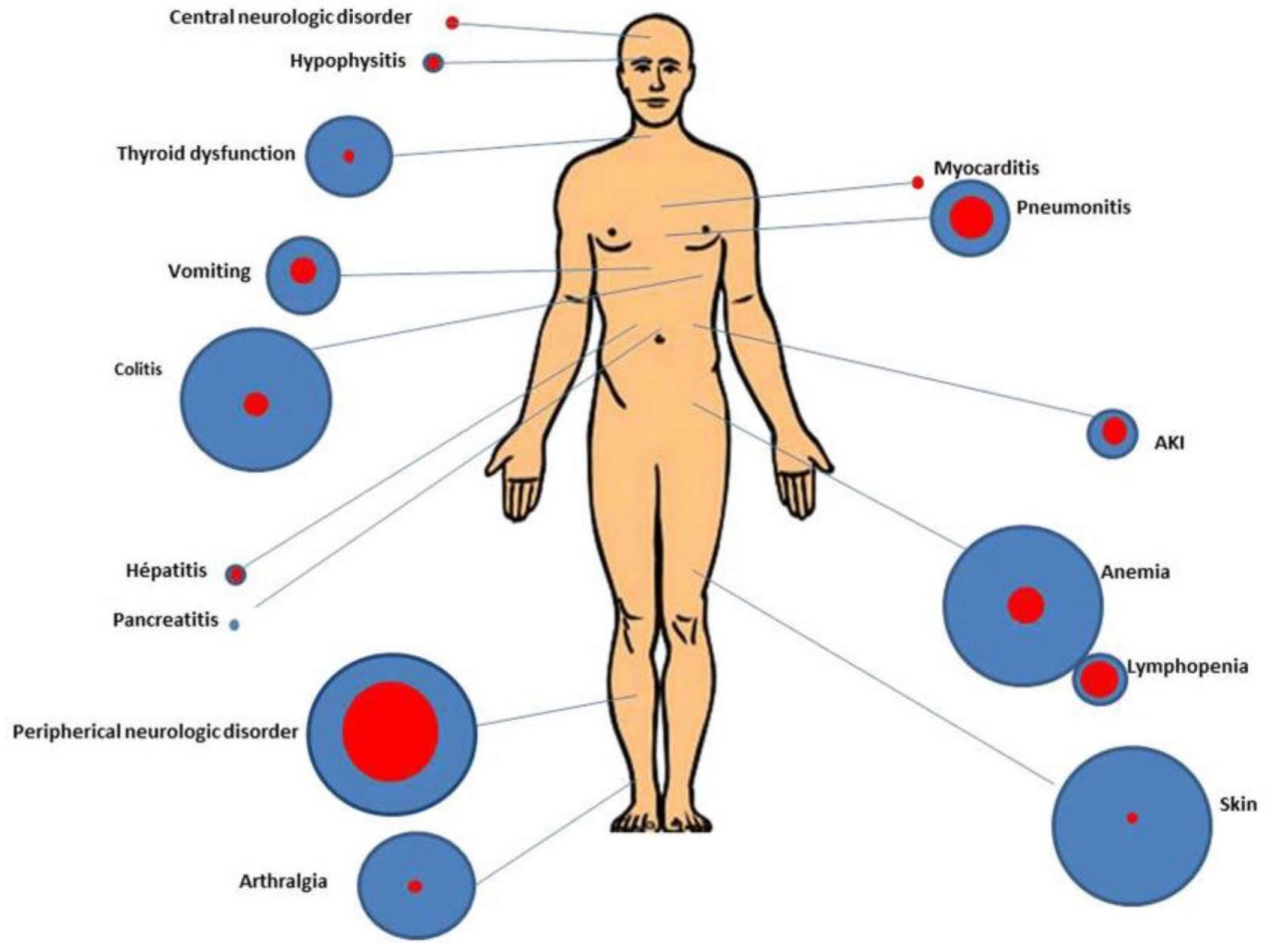
# Brief History of Immune Checkpoint Inhibitors

- Cancer immune therapies target the immune system to encourage an anti-tumor response
- One class of immune therapy is the Immune Checkpoint Inhibitor (ICI)
  - Accounts for 60% of all cancer immunotherapy
  - Block immune checkpoints hijacked by tumors that try an evade the immune surveillance
  - Key examples are CTLA-4, PD-1 pathways
- First ICI was ipilimumab for the treatment of metastatic melanoma in 2011
- Increasing usage, expanded indications = ICI-associated irAEs
- Side effects are quite different than chemotherapy or radiation side effects




https://www.ncbi.nlm.nih.gov/books/NBK519842/figure/neuroendo_hypophysi.F4/

# Variability of irAEs on Organ Systems




https://www.cancer.gov/news-events/cancer-currents-blog/2019/cancer-immunotherapy-investigating-side-effects

# Case Study

- **Ian Mena is a 75 YoM diagnosed with metastatic adenocarcinoma of the lung (Stage T4N3M1c ) with metastasis to the brain, bone. Treatment plan by current oncologist was CARBOplatin / PEMEtrexed / Pembrolizumab. However, molecular testing showed high PDL1 at 90%, therefore the treatment plan was changed to Cemiplimab with the goal of control for metastatic/recurrent 1st line therapy**

- **After first infusion, 3 weeks later, he had improved breathing, endurance, less fatigue. Treatment continued every 3 weeks, and after cycle 4 he experienced some diarrhea, which resolved quickly. Cycle 5 was delayed. After cycle 5, he experienced a rash, which improved after a few days. Thyroid studies obtained at visits remained stable. He proceeded with cycle 6, and after cycle 7 developed a brief macular rash, which resolved in a few days. Cycle 8 and 9 were uneventful.**

- **Scan to determine treatment response at 6 months indicated good response to therapy. (Further decrease in size of right lower lobe mass  measuring 2.7 x 2.2 cm, previously 3.8 x 2.8 cm. Continued central area of hypodensity/nonenhancement. Further decrease in right hilar involvement. Slight decrease in size of right lower lobe satellite nodule measuring 3 mm, previously 4 mm. Additional scattered small pulmonary nodules are stable. Prominent right hilar node is stable. Pre-existing mediastinal nodes have decreased in size, now small. Stable sclerotic lesion involving the sternum consistent with metastases/healing metastases).**

# Case study continued

- **After cycle 11, he presented to clinic with hypoglycemia (glucose level at 44). Labs were ordered such as insulin antibodies assay, C peptide, and serum insulin levels for further evaluation of hypoglycemia. The concern was for potential immunotherapy-induced hyperinsulinemia. Referral was placed for endocrinology.**

- **Endocrinology appointment consult was for the problem of hyperinsulinemia. Labs did indicate an elevated c-peptide with no further hypoglycemia by lab or by symptom. A1c is in the middle of normal range. Clinical opinion was that the elevated c-peptide could have been caused by the stress of chemo or treatment. He continued to be monitored by endocrinology and was screened for hypothyroidism, because he was at risk for autoimmune thyroiditis.**

- **One year imaging indicated continued response and stable disease (MRI Brain showed interval resolution of previously visualized right precentral gyrus lesion. No new lesions are identified. Minimal decrease in size of the right lower lobe opacity consistent with resolving tumor. No apparent change in mediastinal nodal tissue or lung nodules. No newly apparent sites of tumor in the chest, abdomen or pelvis)**

- **Three weeks after cycle 14, he is reported new and sudden constant diarrhea, ongoing for 10 days. At the most severe, the diarrhea episodes were as frequent as six times a day. No abdominal cramping. No associated blood in the stool.**

# Case study 3

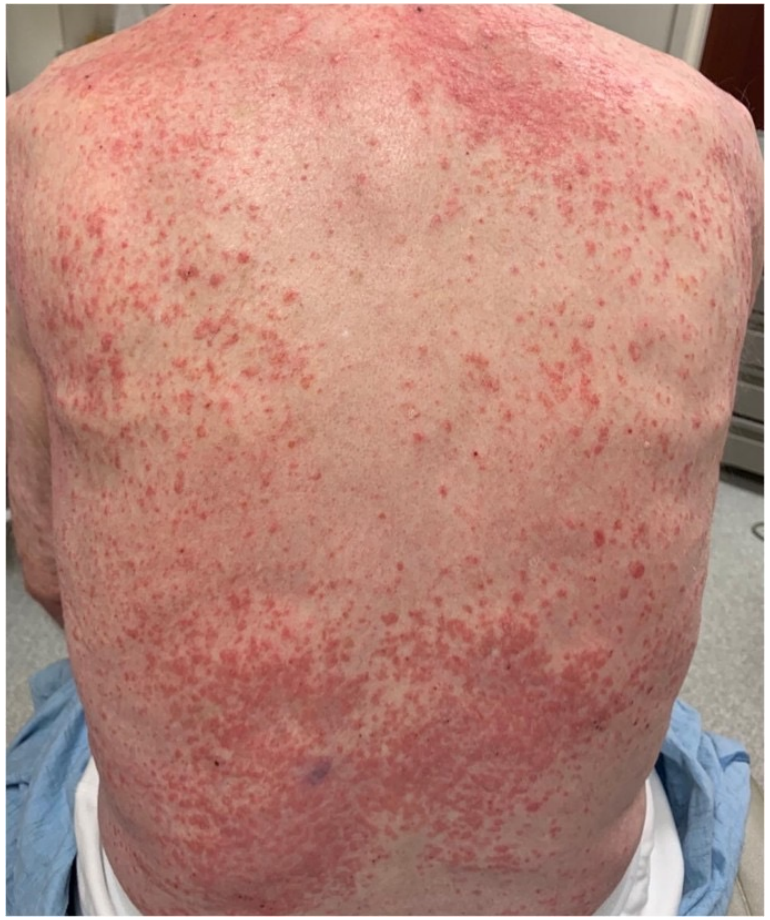
- **Patient was referred to gastroenterology, immune therapy was held.  Findings from the colonoscopy indicated colitis from the immunotherapy. Steroids were initiated (prednisone 40 mg daily) with PPI support, and Loperamide for symptom management (4 mg at first diarrhea, followed by 2 mg after each loose stool for a total of 16 mg/day).**

- **The patient then underwent taper with sulfamethoxazole-trimethoprim and PPI as symptoms improved. No admission was needed.**

# Skin irAEs

- Median time: 4 weeks, range (2-150 weeks)
- Symptoms: inflammatory dermatitis, with or without itching, new or worsening

  skin lesions, macules, papules or plaques with loss of skin pigmentation
- More common with CTLA-4 inhibitors, but can occur with PD-1 therapy
- Early engagement with a dermatologist to guide evidence-based specialty care
- Many can be treated without permanent discontinuation of therapy
- Treatment of skin is based on CTCAE grading and severity
  - Topical emollients/corticosteroids, antihistamines, phototherapy, oral prednisone or IV methypred/admission
- Cutaneous irAes may be surrogate for clinical benefit, however discontinuation is needed for
  - Bullous dermatosis, Severe Cutaneous Adverse Reactions (SCAR), Stevens-Johnson Syndrome

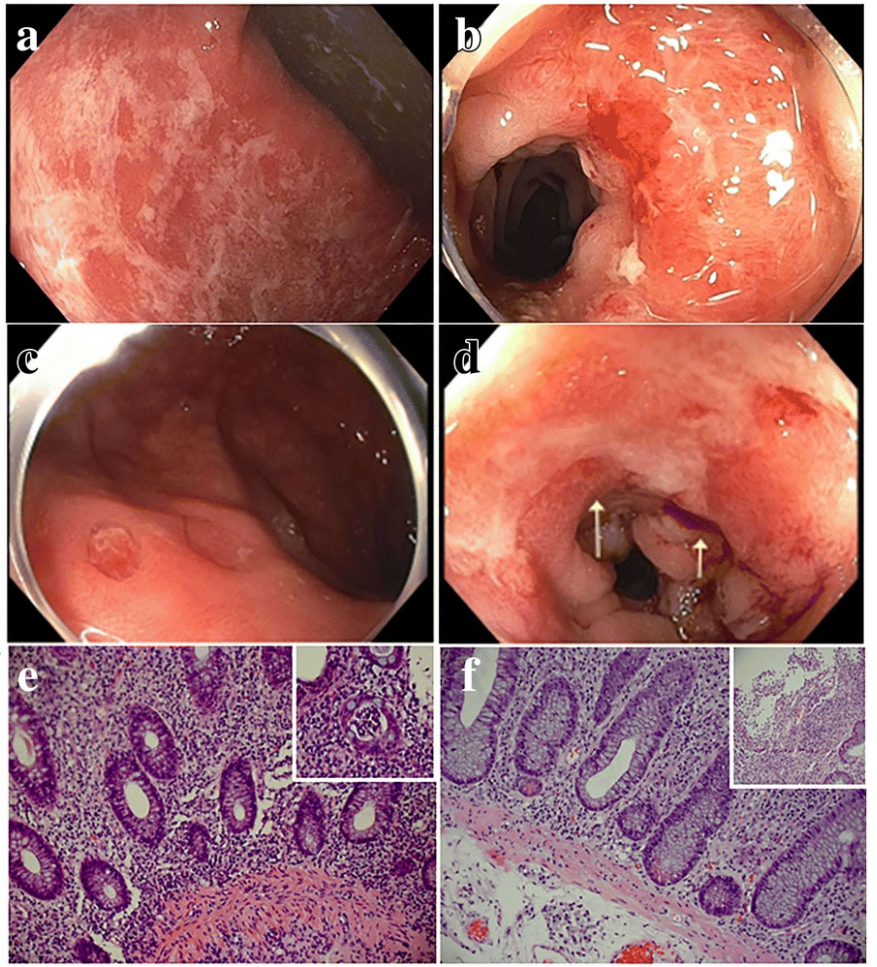




https://www.google.com/search?q=immune+related+skin+reactions+from+CTLA4&rlz=1C1GCEB_enUS920US920&source=lnms&tbm=isch&sa=X&ved=2ahUKEwi4i6ub3N34AhVxDkQIHSEbCiAQ_AUoAXoECAEQAw&biw=1920&bih=937&dpr=1#imgrc=Adl-L0vs1uXj_M

# Gastrointestinal irAEs

- Presentation can be colitis, hepatitis, gastritis, enterocolitis, pancreatitis.
- Median time: 6 weeks (range of 1-107.5 weeks)
- Symptoms: blood and mucus in stool can occur
- Common with incidence of diarrhea 54% in patients treated with CTLA-4, more if in combination with PD-1; PD1 incidence is less than 19%
- Early engagement with a gastroenterologist, endoscopic evaluation
- NSAIDs may increase enterocolitis
- Grade 2 or higher with colitis symptoms, corticosteroid 1-2mg/kg is first line

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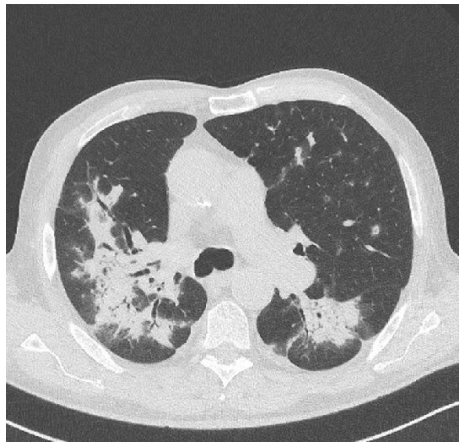
# Pulmonary irAEs: Pneumonitis

- Uncommon but potentially serious toxicity
- Incidence in anti-PD-1/PD-L1 from 0-10% and < 5% in anti-CTLA-4 with higher incidence in combination
- Higher incidence in NSCLC in some studies as compared to melanoma and renal cell
- Common findings on chest imaging: ground glass opacities or patchy infiltrates, predominately in lower lobes
- Corticosteroids is recommended as initial treatment, however 48-hour window before Steroid refractory (infliximab, MMF, IVIG, cyclophosphamide)
- Caveat: immune-related pulmonary reactions may mimic disease progression on imaging and exam, Biopsy can confirm diagnosis

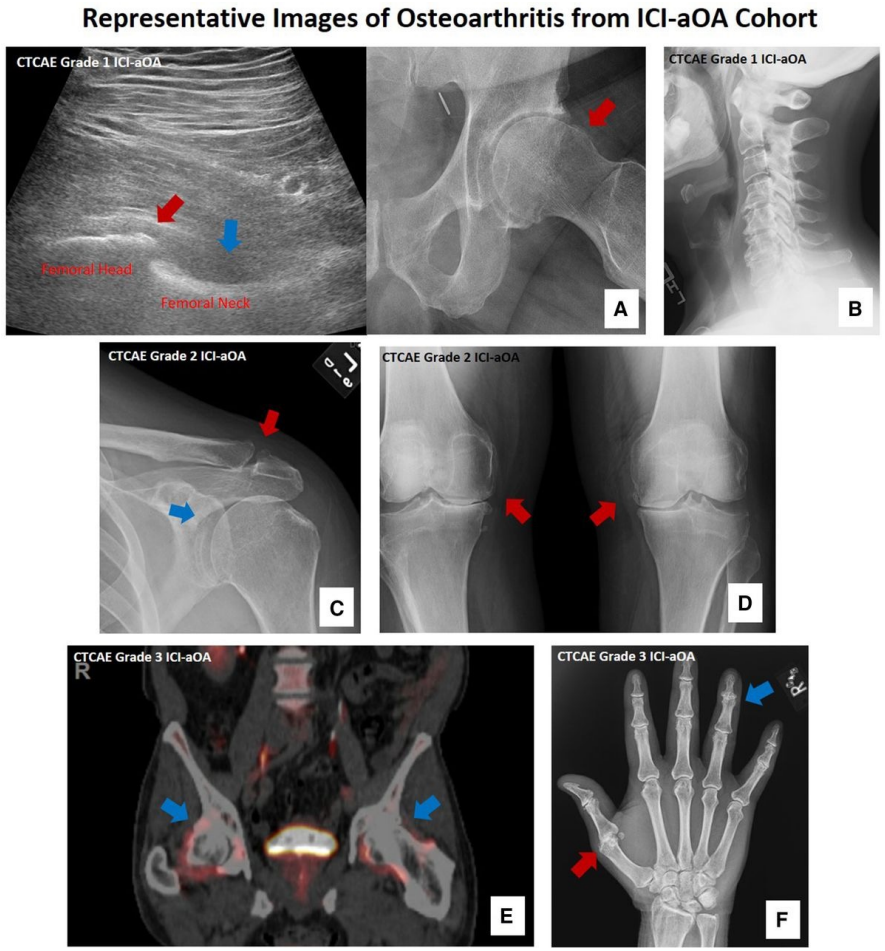


https://www.google.com/search?q=IPCi-related+pneumonitis&rlz=1C1GCEB_enUS920US920&source=lnms&tbm=isch&sa=X&ved=2ahUKEwingPi9ku_4AhW2KkQIHQRHDKgQ_AUoAnoECAEQBA&biw=1920&bih=937&dpr=1#imgrc=ngfflLjRdaGN4M

# Endocrine irAEs

- Median time to onset is 14.5 weeks with a range of 1.5-130 weeks
- Incidence 10% in checkpoint inhibitors
- Presenting symptoms related to immunotherapy induced endocrinopathies may include
    - Pituitary swelling: headache, visual changes,
    - Hypothyroidism: cold intolerance, dry skin, constipation, weight gain, fatigue,
    - Thyrotoxicosis: palpitations, heat intolerance, insomnia, frequent bowel movements, weight loss,
    - Adrenal insufficiency: nausea, vomiting, abdominal pain, syncope, profound fatigue,
    - Diabetes: polyuria, polydipsia, nausea vomiting abdominal pain, and /or visual blurring.
- Challenges:
    - Diagnosis as the site of inflammation as secondary versus primary for treatment (pituitary versus adrenal).
    - Consult to endocrinology is critical for appropriate treatment.
    - In some cases, organ failure is managed with hormone replacement rather than immunosuppressants

# Musculoskeletal irAEs




- Median time to onset is 38 weeks (range 1-127 weeks)
- Common presenting symptoms:
  - joint pain with swelling and/or
  - inflammatory symptoms such as stiffness after inactivity or in the morning (more than 30 minutes)
- 40% incidence of arthralgia and myalgia in clinical trials
- Possible rare and concerning symptoms may be conjunctivitis/urethritis, sicca syndrome, myositis which can lead to fulminant necrotizing course which can involve the myocardium.

https://www.google.com/search?q=osteoarthritis+related+to+immune+checkpoint+inhibitors&rlz=1C1GCEB_enUS920US920&source=lnms&tbm=isch&sa=X&ved=2ahUKEwjOh_3TnO_4AhXNDkQIHVSIAb4Q_AUoAnoECAEQBA&biw=1920&bih=937&dpr=1#imgrc=6I64jgV-C8NfvM

# Neurological irAEs

- Median time to onset is 4 weeks (range 1-68 weeks).
- Symptoms based on the various neurological syndrome: Myasthenia Gravis, Guillain-Barre syndrome, Autonomic neuropathy, Aseptic Meningitis, Encephalitis
- Incidence: reported 1-12%; grade 3-4 toxicities < 1%
- Initial work-up should rule out central nervous system progression of cancer, seizure activity, infection, and metabolic derangements as causes of neurologic symptoms.
- Diagnostic work-up should include
    - MRI brain/and or spine imaging with and without contrast and
    - CSF analysis including cytology to rule or leptomeningeal metastasis

# Overall Management Principles

- Treatment depends on the organ affected, and grade of toxicity
    - Typically, CTCAE grade 1 irAEs do not require interventional treatment
    - Grade 2: stop until symptoms abate, can consider steroids
    - Grade 3 and 4 should receive steroids
- Overall Therapeutic approach
    - Glucocorticoids: mainstay
    - Hormonal replacement
    - Immunosuppressive agents: (mycophenolate, cyclophosphamide, hydroxychloroquine, methotrexate, tacrolimus, cyclosporine, sulfasalazine)
    - IVIG and plasma exchange
    - Monoclonal antibodies: infliximab (TNF-inhibitor)

# Key Take-Away Points

- Follow the **Common Terminology Criteria for Adverse Events** (CTCAE) for grading irAes
- irAEs can be life-threatening, and high index of suspicion of new symptoms
- Patient and caregivers need timely up to date education
- Continue treatment with close monitoring at Grade 1 level except neurologic, hematologic, and cardiac toxicities
- Consider holding for most Grade 2 toxicities, and Grade 4 warrant discontinuation
- Combination of more than one immunotherapy medication can intensify irAEs
- Do not delay to involve a consultant: dermatologist, endocrinologist, gastroenterologist

# ASCO Guidelines on Phone APP

**ASCO Guidelines** 12+

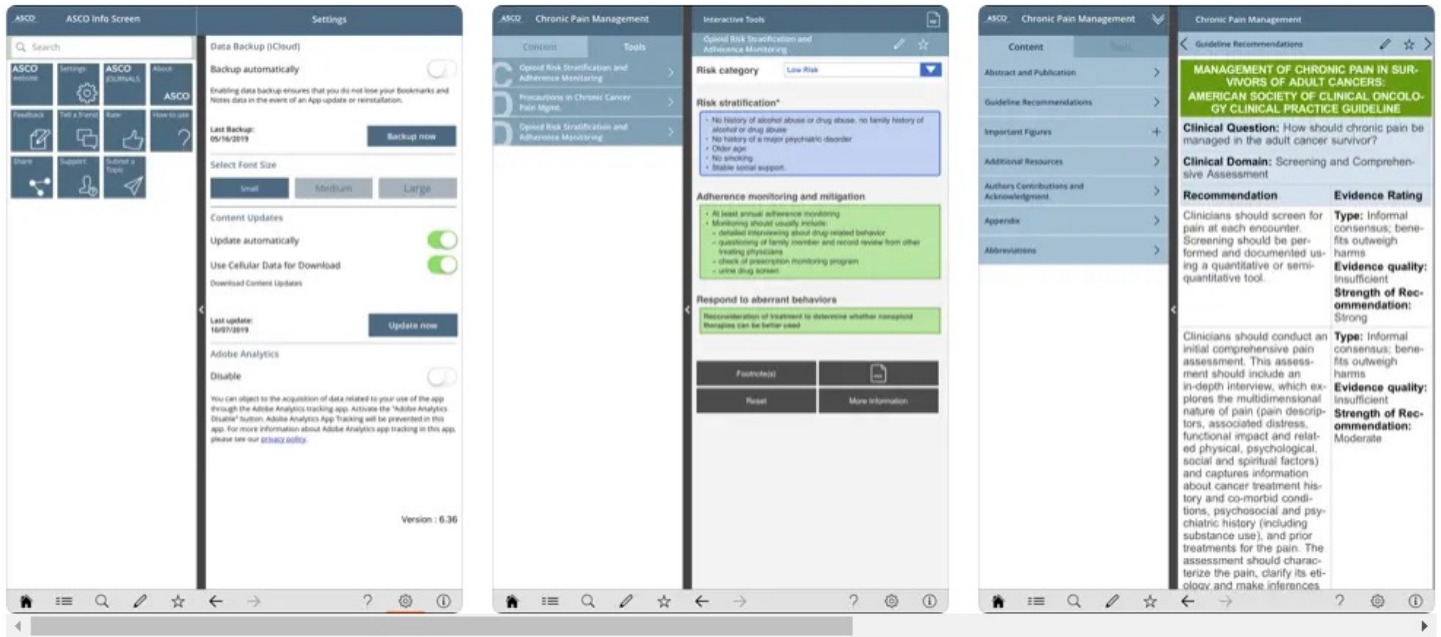
ASCO

Designed for iPad

4.1 • 11 Ratings

Free

**Screenshots** iPad iPhone



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# Thank you

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