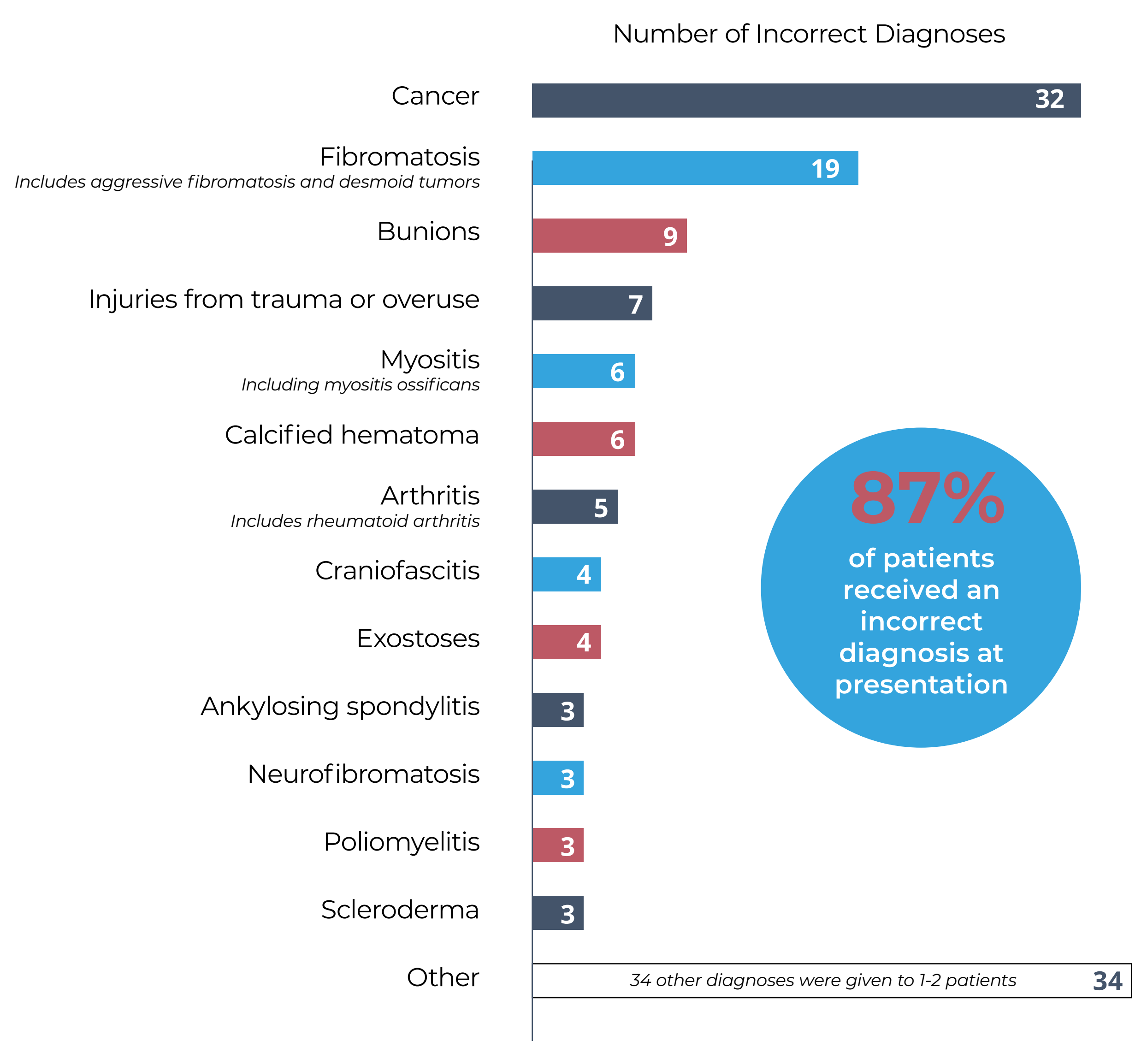
Prevent the Consequences of Incorrect or Delayed Diagnosis of Fibrodysplasia Ossificans Progressiva (FOP)

Clinical Pearls: Diagnosing FOP

History and physical examination may inform or make a diagnosis	Genetic testing confirms a diagnosis	Misdiagnosis is common and can cause harm
Look for great toe abnormality (seen in 100% of newborns with classic FOP).	A recurrent mutation in the *ACVR1* gene is seen in patients with classic FOP: c.617G>A (p.R206H).	87% of patients with FOP are given an incorrect initial diagnosis and unnecessary investigations can be harmful.

Certain Incorrect Diagnoses Are Commonly Given to Patients With FOP



N= 138 patients with FOP

Why Timely Medical Diagnosis and Management Are Critical

Prevents harm

- Heterotopic ossification (HO) can result from intramuscular (IM) injection immunization sites and other IM injections
- HO can result from unnecessary biopsies and invasive surgery
- Unnecessary distress and treatment for other diagnosis, such as cancer, can occur
- Developmental delays can occur, due to undiagnosed hearing deficits

Improves management

- Timely treatment during flare-ups can reduce inflammation and subsquent HO
- Reduces HO due to dental procedures and anesthesia
- Minimizes risk of trauma and may prevent subsequent HO

Things to Do (*and* Avoid) When Making a Diagnosis of FOP

Do Consider the History and Physical Examination

- Can make a diagnosis
- Look for great toe abnormality (hallux valgus), seen at birth in 100% of patients with classic FOP
- If present, be cautious about invasive investigations (eg, biopsy)

Image courtesy of: Edna E. Mancilla, MD

Do Genetic Testing

Confirms a diagnosis

Gene is Activin A receptor type 1 (*ACVR1*, also called *ALK2*)

Patients with classic FOP have a recurrent *ACVR1* mutation: c.617G>A (p.R206H)

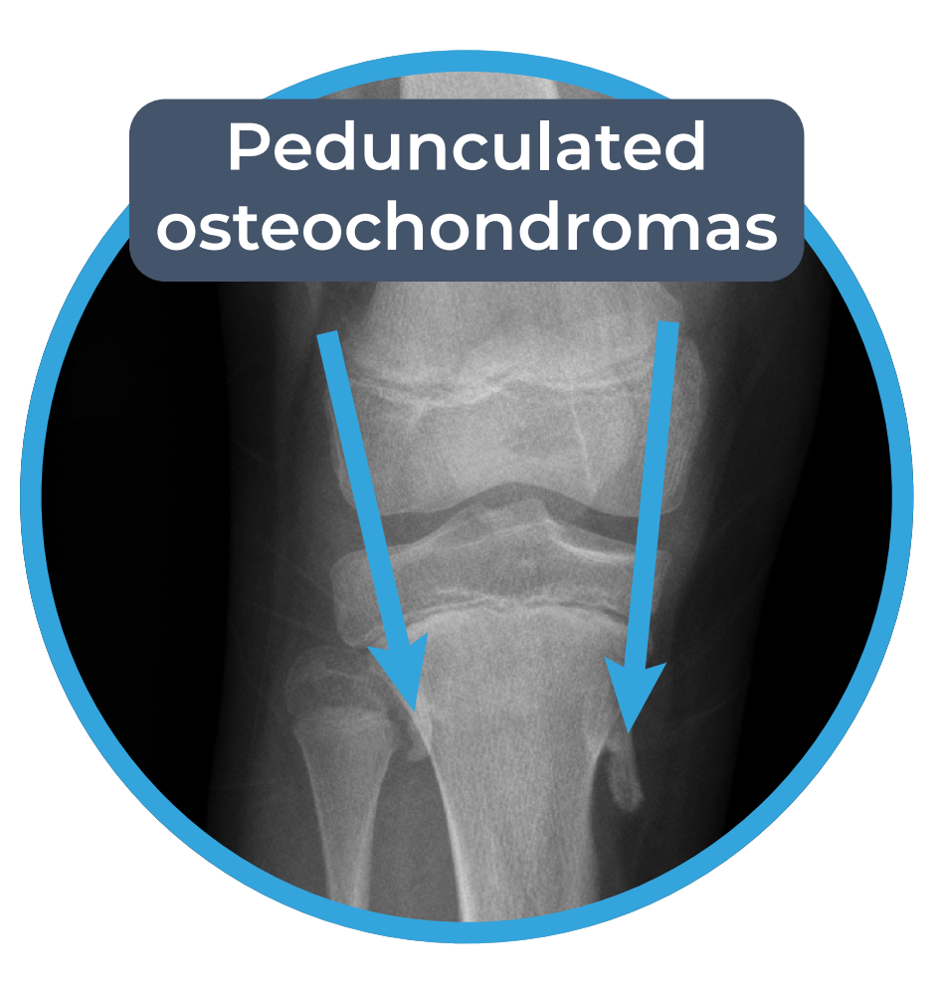
- Found in sporadic and familial cases of classic FOP. Patients with atypical FOP have varying *ACVR1* mutations
- Most cases are de novo (sporadic); few familial cases reported

Where available, genetic testing can confirm FOP in patients with clinical suspicion.

Malformation of great toes with or without soft tissue swelling

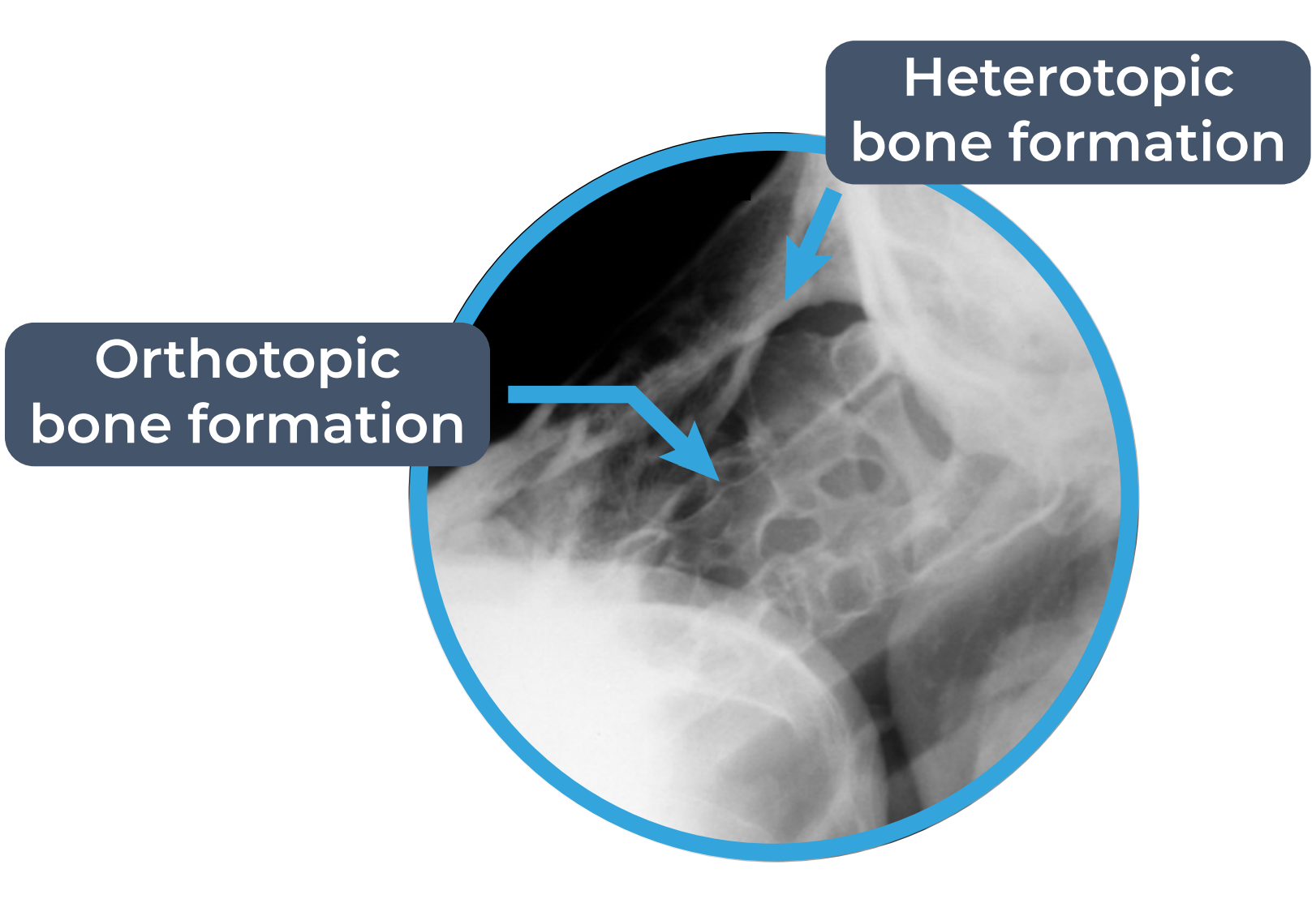
Can identify at-risk family members

Do Consider Imaging Studies



Osteochondromas seen in ≈90% of patients with FOP

Image courtesy of: Edna E. Mancilla, MD



Cervical spine abnormalities seen in ≈80% of patients with FOP

Image from Ref #1

Routine laboratory studies are not helpful to diagnose FOP

- For example, bone metabolism studies, alkaline phosphatase, inflammatory markers, erythrocyte sedimentation rate (ESR), and C-reactive protein (CRP) do not contribute to diagnosis
- Bone metabolism studies likely to be normal
- Alkaline phosphatase, inflammatory markers, ESR, and CRP may be elevated during a flare-up

Avoid biopsies, arterial puncture, IM injections, and anesthetic procedures

- Can cause HO development in patients with FOP (advanced HO formation shown below)

Image from Ref #3

Summary

Prevent incorrect or delayed diagnosis of FOP to avoid serious consequences.

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References

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3. Pignolo RJ et al. *Orphanet J Rare Dis*. 2011;6:80.

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