No Brainer: Why Melorheostosis is Ripe for Drug Discovery

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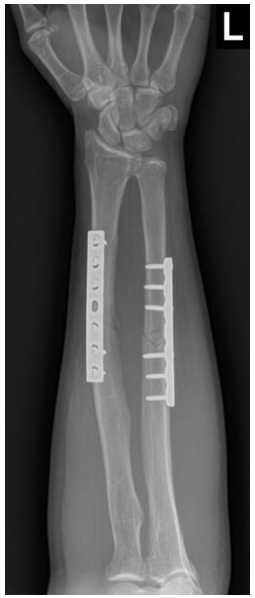

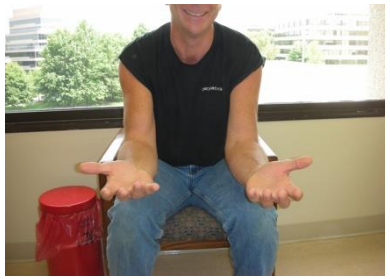

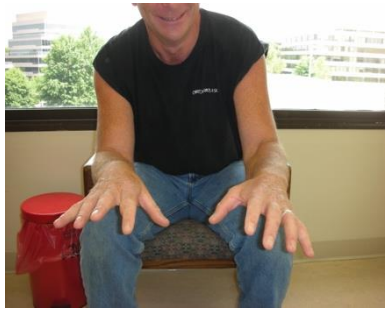

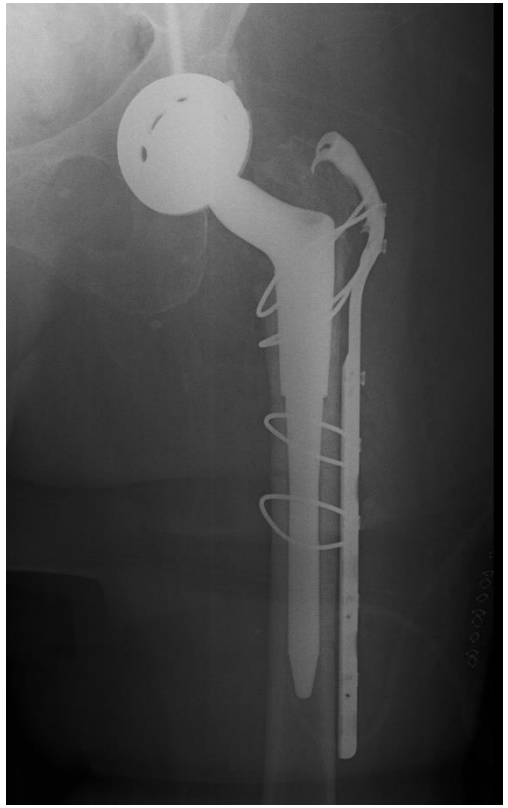

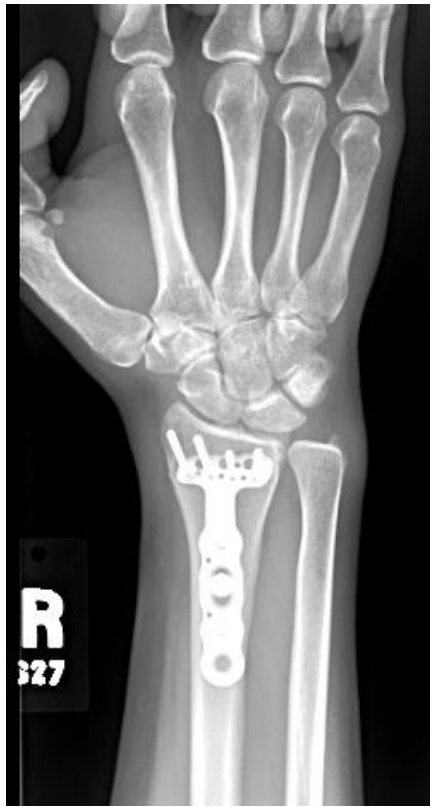

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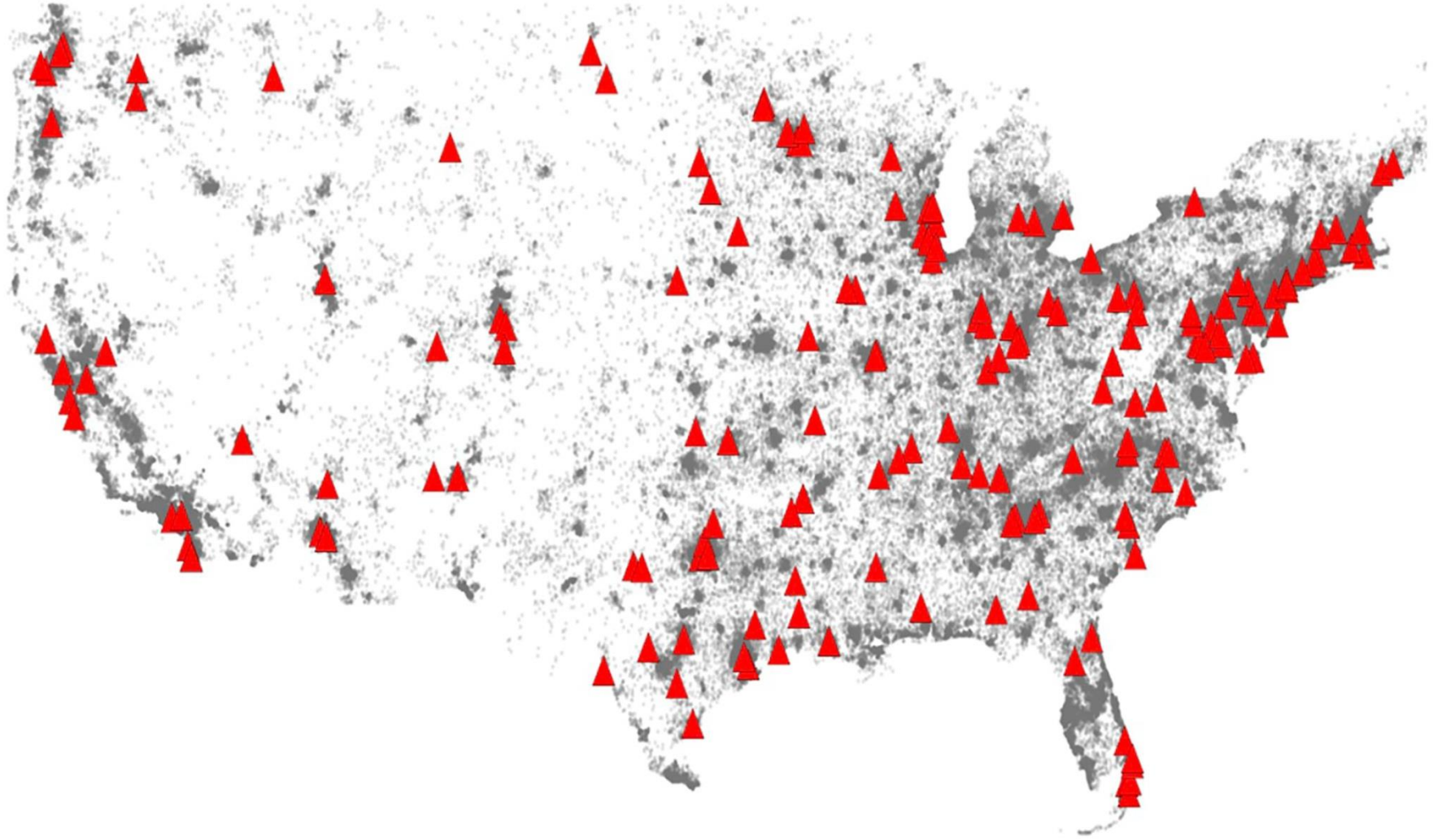
Melorheostosis is an unusually de-risked rare-disease for drug discovery

- Motivated, connected patient base
- Chronic disease burden
- Favorable biology
- Pragmatic measurable endpoints
- FDA Pathways materially shorten time to success

Meaningful prevalence: >300 people in US

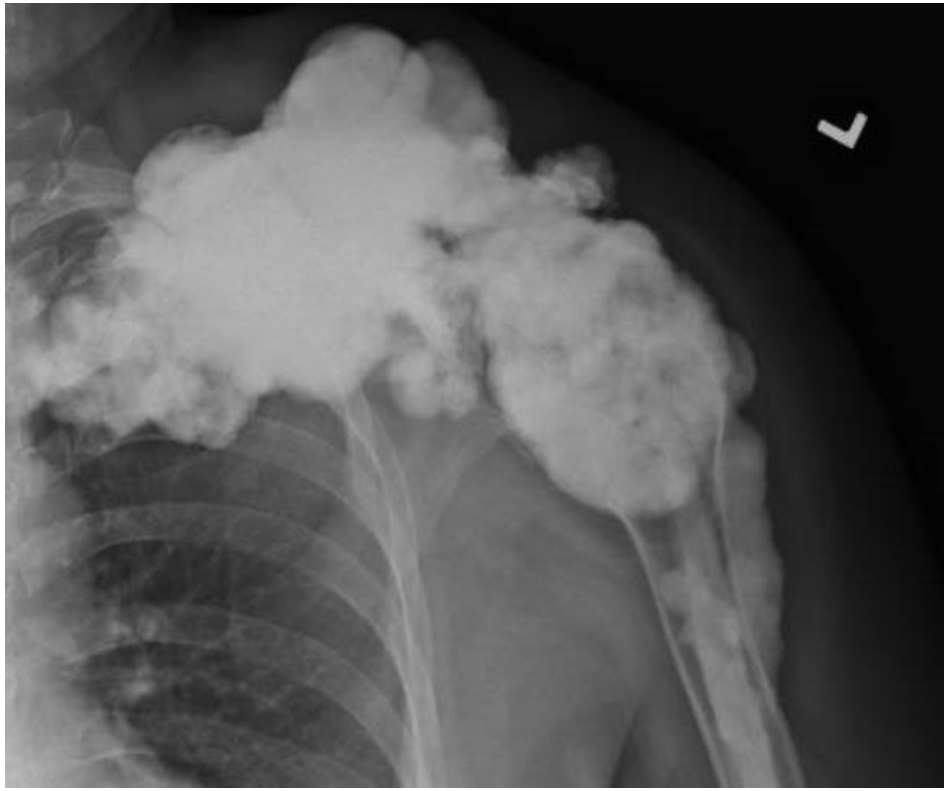


Jha et al Bone 2018

Engaged, responsive patient base

Long-term treatment model

- Age 18 to 80, average 45
- Melorheostosis can worsen over time and commonly involves chronic pain, stiffness, limited range of motion.
- Supports a **long-term treatment model** (maintenance, flare control, adjuncts), not a one-and-done.
- Durable burden → durable treatment value



Rare-disease programs can become mainstream (Option Value)

- **Imatinib (Gleevec)**: first approved for **CML** and then expanded across multiple additional cancers/indications over time.
- **RITUXAN (rituximab)** Oncology start (NHL) → autoimmune indications (e.g., RA) and beyond.
- **Botulinum toxin**: began with therapeutic indications (strabismus/blepharospasm) and later expanded *dramatically* into aesthetic and other uses.

Regulatory tailwinds for rare diseases

Orphan Drug Designation

Incentives that reduce risk and improve ROI:

- Tax credits for qualified clinical testing
- Exemption from certain FDA user fees
- Potential 7-year market exclusivity after approval
- Clear eligibility (<200,000 patients in the U.S.)

Bottom line: fewer patients needed, more sponsor support, and stronger exclusivity

Complementary FDA tools

Fast Track	more frequent FDA interaction
Breakthrough Therapy	intensive guidance for substantial improvement
Accelerated Approval	earlier approval with confirmatory studies
Priority Review	shorter review clock for eligible applications

Sources: FDA “Designating an Orphan Product” page; FDA exclusivities explainer (orphan exclusivity = 7 years).

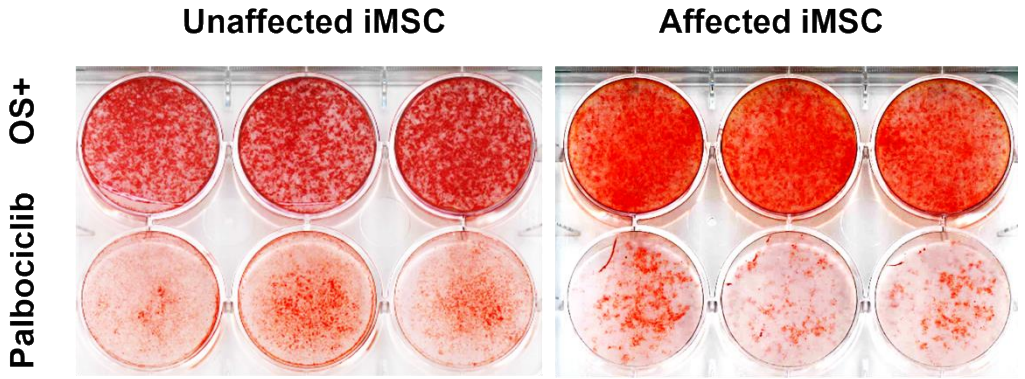
The Biology is Favorable

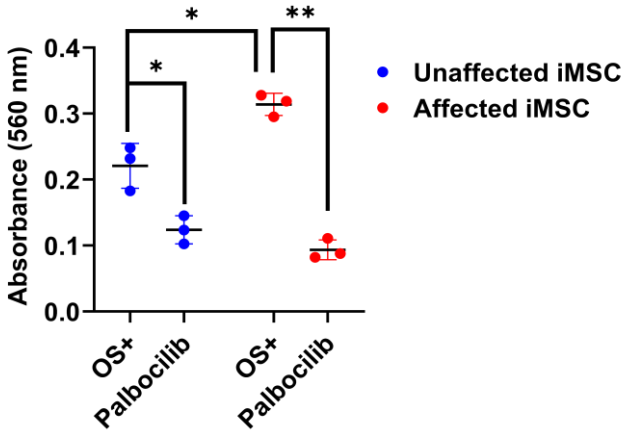
- Dramatic phenotype, but only **0.1% to 9%** of cells are affected
- The disease is mosaic and focal—mutations are found in affected tissue but not unaffected tissue—supporting a model where targeted modulation can have outsized benefit
- Defined pathways to interrogate
  - MEK/ERK, TGF-β/SMAD

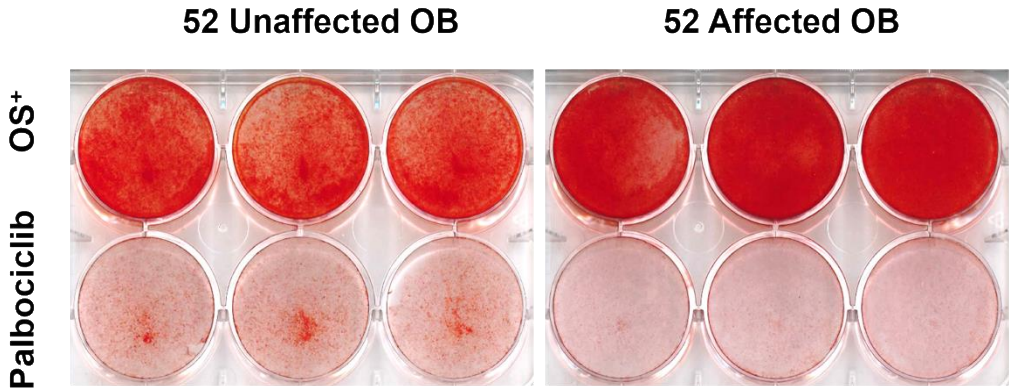
The Biology is Favorable

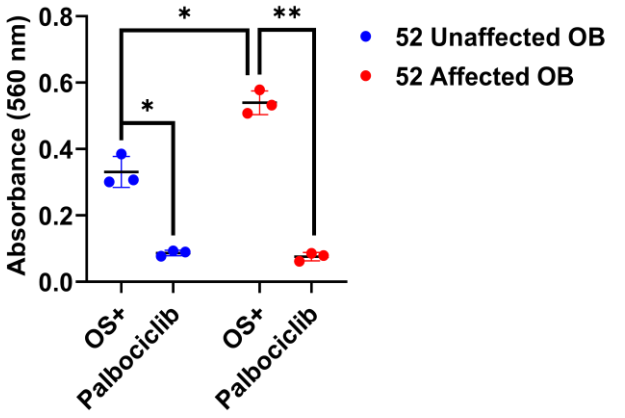
- Just 5 days of palbociclib reduces mineralization

- Maity, Sarvanan et al JBMR 2026



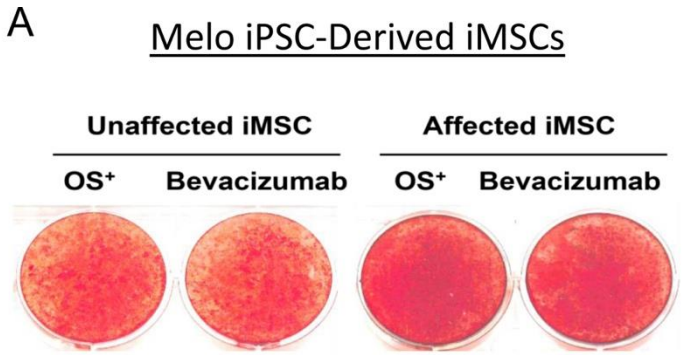


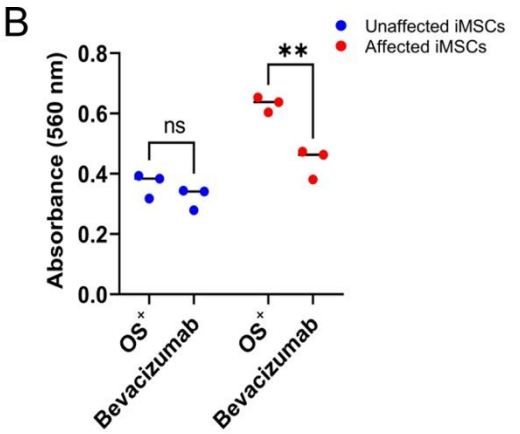


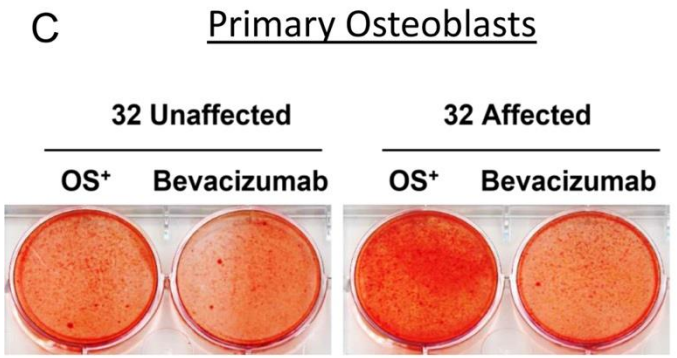


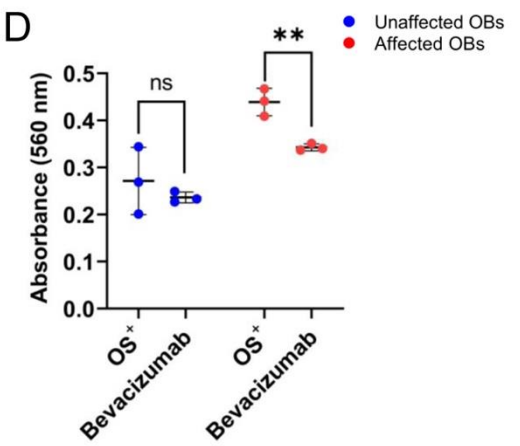
The Biology is Favorable

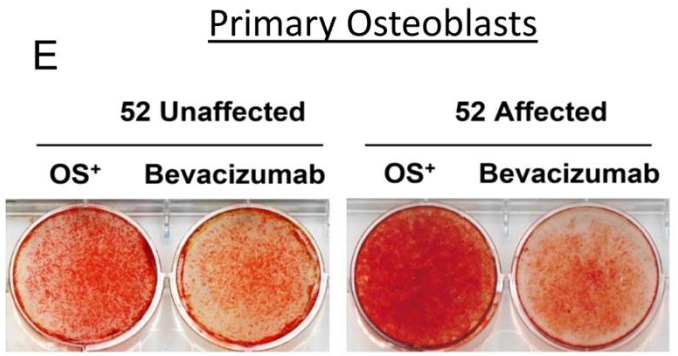
- VEGF inhibition decreases mineralization in vitro
- Albritton-King et al JBMR 2023

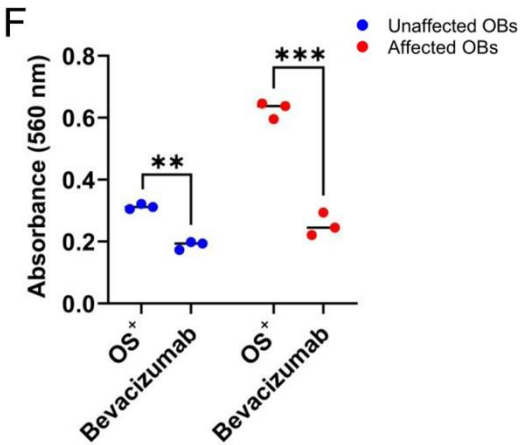






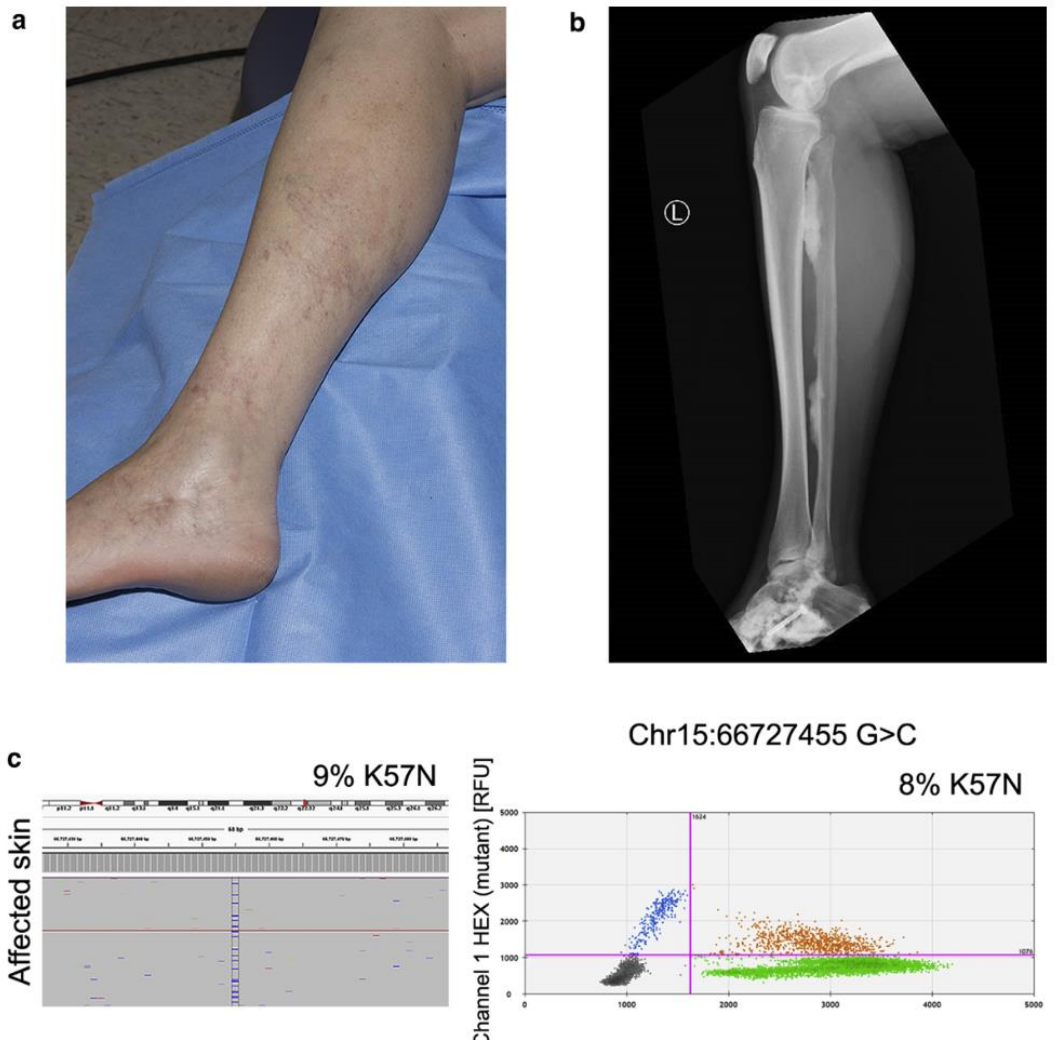






The Clinical Picture is Favorable

- In a recent online survey from the patient organization, 60% of patients would enroll in a drug trial even in there was low chance of benefit
- NaF bone scan serves as a biomarker
- A mild reduction in pain → major positive outcome



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