Management of Aggressive Fibromatosis (Desmoid Tumors)

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Introduction & Background

- **Definition:**
  - Rare, monoclonal fibroblastic proliferation (incidence: 5–6 cases/million/year).
  - Locally aggressive, non-metastatic, but high recurrence risk (25–77%).
- **Clinical Behavior:**
  - Unpredictable course: Spontaneous regression (28–50%), progression, or stability.
  - Infiltrates surrounding tissues → organ dysfunction
  - Compromises quality of life/life expectancy

- **Etiology:**
  - Sporadic (90–95%) or FAP-associated (5–10%).
  - Driven by *CTNNB1* mutations (β-catenin pathway) or *APC* mutations.
  - Trauma, hormonal factors (estrogen)
- **Paradigm Shift:**
  - Surgery no longer first-line; **active surveillance** preferred for asymptomatic patients.

Pathology & Molecular Genetics

- **Key Pathways:**
  - Wnt/β-catenin dysregulation → nuclear accumulation → uncontrolled proliferation.
  - Mutations: *CTNNB1* (exon 3; S45F, T41A) or *APC* (FAP patients).
- **Diagnostic Workup:**
  - **Biopsy** confirmed by expert soft-tissue pathologist.
  - **Molecular testing:**
    - *CTNNB1* mutation → sporadic DT.
    - Wild-type *CTNNB1* + intra-abdominal tumor → screen for FAP (colonoscopy/germline testing).
- **Imaging:**
  - MRI/CT: Heterogeneous T2 hyperintensity, mild-moderate contrast enhancement

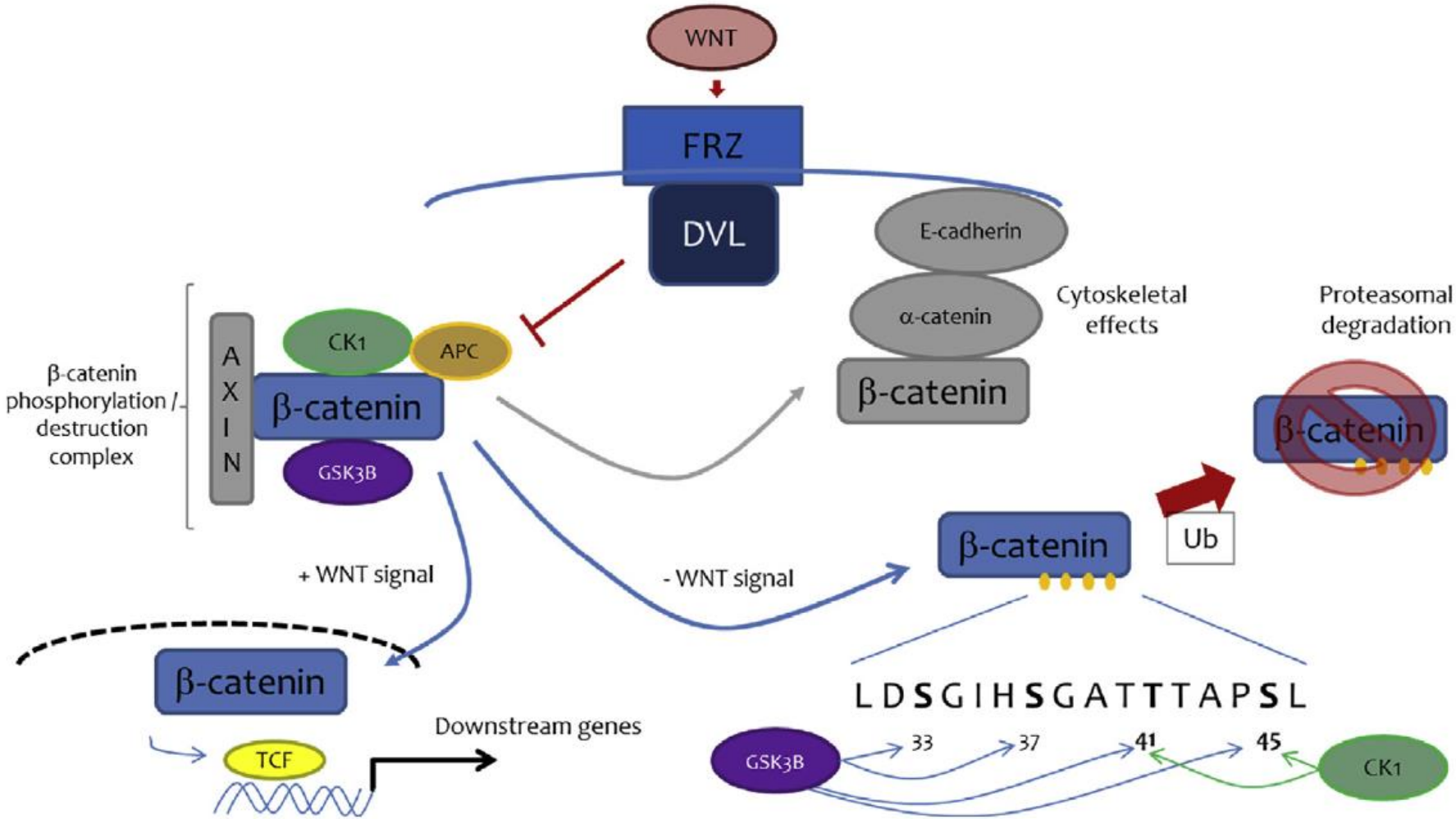


Fig. 2. Either *APC* loss or *CTNNB1* mutation can lead to DT development.

Clinical Presentation & Diagnosis

- **Anatomic Sites:**
  - Extra-abdominal (60%), abdominal wall (25%), intra-abdominal (8–15%).
- **Symptoms:**
  - Pain, functional impairment, mass effect (e.g., bowel obstruction in mesenteric DT).
- **Diagnostic Criteria:**
  - Histopathology + imaging + molecular testing.
  - **Exclude:** Sarcoma, Gardner syndrome (FAP screening if intra-abdominal).

Treatment Approach Overview

- **First-Line: Active Surveillance**
  - **Indications:** Asymptomatic, non-life-threatening tumors.
  - **Monitoring:** MRI/CT every 3–6 months; intervene only if progression/symptoms.
  - **Outcomes:** 50% avoid active treatment; spontaneous regression in 20–50%.
- **When to Treat:**
  - Symptomatic progression, threat to vital organs/function, or rapid growth.

Indications for Active Treatment

Key Factors:

Factor	Favor Observation	Favor Active Treatment
Symptoms	Absent/mild	Severe pain/functional loss
Location	Abdominal wall	Head/neck, mesenteric, chest
Growth Rate	Stable/slow	Rapid progression
FAP Status	Sporadic	FAP-associated (aggressive)

Systemic Therapy Options

- **Goals:** Symptom control, tumor stabilization, avoid mutilating surgery.
- **Hierarchy of Therapies:**
  - **TKIs** (sorafenib, pazopanib, imatinib): First-line systemic therapy.
  - **Chemotherapy:** Low-dose MTX/vinblastine or liposomal doxorubicin.
  - **Hormonal/NSAIDs:** Limited evidence (tamoxifen/sulindac).
- **Response Metrics:**
  - RECIST may underestimate benefit; prioritize symptom relief/PFS.

Tyrosine Kinase Inhibitors (TKIs) in Adults

- **Mechanism:** Block PDGFR, VEGFR, KIT, RAF → inhibit proliferation/angiogenesis.
- **Key Agents:**

Drug	Response Rate	PFS (12mo)	Toxicities
Sorafenib	33%	89%	HFSR, hypertension, fatigue
Pazopanib	37%	86%	Hepatotoxicity, hypertension
Imatinib	6–19%	59–67%	Edema, cytopenias, GI upset

- **Evidence:**
  - Sorafenib: Phase III RCT (HR 0.13 for progression vs. placebo).
  - Pazopanib: Phase II DESMOPAZ trial (82% 6-month non-progression).

TKIs in Pediatric Patients

- **Rationale:** Oral administration, lower acute toxicity vs. chemotherapy.

Dosing & Monitoring:

Drug	Pediatric Dosing	Monitoring
Imatinib	200 mg/m² BID	CBC, LFTs, growth parameters
Sorafenib	200–400 mg/day (titrated)	BP, skin (HFSR), LFTs
Pazopanib	600–800 mg/day (AYA)	LFTs, thyroid, BP, urinalysis

- **Outcomes:**
  - Disease stabilization > shrinkage; symptom relief in 70–80%.
  - Growth/pubertal development surveillance critical.

Comparison of TKIs for Pediatric Use

Parameter	Imatinib	Sorafenib	Pazopanib
Best Evidence	Adult Phase II	Adult RCT	Adult/AYA Phase II
Response Rate	6–19%	33%	37%
Key Toxicities	Edema, cytopenias	HFSR, hypertension	Hepatotoxicity
Pediatric Use	Established	Emerging	Emerging
Monitoring	CBC, LFTs	BP, skin, LFTs	LFTs, thyroid, BP

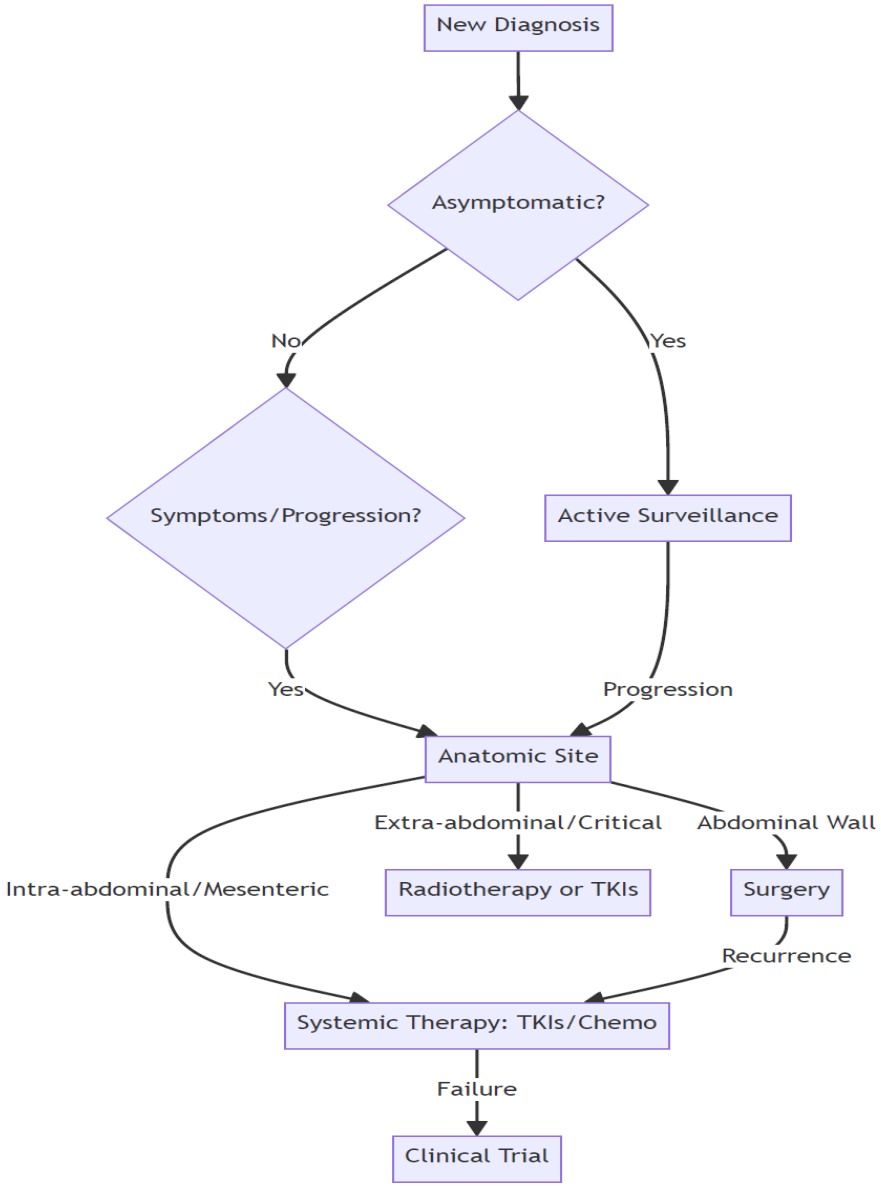
Other Systemic Therapies

- **Chemotherapy:**
  - **Low-dose MTX/vinblastine:** 35–40% response; 12-month PFS 79–92%.
  - **Liposomal doxorubicin:** 35% response; lower cardiotoxicity.
  - **Use:** Progressive disease after TKIs or rapid symptom control needed.
- **Hormonal/NSAIDs:**
  - Tamoxifen/toremifene ± sulindac: 40–51% stabilization (low-quality evidence).
  - **Limitations:** No proven survival benefit; used if TKIs/chemo contraindicated.

Local Therapies

- **Surgery:**
  - **Role:** Second-line for abdominal wall DT (low morbidity).
  - **Limitations:** High recurrence (19–77%); avoid in critical sites (head/neck).
- **Radiotherapy:**
  - **Indications:** Unresectable tumors; local control 65–83%.
  - **Risks:** Fibrosis, secondary malignancies (avoid in children).
- **Ablation (HIFU/Cryo/RFA):**
  - Minimally invasive; 80–100% ablation in selected cases.
  - **Use:** Extra-abdominal DT; palliative for recurrent disease.

Treatment Algorithm



Key Takeaways

- **Active Surveillance First:** 50% of patients avoid active treatment.
- **TKIs are Preferred Systemic Therapy:** Sorafenib/pazopanib for adults; pediatric dosing evolving.
- **Surgery/Radiotherapy Declining:** Reserved for select cases (e.g., abdominal wall DT).
- **Molecular Testing Mandatory:** *CTNNB1/APC* status guides FAP screening.
- **Pediatric Considerations:** Prioritize growth preservation; TKIs over high-dose chemo.
- **Multidisciplinary Care:** Essential for complex cases (e.g., FAP, mesenteric DT).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