DUPUYTREN'S DISEASE

RAY B. RAVEN III, MD, MBA

DISCLOSURES

- Royalties and Consulting Fees
  - Osteomed
  - Advanced Orthopaedic Solutions
- Paid Speaker/Educator
  - Auxilium Pharmaceuticals

GUILLAUME DUPUYTREN (1777-1835)

- French anatomist and military surgeon
- Treated Napoleon's hemorrhoids
- Dissected cadaver of patient with "DD"
  - Concluded exaggerated tension of aponeurosis
  - Noted contracture was released when cord was cut
- First to perform successful fasciectomy

DUPUYTREN'S DISEASE (DD)

- Progressive disease of *genetic origin*
- Fibromatosis of the *palmar fascia*
- Flexion contracture
  - Cords thicken/shorten
  - May result in functional impairment

EPIDEMIOLOGY

- Global Prevalence
  - 3% to 6% among adult Caucasians
    - 13.5 to 27 million people in the United States and Europe
  - Present in all races
- Incidence
  - Peaks in 40s and 50s
- Gender
  - More common in men
- Hereditary Expression
  - AD pattern with variable penetrance

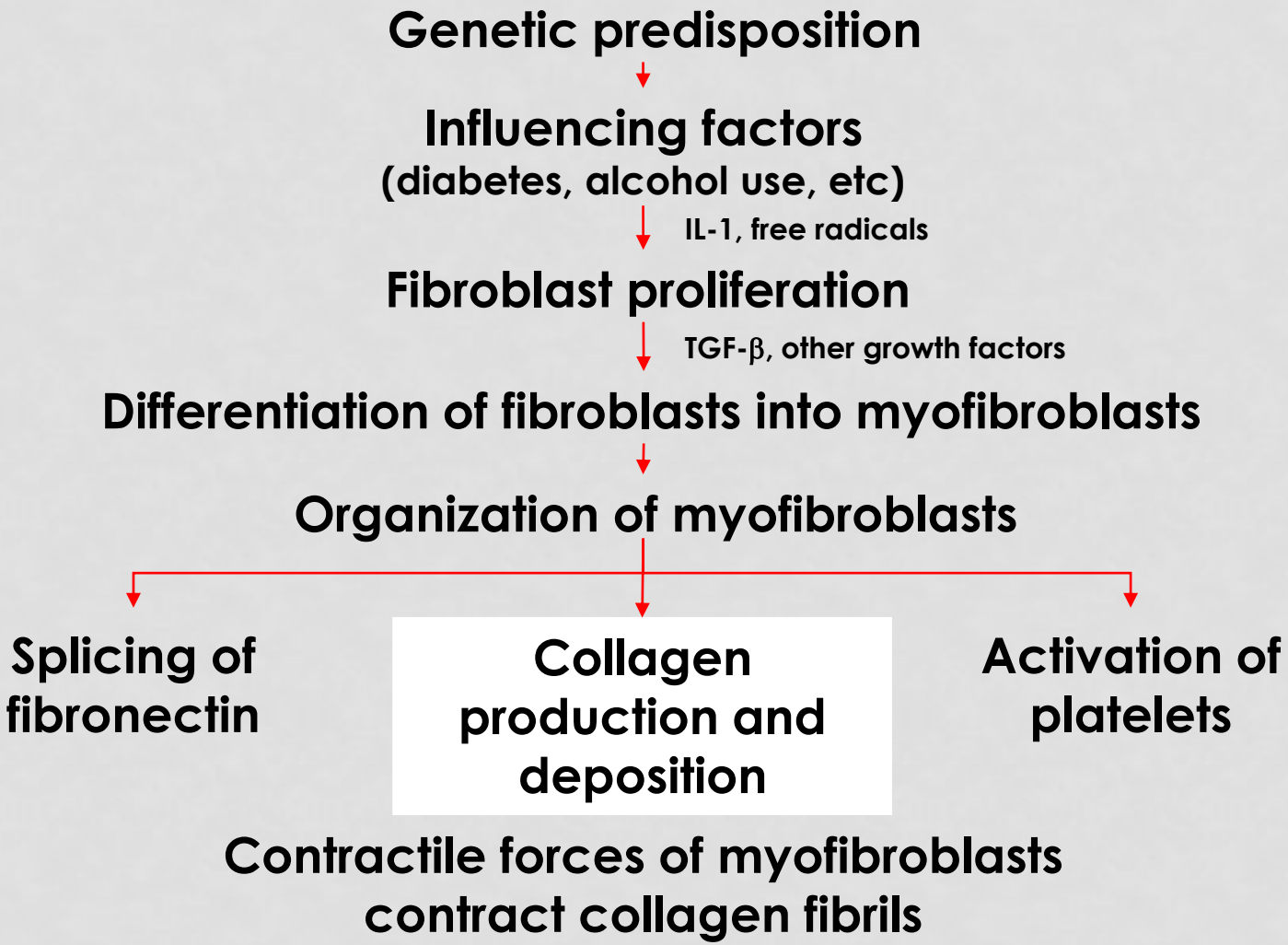
Luck JV. *JBJS.* 1959
Tubiana R et al. *Dupuytren's Disease* 2000

NON-DD PALMAR FIBROMATOSIS

- Often unilateral involvement
- No family history
- No ectopic manifestations
- Prior ipsilateral hand surgery or trauma
- Diabetes mellitus and cardiovascular disease
- Non-progressive or partially regressive
- Does not appear to be genetically inherited

Rayan, Moore. JHS Br 2005

PATHOGENESIS OF DD



Al-Qattan MM. *J Hand Surg.* 2006

COLLAGEN

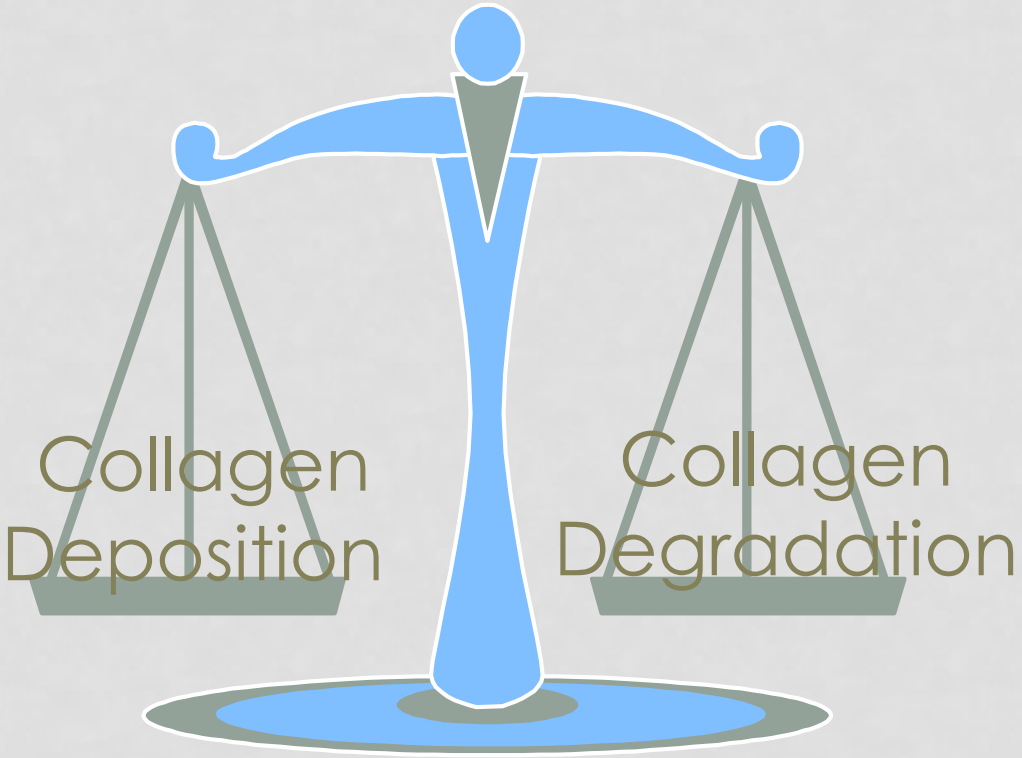
- 30 types - each encoded by a different gene
- 5 fibrillar collagens - triple helix conformation

I	Tendons, bone, and skin
II	Cartilage
III	Forms heterotypic fibrils with type I
V	Forms heterotypic fibrils with type I
XI	Forms heterotypic fibrils with type II

Canty EG and Kadler KE. *J Cell Sci.* 2005

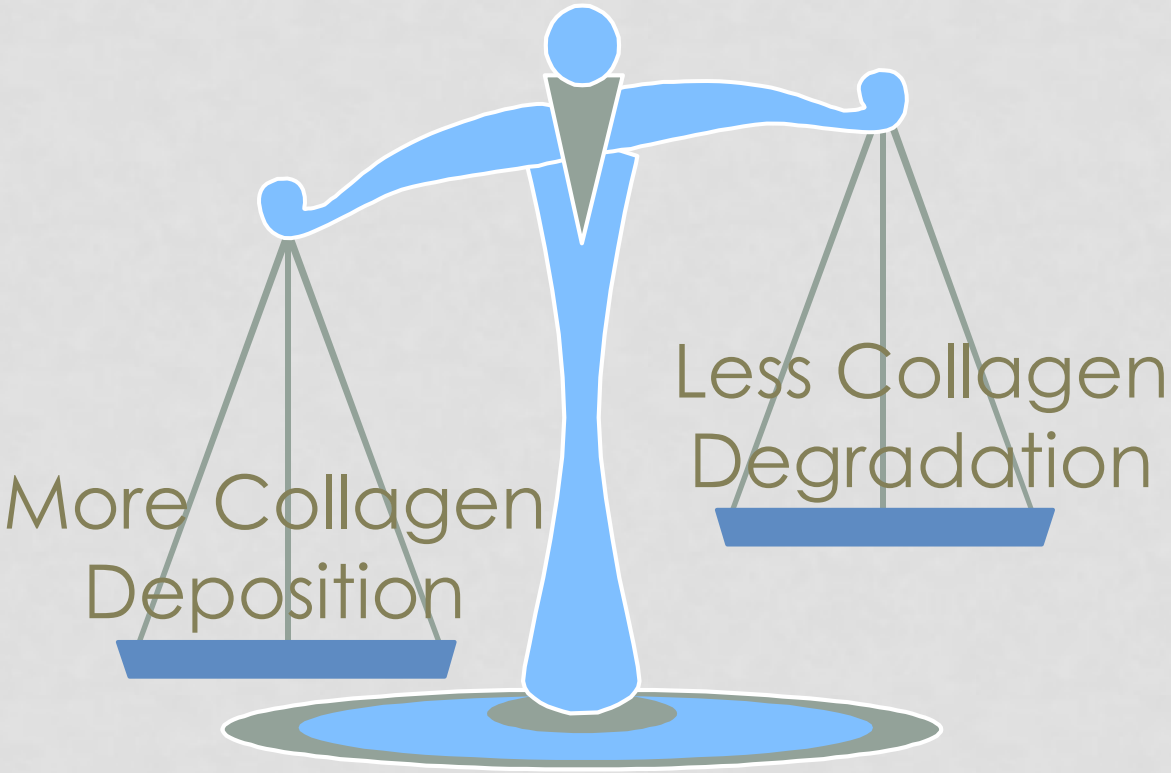
BALANCED COLLAGEN TURNOVER

- *Normal remodeling in trauma/inflammation growth*
- Strength responses to mechanical forces



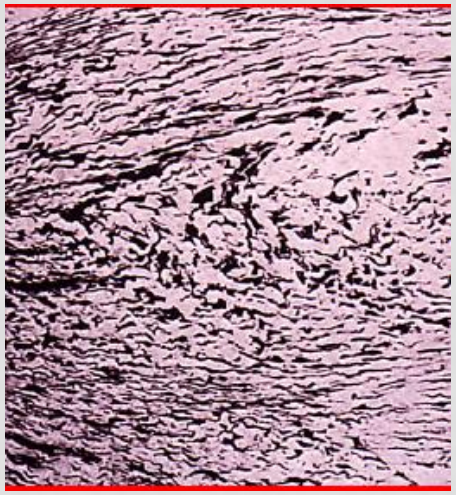
COLLAGEN BALANCE IN DD

- *Unbalanced turnover*
- Change in the proportion of collagen types



ALTERATION OF THE PALMAR FASCIA

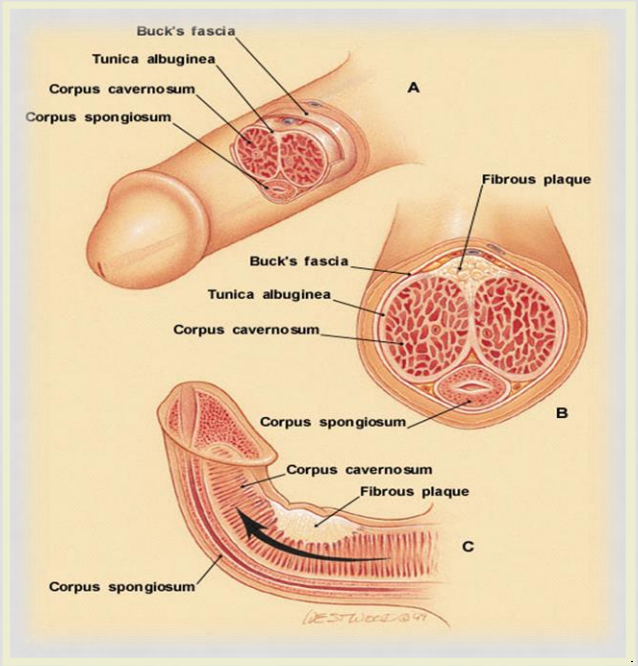
- Fibroblasts ➔ Myofibroblasts
- Myofibroblast proliferation
- Excessive collagen production
- Altered collagen matrix (type I to type III)
- Formation of pathologic cords/nodules



- **Normal Fascia**
  - Type I = 95%
  - Type III = *5%*
- **Dupuytren's Fascia**
  - *Type III = 40%*

ECTOPIC MANIFESTATIONS

- Regional
  - Garrod's nodes (knuckle pads)
- Distant
  - Lederhose disease (plantar fibromatosis)
  - Peyronie disease (penile fibromatosis)



Rayan GM. *Hand Clinics.* 1999

CORDS

- Diagnostic
- Results in predictable deformities

Normal	Pathology	Result
Pretendinous band	**Pretendinous cord**	MP joint deformity
Natatory ligament	**Natatory cord**	Limits digital abduction
Central fibrofatty tissue	**Central cord**	PIP joint deformity
Spiral band	**Spiral cord**	Displaces neurovascular bundle superficially
Lateral digital sheet	**Lateral cord**	PIP/DIP joint contracture

Rayan GM. *Hand Clinics.* 1999
Townley WA et al. *BMJ.* 2006
Tubiana R et al. *Dupuytren's Disease* 2000

JOINT CONTRACTURES

MCP

- Collateral ligaments
  - Slack in ext / tight in flx
- MP volar plate attachments
  - Relatively mobile
- DD Contractures
  - Pretendinous cord
  - Natatory cord < abduction
- Longstanding contractures easily corrected

PIP

- Collateral ligaments
  - Rapidly contract in flexion
- Prolonged flexion
  - Extensor tendon elongated
- DD Contractures
  - Occur in later stages
  - Central Cord
- Longstanding contractures difficult to correct

Tubiana R et al. *Dupuytren's Disease*. 2000

DIATHESIS

Condition that predisposes an individual to a disease

- DD diathesis
  - Positive family history
  - Bilateral involvement
  - Ectopic manifestations
  - Ethnicity
- Predicts progression and severity
- More aggressive course
- Greater tendency for recurrence

Hindocha et al. *JHS* 2006
Hueston JT. *Dupuytren's Contracture* 1963

DISEASE PROGRESSION

- Extension
  - Appearance of new lesions
- Recurrence
  - Reappearance of DD tissue previously treated zone

DIATHESIS AND PROGRESSION

3 year follow-up after surgery

	No Recurrence	Extension	Recurrence
No. of patients (N = 159)	70	41	48
Average age, y	58	55	45
Evidence of diathesis, N (%)			
Plantar lesions	3 (4)	4 (10)	12 (25)
Knuckle pads	14 (20)	17 (41.5)	36 (75)
Family history	10 (12)	4 (10)	13 (27)
Bilateral disease	56 (80)	39 (95)	47 (98)

Recurrence vs. nonrecurrence

- Family history: 2 times more frequent
- Knuckle pads: 3.5 times more frequent
- Plantar lesions: 8 times more frequent
- Young age at initial presentation

Hueston JT. *Dupuytren's Contracture*; 1963.
Tubiana R et al. *Dupuytren's Disease*. 2000

FACTORS AFFECTING RECURRENCE

- Positive family history
- Bilateral involvement
- Garrod's pads
- Male gender
- Onset age <50 years

Predictive risk of recurrence

- 22% when no factors are present
- 71% when all 5 factors are present

Hindocha S et a. JHS 2006
Tubiana R et al. *Dupuytren's Disease*. 2000

TREATMENT CONSIDERATIONS

- Evaluate each patient individually
- Patient should be advised in the context of their
  - Complaints and impact on ADLs
  - Examination
  - Goals and expectations

FASCIECTOMY

- Surgical treatment is the most reliable method Rx
- A means to control rather than to cure the disease

Rayan GM. *JHS* 2008

NEEDLE APONEUROTOMY (NA)

- Debevre, French rheumatologist
- Percutaneous Fasciotomy
- Early treatment method
- Special blade or needle

NEEDLE APONEUROTOMY

- Efficacy
  - 93-98% MCP
  - 57-67% PIP
- Recurrence 35-65%

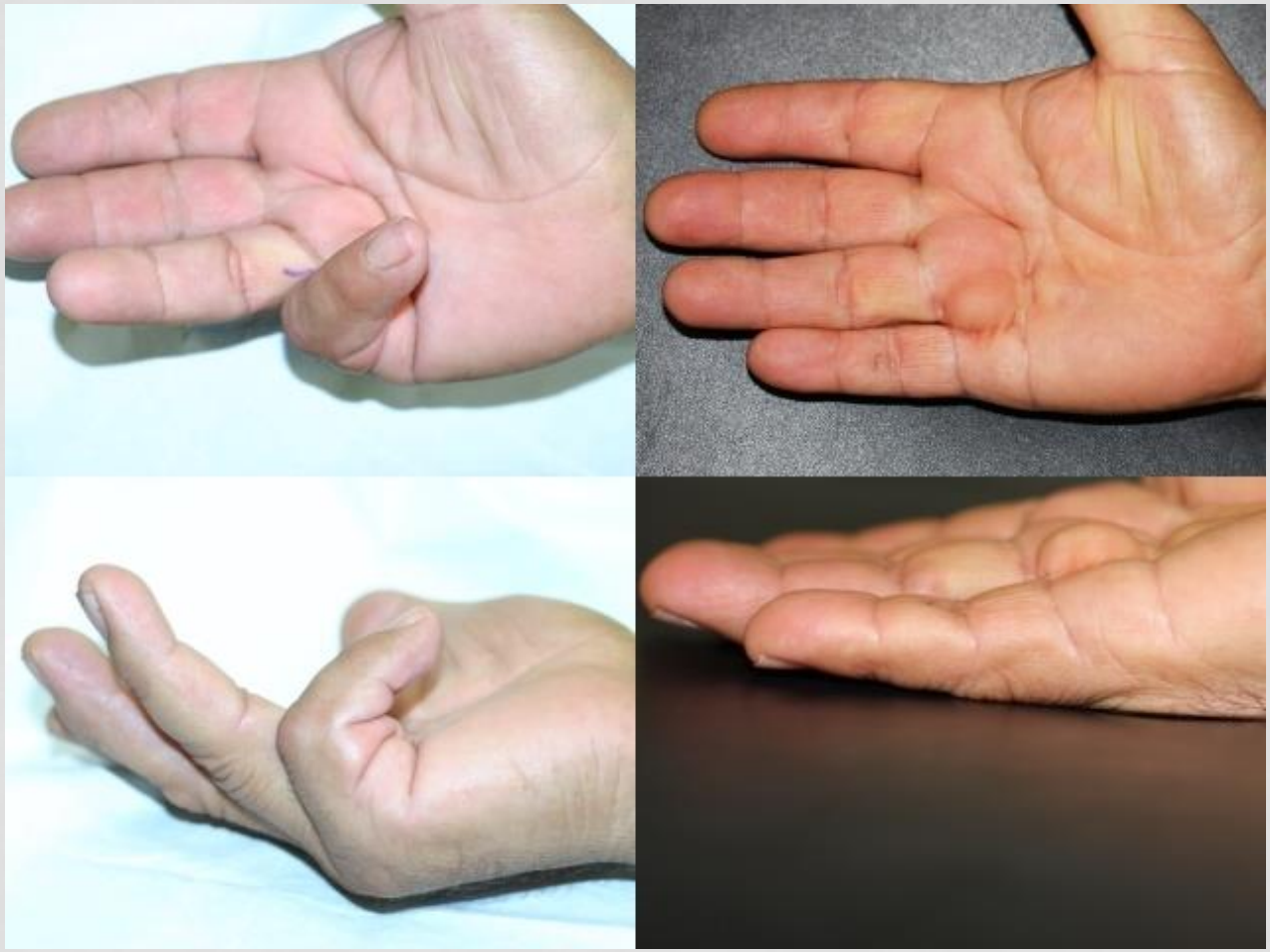
Publication	N	Recurrence	Mean F/U
Badois et al	90 patients	50%	5 y
Badois et al	100 digits	35%	6 mo
Foucher et al	100 patients	58%	3 y
van Rijssen and Werker	55 digits	65%	33 mo
Pess et al	1,013 digits	48%	3 y

NA COMPLICATIONS

- Infection or tendon injury rare
- Risk of digital nerve injury increased with PIP joint
- Postoperative gain prominent at MCP joint level
- Reoperation rate 24%
- Recurrence rate 58%
- disease ‘‘activity’’ 69%

Foucher et al. JHS Br 2003

NA TWO YEARS OUT



CLOSTRIDIAL COLLAGENASE

- Consists of type I and type II collagenases
- Immunologically cross reactive
- Cleaves collagen molecule at different sites
- Type III > I
- Approved by US FDA in 2010

RESEARCH

Two randomized, double-blind, placebo-controlled studies

CORD* I

N=306

United States
(16 US sites)

CORD II

N=66

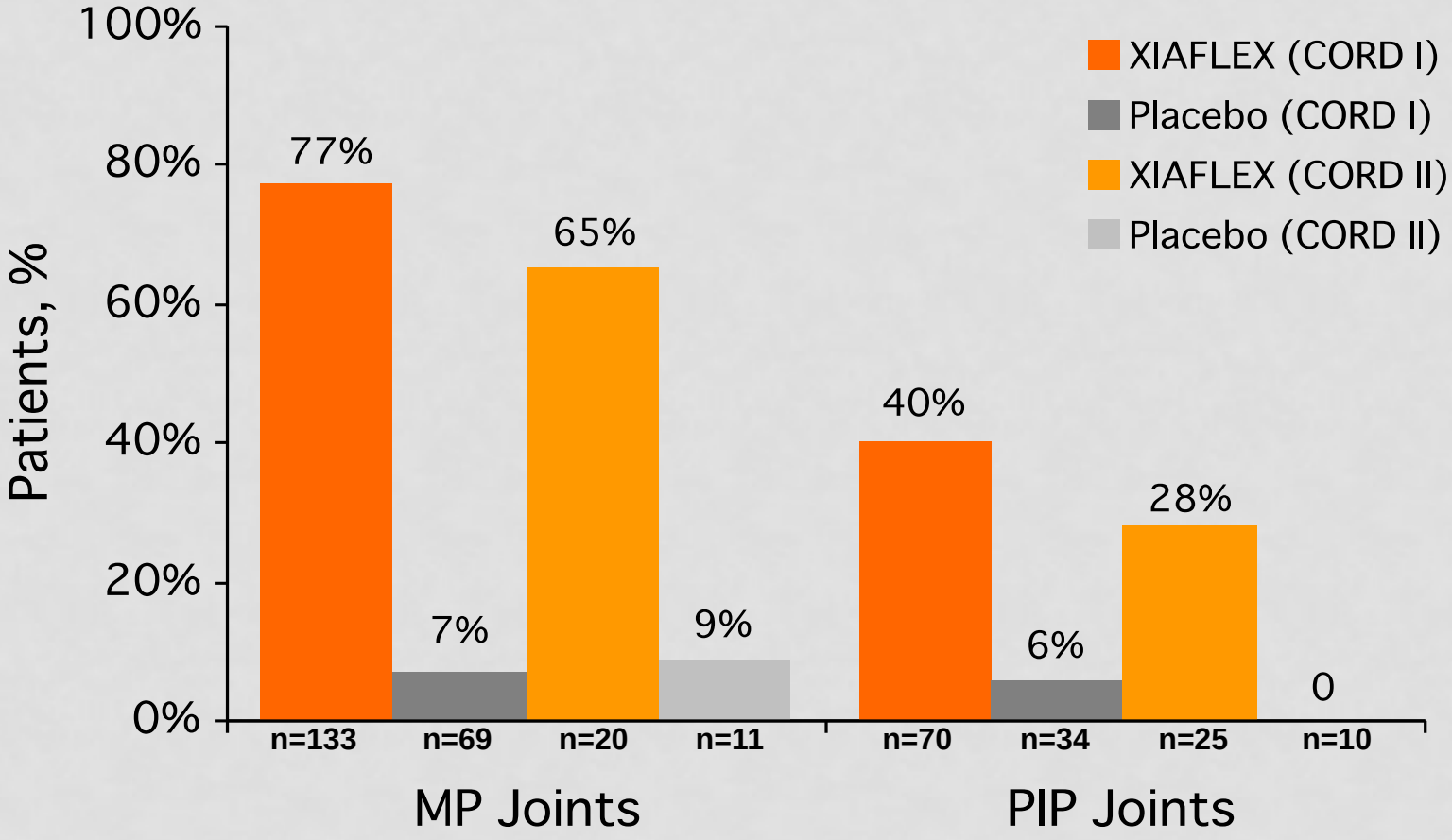
Australia
(5 sites)

MCP joint contracture	**20° - 100°**
PIP joint contracture	**20° - 80°**

CORD: Collagenase Option for Reduction of Dupuytren's

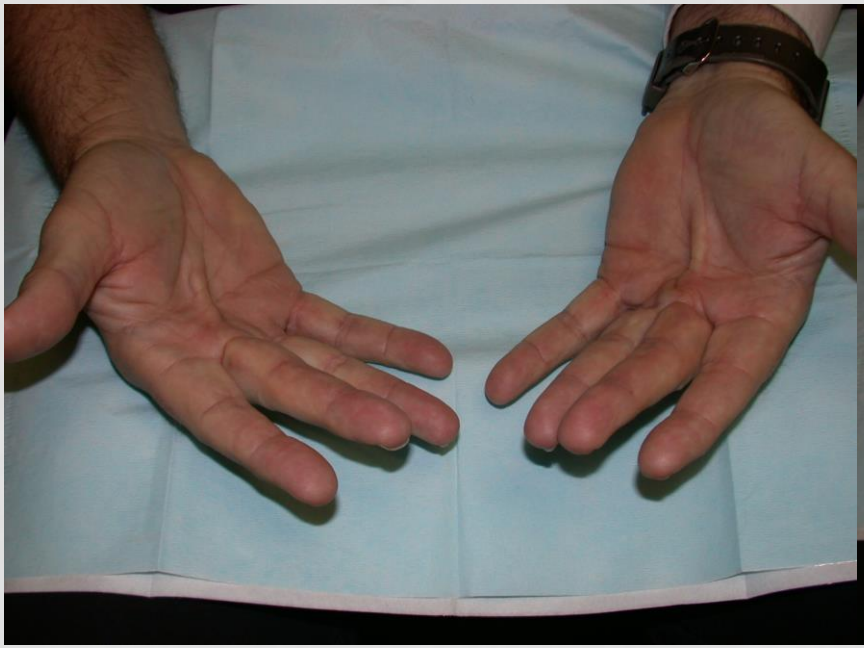
EFFICACY: MP AND PIP JOINTS

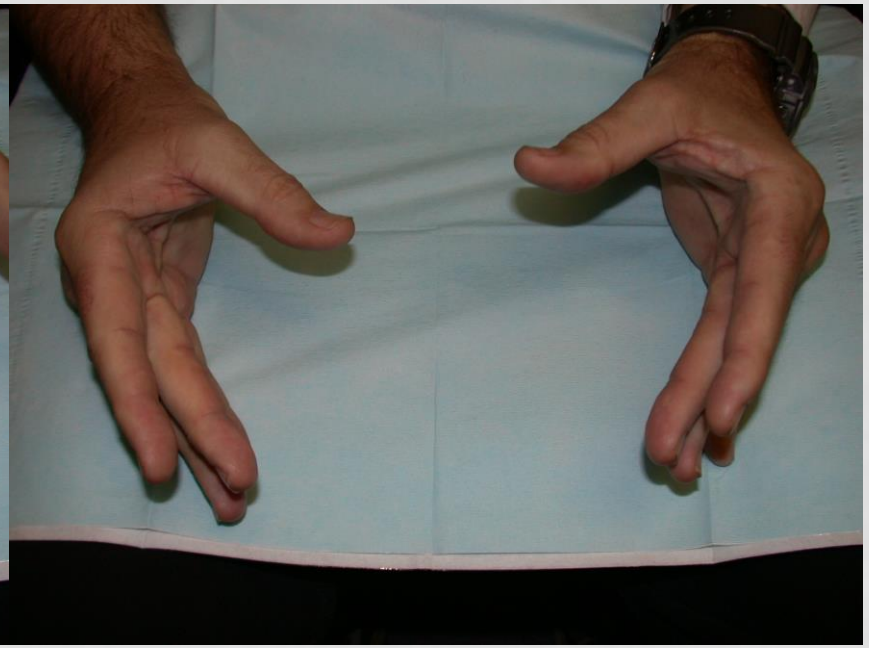
Subjects achieving a reduction in contracture to 0° to 5° of normal in 30 days



COLLAGENASE

Pre-operative





TWO WEEKS AFTER COLLAGENASE

ADVERSE REACTIONS

Adverse Events	XIAFLEX N=249	Placebo N=125
All adverse events	**98%**	**51%**
Edema peripheral[a]	73%	5%
Contusion[b]	70%	3%
Injection site hemorrhage	38%	3%
Injection site reaction[c]	35%	6%
Pain in extremity	35%	4%
Tenderness	24%	0%
Injection site swelling[d]	24%	6%
Pruritus[e]	15%	1%
Lymphadenopathy[f]	13%	0%
Skin laceration	9%	0%
Lymph node pain	8%	0%
Erythema	6%	0%
Axillary pain	6%	0%

NA VS. COLLAGENASE:

NA Group

- 30 patients
- 32 MCP joints 37°
- 18 PIP joints 41°
- 67% clinical success

Collagenase Group

- 29 patients
- 22 MCP joints 40°
- 12 PIP joints 50°
- 56% clinical success

Nydick J, et al. *JHS* 2013

NA VS. COLLAGENASE: OUTCOMES

NA

- Efficacy
  - 93-98% MCP
  - 57-67% PIP
- Recurrence
  - 35-65%

Collagenase

- Efficacy
  - 53-90%
- Recurrence
  - 35-67%

Pess et al JHS 2012
Hurst et al NEJM 2009
Watt et al JHS 2010
Peimer et al JHS 2013

NA VS. COLLAGENASE: COSTS

NA Group

- CPT 26040 - $341.60

Total Cost: $341.60

Collagenase Group

- J70775 - $3,438.72
- E&M 99203 - $117.59
- CPT 20527 $90.99
- CPT 26341 - $108.5

Total Cost: $3,755.8

Medicare fee schedule, Los Angeles, CA 2013

NA VERSUS COLLAGENASE: PATIENT EXPERIENCE

NA Group

- 1 visit
- + Local anesthisia

Collagenase Group

- 2 visits
- +/- Local anesthesia

Adverse Event	NA	Collagenase	P value
Edema	5	29	< 0.01
Ecchymosis	3	28	< 0.01
Skin Tear	15	10	0.29
Lymphadenopathy	0	6	< 0.01
Pruritus	0	7	< 0.01

Nydick J, et al. *JHS* 2013

NA VS. COLLAGENASE:
~ VALUE ~

$$VALUE = \frac{OUTCOME}{COST} \text{ x PATIENT EXPERIENCE}$$

NA offers patients and insurers Superior Value

Porter. N Engl J Med 2010

MY PRACTICE

- Observation
  - Asymptomatic or contractures less than 20°
- Needle Aponeurotomy
  - MP joint contractures
  - Rapid progression PIP contractures
- Collagenase (patient request)
  - MP joint contractures
  - Rapid progression PIP contractures
- Surgery
  - Significant PIP involvement
  - Recurrence
  - Symptomatic nodules

THANK YOU

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WHICH OF THE FOLLOWING TYPES OF COLLAGEN IS LEAST AFFECTED BY THE COLLAGENASE COMPOUNDS UTILIZED IN COLLAGENASE CLOSTRIDIUM HISTOLYTICUM INJECTION FOR THE TREATMENT OF DUPUYTREN'S CONTRACTURE?

A. Type I
B. Types II
C. Type III
D. Type IV
E. Type V

ANSWER: TYPE III

Discussion: The compounds that comprise the collagenase clostridium histolyticum injection are a derived from the bacterium Clostridium histolyticum. Type IV collagen is least affected by these collagenase compounds. This is felt to be significant as type IV collagen makes up the basement membranes of the digital arteries and nerves that are closely opposed to the contracted collagen cord.

References: Desai SS, Hentz VR. The Treatment of Dupuytren's Disease. J Hand Surg 2011;36,5:936-942.

Gilpin D, Coleman S, Hall S, Houston A, Karrasch J, Jones N. Injectable Collagenase Clostridium histolyticum: A New Nonsurgical Treatment for Dupuytren's Disease. J Hand Surg 2010;35A: 2027-2038.

WHICH OF THE FOLLOWING GENES IS UP REGULATED WITHIN DUPUYTREN'S DISEASE TISSUE AS COMPARED WITH THE NORMAL FASCIA?

A. Frizzled-related protein
B. Glutathione peroxidase
C. TIMP metalloproteinase
D. Tenascin C (TNC)
E. Phosphatidic acid phosphatase type 2B

ANSWER: TENASCIN C (TNC)

Discussion: Glutathione peroxidase 3, aldehyde dehydrogenase 1, A1, lysyl oxidase-like 2, Phosphatidic acid phosphatase type 2B, tenascin XB, angiotensin II receptor, type1 frizzled-related protein and TIMP metallopeptidase inhibitor 3 are down regulated in Dupuytren disease. In tissue biopsies, significant fold changes were observed for ADAM12, POSTN, and TNC in the cord and/or nodule when compared with that of normal fascia. ADAM12 and POSTN are associated with accelerated or abnormal cell growth,whereas TNC has been associated with fibrotic diseases and cell migration.

References: Rehman S, Salway F, Stanley J, Ollier WER, Day P, Bayat P. Molecular Phenotypic Descriptors of Dupuytren's Disease Defined Using Informatics Analysis of the Transcriptome. J Hand Surg; 33A:3592008.

Shih B, D Wijeratne, Armstrong DJ, Lindau T, Day P, Bayat A. Identification of Biomarkers in Dupuytren's Disease by Comparative Analysis of Fibroblasts Versus Tissue Biopsies in Disease-Specific Phenotypes. J Hand Surg;34A:124:2009.

THE CELL TYPE ASSOCIATED WITH THE DEVELOPMENT OF A DUPUYTREN'S CONTRACTURE IS:

A. Myofibroblast
B. Fibroblast
C. Osteoblast
D. Dermoblast
E. Pluripotential stem cell

WHICH OF THE FOLLOWING GENES IS UP REGULATED IN DUPUYTREN'S DISEASE TISSUE COMPARED W/ NORMAL FASCIA?

A. Frizzled-related protein
B. Glutathione peroxidase 3
C. TIMP metalloproteinase
D. Tenascin C (TNC)
E. Phosphatidic acid phosphatase type 2B

WHICH OF THE FOLLOWING ANATOMIC STRUCTURES IS NOT INVOLVED IN THE SPIRAL CORD IN DUPUYTREN'S DISEASE?

A. Pretendinous band
B. Spiral band
C. Cleland's ligaments
D. Grayson's ligament
E. Lateral digital sheath

A SPIRAL CORD IN DUPUYTREN'S CONTRACTURE WILL DISPLACE THE NEUROVASCULAR BUNDLE:

A. Distally, dorsally, and away from the midline
B. Proximally, volarly, and towards the midline
C. Distally, volarly, and towards the midline
D. Proximally, dorsally, and away from the midline
E. Distally, volarly, and away from the midline

INVOLVEMENT OF THE DIP JOINT IN DUPUYTREN'S DISEASE IS CAUSED BY WHICH CORD?

A. Spiral
B. Natatory
C. Pretendinous
D. Retrovascular
E. Central

A PATIENT WITH A KNOWN HISTORY OF DUPUYTREN'S DISEASE PRESENTS FOR EVALUATION OF THE LEFT HAND.

- Examination reveals 10 degrees of contracture at the MCP joint of the small finger
- No involvement outside the palm.
- The patient has no functional deficit and can lay his palm flat on the examination table.

THE BEST INITIAL CHOICE IN MANAGEMENT IS:

A. Education and monitoring
B. Injection with collagenase
C. Needle aponeurotomy
D. Open fasciectomy in the palm
E. Full thickness skin grafting

WHICH OF THE FOLLOWING IS MOST PREDICTIVE OF RECURRENCE AFTER SURGERY?

A. Female gender
B. Dupuytren's diathesis
C. The "flare" reaction
D. Presence of spiral cord
E. Simultaneous carpal tunnel release and fasciectomy

WHAT IS THE MOST COMMON LONG-TERM COMPLICATION FOLLOWING COLLAGENASE RX FOR DUPUYTREN'S CONTRACTURE?

A. Chronic regional pain syndrome
B. Tendon rupture
C. Recurrence
D. Neurovascular injury
E. Infection

BILLING AND CODING

HCPCS/ CPT Code	Clinical Description of Code
J0775	Injection, collagenase, clostridium histolyticum, 0.01 mg
99203	Office or other outpatient visit, for the evaluation and management of a new patient
20527	**Injection**, enzyme (eg, collagenase), palmar fascial cord (ie, Dupuytren's contracture)
26341	**Finger Extension**- manipulation, palmar fascial cord (ie, Dupuytren's cord), post enzyme injection (eg, collagenase), single cord (10 day global)
29130	Application of finger splint; static