



Canadian Agency for
Drugs and Technologies
in Health

RAPID RESPONSE REPORT: *SUMMARY WITH CRITICAL APPRAISAL*



TITLE: Needle or Open Fasciotomy for Dupuytren's Contracture: A Review of the Comparative Efficacy, Safety, and Cost-Effectiveness – An Update

DATE: 11 November 2013

CONTEXT AND POLICY ISSUES

Dupuytren's contracture is a progressive condition in which connective cords form, thicken, and shorten (typically in the connective tissue of the palmar fascia), causing permanent flexion contractures of joints and of one or more fingers.¹ The metacarpophalangeal joint (MCP) and the proximal interphalangeal joint (PIP) are most often affected. Eventually, the contractures lead to hand deformity and impaired hand function, and potentially reduced quality of life for the affected individual.¹ Dupuytren's contracture may present as an unilateral or bilateral disease. The primary cause of Dupuytren's contracture has yet to be determined, although there is a strong hereditary component.²

There is no cure for Dupuytren's contracture and only a handful of treatment options exist. The most commonly used treatments are surgery (partial or total fasciectomy), fasciotomy, collagenase clostridium histolyticum injections, or corticosteroid injections.² Surgery (especially open, partial fasciectomy [OPF]) is the mainstay treatment option, which is recommended for functionally impaired patients with contractures more than 30 degrees of the MCP joint.² There is some disagreement as to when surgery is recommended when PIP joints are affected.

There are two types of fasciotomy: open fasciotomy where the surgeon uses a scalpel to section the cords, and closed fasciotomy or percutaneous needle fasciotomy (also called aponeurotomy [PNF]), which involves a minimally invasive technique whereby a small needle is used to weaken and manipulate the cords. With percutaneous needle fasciotomy, the cords eventually break after being weakened by means of passive finger extension.

Collagenase clostridium histolyticum (CCH) has recently been approved by Health Canada as treatment for Dupuytren's contracture in adults with a palpable cord. The monthly injection of CCH (up to three injections per Dupuytren's cord) hydrolyzes the collagen in the Dupuytren's cord, thereby resulting in enzymatic disruption of the cord and release of the contracture.

The objective of this report is to conduct a review of the clinical evidence regarding open and closed fasciotomy for treating Dupuytren's contracture compared with fasciectomy and collagenase clostridium histolyticum. The cost-effectiveness of the fasciotomy techniques will also be reviewed. This is an update to a previous Rapid Response report.

RESEARCH QUESTIONS

1. What is the clinical efficacy of needle or blade fasciotomy compared to with radical and partial fasciectomies or collagenase clostridium histolyticum for the treatment of Dupuytren's Contracture?

2. What is the safety of needle or blade fasciotomy compared to with radical and partial fasciectomy or collagenase clostridium histolyticum for the treatment of Dupuytren's Contracture?
3. What is the cost-effectiveness of needle or blade fasciotomy compared to with radical and partial fasciectomy or collagenase clostridium histolyticum for the treatment of Dupuytren's Contracture?
4. What are the evidence based guidelines for the treatment of Dupuytren's Contracture.

KEY FINDINGS

Limited evidence suggests that percutaneous needle fasciotomy is associated with higher recurrence of contracture than open partial fasciectomy or collagenase clostridium histolyticum injections. Percutaneous needle fasciotomy is cost-effective, while collagenase injections may be cost-effective at a reduced price. Open partial fasciectomy was not found to be a cost-effective strategy for treatment of Dupuytren's contracture.

METHODS

Literature Search Strategy

A limited literature search was conducted on key resources including PubMed, The Cochrane Library (2012, Issue 9), University of York Centre for Reviews and Dissemination (CRD) databases, Canadian and major international health technology agencies, as well as a focused Internet search. No filters were applied to limit the retrieval by study type. The search was also limited to English language documents published between January 1, 2002 and October 4, 2012.

An updated search was conducted October 8, 2013 to capture any literature published since the original report. An additional grey literature search was conducted to identify clinical practice guidelines for the treatment of Dupuytren's Contracture published since January 1, 2008.

Selection Criteria and Methods

One reviewer screened the titles and abstracts of the retrieved publications and evaluated the full-text publications for the final article selection, according to selection criteria presented in Table 1.

Table 1: Selection Criteria

Population	Patients with Dupuytren's contracture
Intervention	Needle or blade fasciotomy
Comparator	Radical or partial fasciectomy Collagenase clostridium histolyticum
Outcomes	Clinical effectiveness <ul style="list-style-type: none"> • Reintervention (repeated procedure at a later date) • Recovery time • Functional capacity (e.g. back to work)

	<ul style="list-style-type: none"> • Quality of life • Flexibility Harms Cost-effectiveness, cost recovery
Study Designs	Health technology assessments Systematic reviews/Meta-analyses Randomized controlled trials Economic evaluations Evidence-based guidelines

Exclusion Criteria

Studies were excluded if they did not meet the selection criteria, were duplicate publications or included in a selected systematic review, or were published prior to 2002.

Critical Appraisal of Individual Studies

The quality of included systematic reviews was assessed using the Assessment of Multiple Systematic Reviews (AMSTAR) tool.³ The quality of the included studies was assessed using the Downs and Black checklist.⁴ The guidelines for appraisal of economic studies by Drummond et al.⁵ were followed in assessing the included cost-effectiveness study. A numeric score was not calculated for each study. Instead, strengths and weaknesses of each study were summarized and described.

SUMMARY OF EVIDENCE

Quantity of Research Available

A total of 49 citations were identified in the original literature search. Following screening titles and abstracts, 43 citations were excluded and six potentially relevant reports were retrieved for full-text review. Of the six potentially relevant reports, two publications did not meet the inclusion criteria. As a result, four publications were included in the original review. A total of fourteen citations were identified in the search update. Of these, four were retrieved for full-text review, and two publications met the inclusion criteria. Appendix 1 describes the PRISMA flowchart of the included studies in the review.

Summary of Study Characteristics

Details on study characteristics of the included reports can be found in Appendix 2.

Study design

One systematic review,⁶ two quasi-randomized controlled trials,^{7,8} and three economic evaluations⁹⁻¹¹ met the inclusion criteria. No relevant health technology assessments were identified.

Population

The population of the included studies was patients with Dupuytren's contracture; studies were comparable in terms of baseline demographics and focused on contracture of the hand. Three studies were from the U.S.^{6,9,11}, two were from The Netherlands,^{7,8} and one was Canadian.¹⁰The

systematic review included 13 studies: six studies on OPF (n=37 to 261 patients); three studies on PNF (n=117 to 211 patients); and four studies on CCH (n=13 to 204).⁶ The quasi-randomized controlled trials included 111 and 113 patients, respectively.^{7,8} One of the trials followed patients for six weeks and the other was a five-year follow-up following the initial six-week phase. In both trials, the mean age was 62 to 64 years and the study groups were comprised mostly of men (>78%). The Canadian economic evaluation modeled cost-effectiveness of OPF, PNF, or collagenase injection for patients with Dupuytren's contracture affecting a single finger. Complication, recurrence and failure rates for each procedure were derived from a systematic review of the literature, with utility values based on the systematic review by Chen et al.⁹ One economic evaluation was based on a retrospective chart review of matched groups of patients undergoing PNF (n=24) or OPF (n=24).¹¹ The final economic evaluation⁹ was authored by the same investigators and considered the same population from the included systematic review.⁶

Interventions and comparators

The systematic review⁶ compared OPF with PNF or CCH. The inclusion criteria for the systematic review included randomized active- or placebo-controlled trials, prospective or retrospective comparative studies, and case series. Hence, seven of the 13 reviewed studies were comparative (two for OPF, two for PNF, and three for CCH). The Canadian economic evaluation¹⁰ was a cost-utility analysis using a decision tree model comparing OPF, PNF, and CCH; however, the utility inputs were taken from an earlier economic evaluation.⁹ Probabilities of complication, recurrence, and treatment failure were derived from a systematic review conducted with the purpose of informing the evaluation. The analysis was conducted using a societal perspective. A decision model was run over a 15-year time horizon. One economic evaluation was a cost-utility analysis using a decision tree model comparing OPF, PNF, and CCH with no treatment; however, the efficacy and safety inputs were taken from the aforementioned systematic review that included treatment arms from active comparator randomized controlled trials.⁹ The authors stated that the analysis was conducted using a societal perspective; however, the costs described do not support this perspective. A decision model was run over a 20-year time horizon. One included economic study¹¹ reported direct costs associated with PNF or OPF based on a retrospective chart review from a single US institution.

Both quasi-randomized controlled trials compared PNF with OPF.^{7,8}

Outcomes

The efficacy outcomes of interest in the systematic review were recurrence and disease progression to other joints. It extracted data on specific adverse events: nerve division; neurapraxia; infection; complex regional pain syndrome (CRPS); and skin tear.

Total passive extension deficit and patient satisfaction were endpoints in both quasi-randomized controlled trials; however, the six-week study⁸ also assessed hand-function recovery and adverse events, while the five-year study⁷ listed recurrence, flexion, and sensibility as outcomes, but did not report data for the latter two.

For the Canadian economic evaluation, utility values were derived from the economic evaluation by Chen et al., while probabilities for complications (nerve injury or CRPS), recurrence, or immediate treatment failure were derived from a systematic review of the literature. Procedure-

specific, follow-up appointment and anesthetic costs were derived from the Ontario Health Insurance Program Schedule of Benefits. Hospital-related costs were obtained from two tertiary level hand surgery units. Patient-incurred costs such as parking costs and loss of income were also considered. The cost of collagenase was based on the US market price. The outcome was cost per quality-adjusted life years (QALY), with the threshold for cost-effectiveness set at \$50,000 CAN per QALY and the threshold for affordability set at \$100,000 CAN per QALY.

The US cost analysis based on a retrospective chart review and hospital billing records reported direct costs associated with PNF or OPF, including facility costs (costs billed from hospital charges) and professional charges (surgeon and anesthesia fees).

For the economic evaluation by Chen et al., data to populate the model were based on the results of the systematic review comparing the cost-effectiveness of OPF, PNF, and CCH; and, a survey of 50 members of the general public to derive utility values. The clinical data obtained from the systematic review consisted of recurrence rates and adverse events (nerve division and CRPS). U.S. Medicare costs included facility-related costs, cost for the procedure, anesthesia, hand therapy and splint. For CCH, administration and facility costs were described only; the cost of the drug was not included. The outcome was the cost per QALYs versus no treatment. The threshold for cost-effectiveness was \$50,000 USD per QALY.

Summary of Critical Appraisal

Overall, the quality of the included reports was assessed as low to moderate. A detailed summary of the critical appraisal conducted for selected studies can be found in Appendix 3.

The systematic review by Chen et al.⁶ described the research question and selection criteria; multiple data bases were searched without limits to publication date or language. The authors evaluated the scientific quality of the included articles based solely on the design of the study and gave each a rank based on criteria defined by the Centre for Evidence Based Medicine, Oxford, U.K. (Level I, high-quality randomized controlled trial to Level V, expert opinion).¹² However, the systematic review also had numerous limitations, as described in Appendix 3. Of note, the primary analysis of the systematic review was a naïve indirect comparison between the three treatment modalities. The analysis appeared to pool data for each treatment regardless of the study design. This method does not preserve randomization from randomized controlled trials and likely biases the comparison of recurrence rates between the treatments. Moreover, it is unclear what variables were used to adjust the analysis; hence there is uncertainty as to how well the authors adjusted for the high degree of heterogeneity within and between the three treatment groups.

Both quasi-randomized controlled trials had clearly defined research questions, eligibility criteria, and intervention and outcome definitions. They also made direct comparisons between two well-accepted treatments for Dupuytren's, fasciectomy and needle fasciotomy, and hence making clinically relevant comparisons. However, both trials used quasi-randomization to assign patients to treatment groups and investigators were not blinded to the intervention. Analyses were not based on intention-to-treat principles, hence, failure to include all patients in the analysis may bias the results due to non-random loss of the patients.

The economic evaluation by Chen et al. modelled clinical success and main safety events on a time horizon of 20 years. However, the evaluation provided limited information on the clinical inputs, such as effectiveness and utility gain per intervention, thereby preventing full assessment of the study. Resource use and associated costs were not appropriately described and justified. The analysis was limited to patients with a “functionally limiting contracture involving the small and ring fingers”.⁹ It is unclear if the effectiveness data are specific to these digital rays. The study was conducted using U.S. cost information, which may limit its generalizability to Canada.

The Canadian economic analysis¹⁰ modeled clinical success on a time horizon of 15 years. Detailed information on the sources of clinical inputs and utilities for each intervention was provided. However, utility gain per intervention was derived from the evaluation by Chen et al.⁹ and therefore is subject to the same limitations described for that study. Resource use and associated costs were described. Sensitivity analyses were conducted, but the range or distribution of values used was not described. The analysis was limited to patients being treated for Dupuytren’s Contracture in a single finger. Effectiveness data used was specific to this population, but this may limit the generalizability to other contexts.

The US cost study¹¹ clearly described the clinical scenario for each treatment group, however the outcomes were limited to direct costs associated with treatment only, and no cost-effectiveness analysis was performed. The study considered only surgical treatment of Dupuytren’s contracture (i.e. PNF or OPF) and did not consider collagenase injections. Clinical differences were reported between the treatment groups, and it is unclear whether these differences were accounted for when deriving costs. Detailed reporting on resource use and costs was not provided. The generalizability of the study may be limited as it was conducted using clinical and cost information from a single US institution.

Summary of Findings

Details of the main study findings and authors’ conclusions are presented in Appendix 4.

Clinical effectiveness of needle fasciotomy

The systematic review by Chen et al.⁶ reported the rates of recurrence following OPF, PNF, and CCH ranged from 0% to 39%, 50% to 58%, and 10% to 31%, respectively. Recurrence rates were compared between treatment groups using the Kruskal-Wallis H non-parametric statistic, which is interpretable in much the same way that the F statistic from performing an analysis of variance (ANOVA) is interpreted. The recurrence rates between groups were significantly different (adjusted Kruskal-Wallis H statistic = 18.69; P=0.001). Using a naïve indirect comparison, Chen and colleagues reported PNF had significantly higher recurrence rates than OPF (adjusted H statistic = 17.25; P=0.001), while OPF had significantly higher recurrence rates compared with CCH (adjusted H statistic = 14.95; P=0.001). Statistical testing of recurrence rates between PNF and CCH was not performed.

van Rijssen et al. conducted two quasi-randomized controlled trials comparing outcomes of PNF with those of OPF over six weeks⁸ and five years,⁷ respectively. Total passive extension deficit improvement (the primary outcome in the six-week study) improved on average by 63% and 79% (P=0.001) for PNF and OPF, respectively. PNF was reported as more effective among patients with mild to moderate versus severe contracture (i.e., a total passive extension deficit $\leq 90^\circ$). Patients treated with PNF were more satisfied at six weeks than those treated by OPF

($P=0.003$); however, after five-years of follow-up, the opposite was found ($P<0.001$). Nonetheless, the score for choosing the same procedure as preferred future treatment was significantly higher in the PNF group than in the OPF group after five years. Both scores were correlated with recurrence, so that lower satisfaction and less preference for the same treatment were reported among patients with recurrent contracture.⁷

In the six-week quasi-randomized controlled trial patients were asked to complete the Dutch translation of the Disabilities of the Arm, Shoulder, and Hand (DASH) questionnaire.^{13,14} Ninety-seven patients (50 from the PNF group and 47 from the OPF group) completed the questionnaire to an extent that they could be analyzed statistically. Before surgery DASH scores did not differ between groups: 16 (standard deviation [SD]=14) in the PNF group and 14 (SD=12) in the LF group ($P=0.584$). After five weeks of treatment, the mean DASH score in the PNF group decreased to a mean score of nine (SD not reported). The DASH score for the OPF group increased after five weeks (score=16 [SD not reported]). The final DASH scores between the groups differed significantly ($P=0.017$ at 5 weeks).

The primary objective of the five year quasi-randomized controlled trial was to compare differences between PNF and OPF in terms of recurrences. The recurrence rate after five years in the PNF group (45/53 hands [84.9%]) was significantly higher than in the OPF group (9/43 hands [20.9%]) ($P=0.001$), and occurred significantly sooner in the PNF group (Kaplan-Meier estimated $P=0.001$).

Safety of needle fasciotomy

According to Chen et al., adverse events, namely nerve division, neurapraxia, infection, and CRPS were most commonly reported in studies on OPF as compared with PNF and CCH.⁶ Of note, CRPS occurred in 0% to 13% of patients treated with OPF. Skin tear (9% to 25%) and neurapraxia (2% to 3%) were the most frequently reported adverse events among patients treated with PNF, while patients injected with CCH experienced skin tear (9% to 15%).

Of the two quasi-randomized controlled trials, only the six-week trial collected data on adverse events.⁸ Fifty-five percent (33/60) of PNF-treated hands and almost 30% (17/57) of OPF-treated hands experienced adverse events. In the PNF group, 33 trial-defined minor adverse events were reported, consisting of 29 skin fissures and 4 cases of paresthesia. No major adverse events, defined as infection, skin slough, hematoma, transected artery, suspected digital nerve injury, re-exploration, and suspected division of a flexor tendon, occurred. In the OPF group, 13 minor adverse events (all cases of paresthesia) and 3 major adverse events, namely infection, hematoma, and digital nerve injury, occurred.

Cost-effectiveness

The authors of the Canadian economic evaluation¹⁰ used PNF as an index treatment, as it was found to be the least costly option. Compared with PNF, collagenase had an incremental cost-effectiveness ratio (ICER) of \$284,383 CAN (2011) per QALY gained. By comparison, OPF was dominated, indicating that there was a higher cost, with lower expected effectiveness compared with other treatments. This analysis was based on the assumption of \$3,000 for a complete series of collagenase injections and the use of OPF as the salvage procedure following unsuccessful release. If PNF was assumed to be the salvage procedure, the ICER for collagenase increased to \$891,171. In the sensitivity analyses, collagenase reached the threshold for cost-effectiveness (\$50,000/QALY) compared to PNF at a cost of \$875 and the

threshold for affordability (\$100,000/QALY) at a cost of \$1250. Collagenase became the preferred strategy at a cost of \$470 for a complete series of injections.

In the US cost evaluation,¹¹ the mean direct costs for OPF were \$11,240 USD (ranging from \$4061 to \$20,915). Hospital charges accounted for 61% of these costs, with the remaining 39% derived from professional charges. The mean cost for PNF was \$4657 (range \$3910 to \$6514). The proportion of costs derived from hospital or professional charges was not provided, but the authors stated that the distribution of charges was similar to those seen for OPF.

Chen et al.⁹ reported the cost-effectiveness of PNF was estimated to be \$96,474 USD (2009) per QALY gained compared with no treatment. By comparison, OPF was estimated at \$820,114 USD per QALY gained compared with no treatment. Using the U.S. market price of \$5,400 USD for an average course of CCH treatment, the cost per QALY gained was \$166,268 USD. In the sensitivity analysis, certain model parameters were altered until the intervention reached the threshold for cost-effectiveness, set at \$50,000 per QALY gained. When PNF success rates were set at 100% and the adverse event rate at 0%, the cost per QALY gained decreased to \$49,631 USD. Results were also sensitive to cost of the interventions and where PNF was conducted; when excluding the cost of a surgical center, anesthesia and physiotherapy costs, the results decreased to \$36,570 USD per QALY gained; if the injection series for complete CCH injection series was priced at \$250 USD (3 injections per cord), the result decreased to \$31,856 USD, if priced at \$945 USD, the result is \$49,995 USD per QALY gained.

LIMITATIONS

The evidence comparing PNF with OPF and CCH is, overall, limited in terms of quantity and quality. The included systematic review, for example had several limitations, notably it included and pooled data from both randomized clinical trials and non-comparative observational studies. The systematic review used a naïve indirect comparison to compare recurrence rates between the three treatments, thereby comparing results of individual treatment arms from different comparative (and non-comparative) studies as if they were from the same study. In the case of randomized controlled trials, this indirect method breaks randomization and has increased susceptibility to bias; hence, the treatment effect may be over- or underestimated. Additionally, there was marked heterogeneity in study characteristics within and between treatments, and information regarding loss to follow-up and outcome definitions in the included studies, which are likely correlated with the outcomes.

The two trials comparing PNF with OPF provided head-to-head evidence for these treatment modalities over the long-term. However, patients were allocated to treatment by quasi-randomization methods and neither of the studies conducted analyses based on the intention-to-treat principle. As well, the five-year follow-up study did not assess adverse event rates, hence long-term comparative safety information is lacking for these treatments.

Moreover, no comparative studies were identified that evaluated open fasciotomy versus OPF or CCH, nor were there direct comparisons of CCH with other Dupuytren's treatments. There was also a dearth of adverse event data reported for PNF and CCH, making it difficult to assess the safety of these treatments.

Given the limited information provided on data inputs and the lack of transparency regarding the methods used, it was difficult to fully appraise one of the included economic evaluations. The authors stated that the analysis was conducted using a societal perspective; however, the costs

described do not support this perspective. It can be noted that the results apply to a limited patient population and there may be concerns regarding the generalizability to a Canadian setting. One Canadian economic evaluation was identified, however it was limited to patients being treated for Dupuytren's contracture in a single finger, and therefore may not be generalizable to a broader population.

CONCLUSIONS AND IMPLICATIONS FOR DECISION OR POLICY MAKING

In total, one systematic review, two quasi-randomized controlled trials, and three economic evaluations were included in this review. The systematic review provided (naïve) indirect evidence on the recurrence and adverse event rates between PNF, OPF and CCH, while both trials directly compared the long-term effectiveness and patient satisfaction between PNF and OPF. The cost-effectiveness of PNF, OPF and CCH were compared to each other or versus no treatment. Direct costs associated with PNF or OPF, without cost-effectiveness analysis, were examined in one study.

Evidence from these studies indicated that recurrence rates were significantly higher for PNF versus OPF and CCH. However, the aforementioned limitations of the included studies likely limits the conclusions that can be drawn from this evidence. There is also uncertainty regarding patient satisfaction with PNF versus OPF; the reported higher recurrence rates with PNF likely impacts patient satisfaction. PNF appears to have fewer serious adverse events, such as nerve damage and CRPS compared with OPF. However, long-term comparative adverse event data are lacking and caution should be used when drawing conclusions around the safety of PNF.

Direct costs associated with PNF are lower than OPF, and PNF appears to be cost-effective compared with OPF and CCH. OPF was not found cost-effective and CCH was cost-effective in one study when priced under \$945 USD. However, several limitations related with this analysis require caution when interpreting this economic evidence. These findings are supported by a recent Canadian evaluation which found that PNF was the most cost-effective strategy and collagenase became cost-effective when priced under \$875.

There remain numerous evidence gaps regarding the treatment of Dupuytren's contracture in general, and for the use of PNF specifically. Well-designed, large-scale, long-term randomized controlled trials comparing PNF with other standards of care for Dupuytren's contracture are required.

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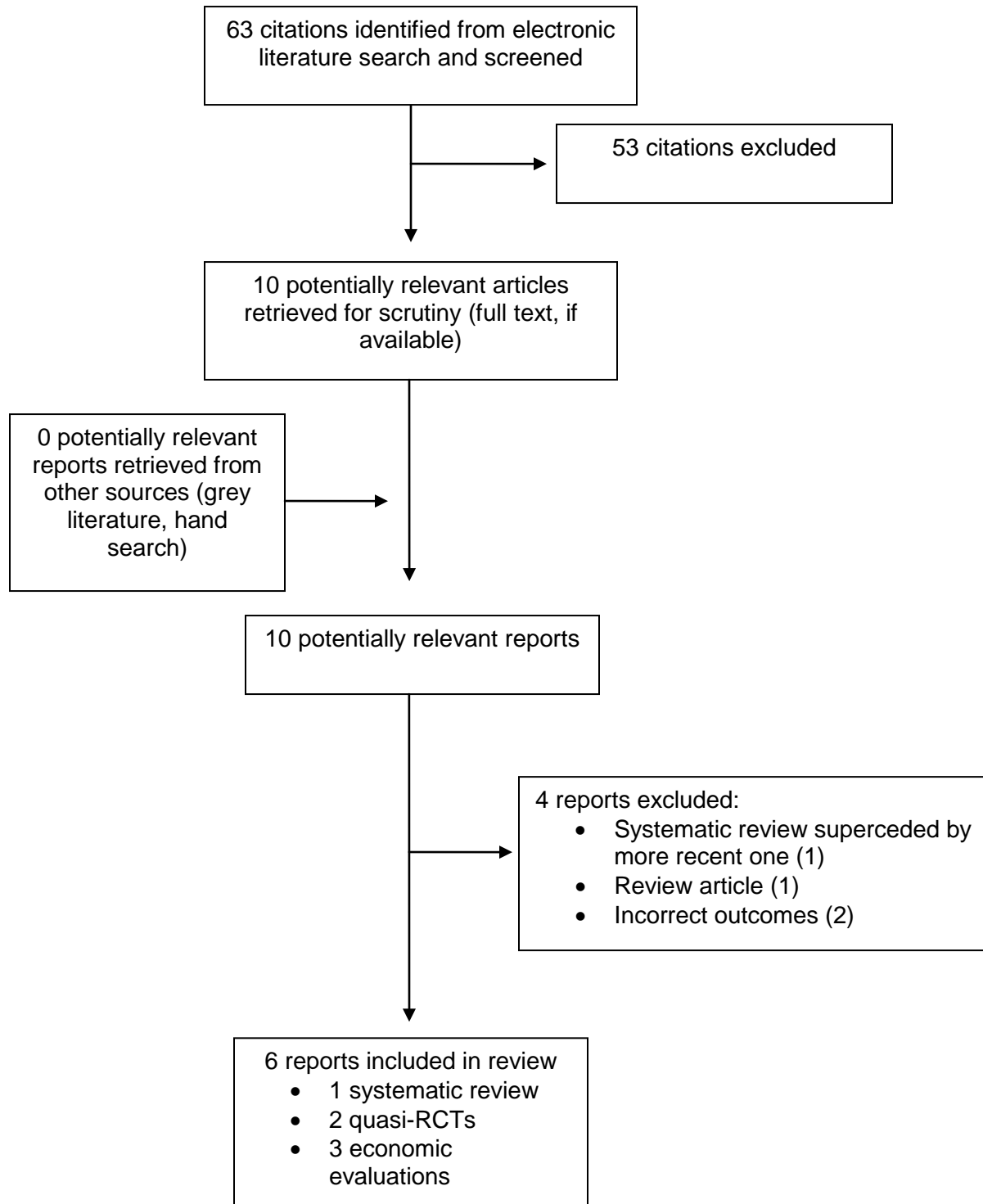
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APPENDIX 1: Selection of Included Studies



APPENDIX 2: Summary of Study Characteristics

Table A2.1: Summary of Study Characteristics of Included Systematic Reviews

First Author, Publication Year, Country	Study Design, Length of Follow-up	Patient Characteristics, Sample Size (n)	Intervention	Comparator(s)	Clinical Outcomes
Chen, 2011 ⁶ U.S.	Systematic review Included 13 studies: <u>OPF</u> : 6 studies (2 RCTs, 4 NCRS); FU: 1.5–7.3 yrs <u>PNF</u> : 3 studies (1 QRCT, 2 NCRS); FU: 6 wks–5 yrs <u>CCH</u> : 4 studies (3 RCTs, 1 NCPS); FU: 120 days–4 yrs	<u>OPF</u> : n: 37–261 Age range (yrs): 55–67 % male: 78–86 <u>PNF</u> : n: 117–211 Age range (yrs): 58–65 % male: 82–88 <u>CCH</u> : n: 13–204 Age range (yrs): 61–65 % male: 79–91	OPF PNF CCH	<u>OPF</u> : DF OPF (different techniques) <u>PNF</u> : OPF <u>CCH</u> : Placebo	Major AEs (nerve division, arterial division), minor AEs (neurapraxia, wound complications, infection, CRPS or RSD), recurrence, disease progression
<p>AE=adverse event; CCH=collagenase clostridium histolyticum; CRPS=complex regional pain syndrome; DF=dermofasciectomy; FU=follow-up; NCPS=non-comparative prospective studies; NCRS=non-comparative retrospective studies; OPF=open partial fasciectomy; PNF=percutaneous needle fasciotomy; QRCT=quasi-randomized controlled trial; RCT=randomized controlled trial; RSD=reflex sympathetic dystrophy; wks= weeks; yrs=years</p>					

Table A2.2: Summary of Study Characteristics of Included Quasi-Randomized Controlled Trials

First Author, Publication Year, Country	Study Design, Length of Follow-up	Patient Characteristics, Sample Size (n)	Intervention	Comparator(s)	Clinical Outcomes
van Rijssen, 2012 ⁷ Netherlands	QRCT 5 yrs	n=111 patients (292 joints) with Dupuytren's contracture (a flexion contracture of $\geq 30^\circ$ in the MCP or PIP and a palpable cord) Mean age (yrs) PNF: 62.8 OPF: 63.1 % male PNF: 84.6 OPF: 78.0	PNF (n=52; 167 joints)	OPF (n=41; 125 joints)	Recurrence TPED, patient satisfaction, flexion, sensibility
van Rijssen, 2006 ⁸ Netherlands	QRCT 6 wks	n=113 patients (166 joints) with Dupuytren's contracture (a flexion contracture of $\geq 30^\circ$ in the MCP, PIP, or DIP joints and a palpable cord) Mean age (yrs) PNF: 64 OPF: 64 % male PNF: 86.0 OPF: 80.4	PNF (n=57; 88 rays)	OPF (n=56; 78 rays)	TPED Patient satisfaction, hand-function recovery, AEs
<p>AE=adverse event; CCH=collagenase clostridium histolyticum; DB=double-blind; DIP=distal intraphalangeal joint; MCP=metacarpophalangeal joint; OL=open-label; OPF=open partial fasciectomy; PC=placebo-controlled; PIP=proximal intraphalangeal joint; PNF=percutaneous needle fasciotomy; QRCT=quasi-randomized controlled trial; RCT=randomized controlled trial; TPED=total passive extension deficit; wks= weeks; yrs=years</p>					

Table A2.3: Summary of Study Characteristics of Included Economic Studies

First Author, Publication Year, Country	Type of Economic Evaluation, Study Perspective	Patient Population	Intervention (n)	Comparator(s) (n)	Assumptions
Baltzer, 2013 ¹⁰ Canada	CUA, societal perspective	Patients with Dupuytren's contracture of a single finger	OPF (n=NR)	PNF (n=NR) Collagenase (n=NR)	<ul style="list-style-type: none"> • Mean age of presentation male of 63 years with mean life expectancy of 78 years (15 year time horizon) • Cost of collagenase based on US market price, and assumed to include a full course of injections • Recurrence at 3 years was assumed. Recurrence rates: OPF 20%; PNF 51%; CCH 21% • Rates of CRPS and digital nerve injury were both 7.5% and 2% in OPF, 0.27% of digital injury in PNF and 0.2% of CRPS in CCH • OPF would be default salvage procedure after unsuccessful release, with one year lag for salvage assumed
Herrera, 2013 ¹¹ U.S.	Cost comparison, direct costs	Patients with Dupuytren's contracture	OPF (n=24)	PNF (n=24)	<ul style="list-style-type: none"> • Direct costs defined costs billed from hospital charges and professional charges (surgeon and anesthesia fees) • Costs drawn from financial and medical records of each patient • No long term costs considered

First Author, Publication Year, Country	Type of Economic Evaluation, Study Perspective	Patient Population	Intervention (n)	Comparator(s) (n)	Assumptions
Chen, 2011 ⁹ U.S.	CUA, societal perspective	Patients with Dupuytren's contracture	OPF (n=NR) CCH (n=NR) PNF (n=NR)	No treatment (n=NR)	<ul style="list-style-type: none"> • Mean age of presentation of 63 yrs (20 yr time horizon) • Recurrence rates: OPF 30%; PNF 60%; and CCH 15% • Rates of CRPS and digital nerve injury were both 5% in OPF, 5% of digital injury in PNF and none in CCH • OPF would be preferred technique upon failure of PNF or CCH
<p>CCH=collagenase clostridium histolyticum; CRPS=complex regional pain syndrome; CUA=cost-utility analysis; NR=not reported; OPF=open partial fasciectomy; PNF=percutaneous needle fasciotomy; yrs=years</p>					

APPENDIX 3: Summary of Critical Appraisal

First Author, Publication Year	Strengths	Limitations
Systematic Reviews		
Chen, 2011 ⁶	<ul style="list-style-type: none"> • Comprehensive literature search based on pre-defined criteria, no limits on date or language • Scientific quality of included studies assessed, but only based on level of evidence (Level I, high-quality RCT to Level V, expert opinion) as defined by the Centre for Evidence-Based Medicine (Oxford, U.K.) 	<ul style="list-style-type: none"> • Unclear if duplicate study selection and data extraction was performed (article states studies were reviewed by 3 independent surgeons) • Unclear whether grey literature was searched • No list of included and excluded studies provided • Description of included study characteristics and comparators was not explicit • Conflicts of interest were not stated • No subgroup analyses (e.g., MP or PIP joints; baseline severity; prior interventions) • Almost half of the included studies were non-comparative observational studies • For included comparative studies, effect sizes and 95% confidence intervals were not reported • Primary analysis pooled data from all study types • Naïve indirect comparison between treatments likely is biased; the method does not preserve randomization from RCTs and likely results in over- or under-estimated effect sizes and it is unclear what factors the analyses were adjusted for
Quasi-Randomized Controlled Trials		
van Rijssen, 2012 ⁷	<ul style="list-style-type: none"> • Research question, eligibility criteria, intervention and outcomes were explicit • Sample size and power calculations conducted • Direct comparison between two standard treatments • 5-year follow-up period • No conflict of interest 	<ul style="list-style-type: none"> • Patients were quasi-randomized to treatment by pulling a numbered envelope from a box containing a note with the treatment group label • Patients and outcome assessors did not appear to be blinded • Per-protocol analysis • Adverse events were not assessed
van Rijssen, 2006 ⁸	<ul style="list-style-type: none"> • Research question, eligibility criteria, intervention and outcomes were explicit • Sample size and power calculations conducted • Direct comparison between two standard treatments • No conflict of interest 	<ul style="list-style-type: none"> • Patients were quasi-randomized to treatment by pulling a numbered envelope from a box containing a note with the treatment group label • Patients and outcome assessors did not appear to be blinded • Per-protocol analysis • 6-week follow-up period
Economic Evaluations		
Baltzer, 2013 ¹⁰	<ul style="list-style-type: none"> • Clearly described research question and specified viewpoint (societal) • Appropriately defined comparators 	<ul style="list-style-type: none"> • Range or distribution of values for sensitivity analyses not described • The analysis applied only to patients being

First Author, Publication Year	Strengths	Limitations
	<ul style="list-style-type: none"> • Modelled clinical success and main safety events over an appropriate time horizon • Provided detailed information on clinical inputs such as effectiveness and utilities • Resource use and costs were described • ICERs calculated using discounted outcome values • Study was conducted using Canadian (OHIP) cost information. 	<p>treated for Dupuytren’s contracture in a single finger. Effectiveness data was specific to this population.</p>
Herrera, 2013 ¹¹	<ul style="list-style-type: none"> • Clearly described purpose of the study • Clinical scenario for each treatment group clearly described 	<ul style="list-style-type: none"> • No cost-effectiveness analysis, reported on direct costs associated with treatment only • Considered only surgical treatment of Dupuytren’s contracture. Collagenase treatment not considered. • Clinical differences (e.g. severity) were reported between treatment groups, which may impact the associated costs. • Detailed reporting on resource use and costs was not provided • The study was conducted using cost information from a single U.S. institution which may limit the generalizability to other contexts
Chen, 2011 ⁹	<ul style="list-style-type: none"> • Clearly described research question and specified viewpoint (societal) • Appropriately defined comparators • Modelled clinical success and main safety events over an appropriate time horizon 	<ul style="list-style-type: none"> • Limited information provided on the clinical inputs (such as effectiveness and utility gain per intervention); thus preventing full assessment of the study • Resource use and costs were not appropriately described and justified and it was unclear how they were incorporated into the cost-effectiveness model • No discounting is reported. • As for sensitivity analyses, the range or distribution of values were not appropriately described nor justified. • The analysis applied only to patients with a “functionally limiting contracture involving the small and ring fingers”. It is unclear if the effectiveness data were specific to this disease severity • The study was conducted using U.S. cost information which may impact its generalizability to Canada

OHIP = Ontario Health Insurance Program

APPENDIX 4: Summary of Findings

First Author, Publication Year	Main Study Findings	Authors' Conclusions
Systematic Reviews		
Chen, 2011 ⁶	<p><u>Indirect comparison – Recurrence rates:</u> Between 3 treatment groups: adjusted H, 18.69; P=0.001 OPF < PNF: adjusted H, 17.25; P=0.001 OPF > CCH: adjusted H, 14.95; P=0.001 PNF vs. CCH: Not estimated</p> <p><u>Open partial fasciotomy:</u> 1 RCT: longitudinal incision OPF vs. Z-plasty closure with modified Bruner incision OPF 1 RCT: OPF vs. DF 5 NCRS: recurrence, AEs post-OPF (1 used only for AEs)</p> <p>Recurrence rates: 0%–39% (6/6 studies) AEs: - Nerve division: 0%–5% (4/7 studies) - Neurapraxia: 0%–52% (5/7 studies) - Infection: 0%–12% (5/7 studies) - CRPS: 0%–13% (5/7 studies) - Skin tear: 2% (1/7 studies)</p> <p><u>Percutaneous needle fasciotomy:</u> 1 QRCT: PNF vs. OPF (recurrence and progression not measured; included only for AEs) 2 NCRS</p> <p>Recurrence rates: 50%–58% (2/3 studies) AEs: - Nerve division: 0.4% (1/3 studies) - Neurapraxia: 2%–3% (3/3 studies) - Infection: 2% (1/3 studies) - CRPS: 0.4% (1/3 studies) - Skin tear: 9%–25% (3/3 studies)</p> <p><u>Collagenase clostridium histolyticum:</u> 3 RCTs (2 phase III, 1 phase IIa/b): CCH vs. placebo 1 NCPS</p> <p>Recurrence rates: 10%–31% (4/5 studies) AEs: - Nerve division: NR - Neurapraxia: NR - Infection: NR - CRPS: 0.3% (1/4 studies) - Skin tear: 9% - 15% (3/4 studies)</p>	<p>“The recurrence rates and types of complications differ between open partial fasciotomy and needle aponeurotomy or collagenase injection. Long-term outcomes have not been well reported.” (P.250)</p>
Quasi-Randomized Controlled Trials		
van Rijssen, 2012 ⁷	<p>93/111 (84%) of patients completed 5-year follow-up</p> <p>Recurrence*:</p>	<p>“Although percutaneous needle fasciotomy is equally effective for mild to moderate</p>

First Author, Publication Year	Main Study Findings	Authors' Conclusions
	<p>PNF: 84.9% OPF: 20.9%; P<0.001</p> <p>Recurrence occurred significantly later after OPF vs. PNF (Kaplan-Meier P=0.001)</p> <p><u>Patient satisfaction:</u> - Mean satisfaction (0 [very negative] to 10 [very positive]) PNF = 6.2 OPF = 8.3; P<0.001 - Would choose the same procedure for future treatment (0 [no] to 10 [yes]) PNF = 8.7 OPF = 7.0; P<0.001</p> <p>Changes in flexion and sensibility not reported</p>	<p>Dupuytren's disease (Tubiana stages I and II), as we have shown in previous studies, recurrence rates are significantly higher than after limited fasciectomy. A higher age at disease presentation correlates with a lower tendency for recurrence. For this reason, we believe that percutaneous needle fasciotomy treatment is best suited for well-informed elderly patients with relatively mild contractures (Tubiana stages I and II) and for those who are willing to accept a higher recurrence risk in the context of a lower complication rate, a faster recovery, and minimal invasiveness." (P.476)</p>
<p>van Rijssen, 2006⁸</p>	<p>A total of 125 hands (121 patients) randomized; 4 patients with bilateral disease 6 patients (6 hands) withdrew prior to treatment; complete data for 113 patients (117 hands; 166 rays treated; 88 rays by PNF; 78 rays by OPF)</p> <p><u>Mean % reduction (SD) in PED at 6 wks:</u> MCP: PNF: 75 (26); OPF: 87 (22); P=0.003 PIP: PNF: 33 (42); OPF: 49 (46); P=0.062 DIP: PNF: 61 (59); OPF: 83 (40); P=0.441 TPED: PNF: 62 (32); OPF: 79 (25); P=0.001</p> <p>OPF significantly larger mean % reduction in TPED vs. PNF if baseline TPED ≥90°: Tubiana Grade III P=0.000; Grade IV P=0.004</p> <p><u>Patients satisfaction:</u> Patients treated with PNF more satisfied with hand function at 6 wks than those treated by OPF (P=0.003)</p> <p>OPF associated with significantly more discomfort (P=0.002)</p> <p><u>Hand function recovery (DASH questionnaire†):</u> Baseline DASH scores: PNF (n=50): mean 16 (SD 14) OPF (N=47): mean 14 (SD 12) After 5 wks: PNF: mean 9 (SD NR) OPF: mean 16 (SD NR); P=0.017</p> <p><u>AEs‡:</u></p>	<p>"Overall PNF is less effective than OPF as a treatment for Dupuytren's disease, especially in cases with moderate to severe contractures. The difference is especially true at the MCP level. At the PIP joint the difference is borderline significant and at the DIP joint no difference in short-term outcome was found. The complication rate of PNF is low, however, and patients do not have to be admitted to the hospital. Finally, patients recover more quickly from PNF than from OPF. Therefore PNF is useful to treat patients with Tubiana grade I and II disease to whom quick recovery is important. Careful selection of patients helps to get maximum results from treatment with PNF." (P.724)</p>

First Author, Publication Year	Main Study Findings	Authors' Conclusions
	<p>Total: PNF: 33/60 hands (55%); OPF: 17/57 hands (30%) "Major": PNF: 0; OPF: 3/57 hands (5%) (infection 1; hematoma 1; nerve injury 1) "Minor": PNF: 33/60 hands (55%) (skin fissure 29; paresthesia 4); OPF: 14/57 hands (25%) (paresthesia 13; changed Semmes-Weinstein monofilament 1)</p>	
Economic Evaluations		
<p>Baltzer, 2013¹⁰</p>	<p>Model: expected-value decision analysis model with an arm representing each treatment A systematic review was conducted to determine baseline probabilities for complication, recurrence, or treatment failure for each treatment arm. Utilities were based on the analysis by Chen et al.⁹ The threshold for a cost-effective treatment was based on a willingness-to-pay of \$50,000 CAN per QALY. Treatments were considered affordable if the cost was <\$100,000 CAN per QALY</p> <p>Cost effectiveness analysis (ICER, 2011 \$CAN): PNF: Used as comparator strategy (least costly option) OPF: Dominated (higher cost for lower effectiveness) Collagenase: \$284,383 per QALY</p> <p>Sensitivity analyses: If PNF was assumed to be the salvage procedure for recurrence, the ICER for collagenase increased to \$891,171</p> <p>PNF lost preference to collagenase with increases of complication, recurrence, or failure rates above certain thresholds, however the values at which PNF lost preference were outside the ranges reported in the literature.</p> <p>There was no change in model preference between forms of treatment with varied patient-incurred costs.</p> <p>Collagenase reached the \$50,000 cost-effectiveness threshold at a cost of \$875 for a complete series of injections, and the \$100,000 affordability threshold at \$1250. Collagenase became the preferred strategy at a cost of \$470.</p>	<p>"...our model supports the trend towards non-surgical interventions for managing Dupuytren's contracture affecting a single finger. Injectable collagenase will only be feasible in our publicly funded healthcare system if it costs significantly less than current United States pricing." (p. 1094)</p>
<p>Herrera, 2013¹¹</p>	<p>Study design: retrospective cost review of 24 OPF patients and 24 PNF patients</p> <p>Immediate postoperative contracture correction was similar between the OPF and PNF groups. Two of 24 patients in the OPF group and 0 of 24 in the PNF group experienced complications.</p> <p>Mean cost (range):</p>	<p>"Percutaneous NA is associated with decreased direct costs in the short-term compared to traditional open fasciectomy with comparable deformity correction" (p. 454)</p>

First Author, Publication Year	Main Study Findings	Authors' Conclusions
	<p>OPF: \$11,240 (\$4061 to \$20,915) 61% of costs derived from hospital charges, 39% from professional charges (surgeon and anesthesia fees)</p> <p>PNF: \$4657 (\$3910 to \$6514) Similar distribution of hospital and professional charges as OPF</p> <p>Mean difference: \$6603 (95% CI \$4718 to \$8486)</p>	
Chen, 2011 ⁹	<p>Model: expected-value decision analysis model with an arm representing each treatment. A survey was administered to a cohort of 50 consecutive members of the general public to determine utilities of different interventions. The threshold for a cost-effective treatment based on the traditional willingness-to-pay of \$50,000 USD per QALY gained.</p> <p>The cost of OPF: USD \$820,114 per QALY gained vs. no treatment</p> <p>The cost of PNF: \$96,474 USD per QALY gained vs. no treatment</p> <p>Sensitivity analysis:</p> <ul style="list-style-type: none"> - Set the success rate at 100% and AE rate at 0%, the cost of PNF = \$49,631 USD per QALY gained vs. no treatment - PNF performed without surgical center or anesthesia costs and with reduced hand therapy: the cost = \$36,570 USD per QALY gained vs. no treatment <p>The cost of CCH (complete series of 3 injections per cord):</p> <ul style="list-style-type: none"> - Priced at \$5,400 USD (manufacturer's U.S. market price): cost was \$166,268 USD per QALY gained <p>Sensitivity analysis:</p> <ul style="list-style-type: none"> - Priced at \$250 USD: cost was \$31,856 USD per QALY gained - Priced at \$945 USD: cost was \$49,995 USD per QALY gained 	<p>"In the current model, open partial fasciectomy is not cost-effective. Needle aponeurotomy is cost-effective if the success rate is high. Collagenase injection is cost-effective when priced under \$945." (P. 1826)</p>

AE=adverse event; CCH=collagenase clostridium histolyticum; CRPS=complex regional pain syndrome; DASH=Disabilities of the Arm, Shoulder, and Hand questionnaire; DF=dermofasciectomy; DIP=distal intraphalangeal joint; FU=follow-up; ICER=incremental cost-effectiveness ratio; MCP=metacarpophalangeal joint; NA=needle aponeurotomy; NCPS=non-comparative prospective studies; NCRS=non-comparative retrospective studies; NR=not reported; OPF=open partial fasciectomy; PED=passive extension deficit; PIP=proximal intraphalangeal joint; PNF=percutaneous needle fasciectomy; QALY=qualityadjusted life year; QRCT=quasi-randomized controlled trial; RCT=randomized controlled trial; RSD=reflex sympathetic dystrophy; SD=standard deviation; TPED=total passive extension deficit; USD=U.S. dollars; wks= weeks; yrs=years

* Recurrence was defined as an increase in joint contracture to $\geq 30^\circ$ compared with the sixweek value

† DASH questionnaire: The DASH questionnaire^{13,14} is a validated instrument used to score disabilities of the upper extremity during daily activities. It consists of 30 items that address disability and symptoms of the upper extremity on a scale from 0 to 5. The scores are added and transformed into a 100-point scale, with lower scores indicating less disability. The scores were completed by all patients before surgery and 1, 2, 3, 4, and 5 weeks after treatment.

‡ Major AEs included: infection, skin slough, hematoma, transected artery, suspected digital nerve injury, re-exploration, and suspected division of a flexor tendon. Minor AEs included: skin fissure and paresthesias.