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CLINICAL ARTICLE

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Peripheral nerve repair throughout the body with processed nerve allografts: Results from a large multicenter study

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Abstract

Background: Peripheral nerve damage resulting in pain, loss of sensation, or motor function may necessitate a reconstruction with a bridging material. The RANGER® Registry was designed to evaluate outcomes following nerve repair with processed nerve allograft (Avance® Nerve Graft; Axogen; Alachua, FL). Here we report on the results from the largest peripheral nerve registry to-date.

Methods: This multicenter IRB-approved registry study collected data from patients repaired with processed nerve allograft (PNA). Sites followed their own standard of care for patient treatment and follow-up. Data were assessed for meaningful recovery, defined as ≥S3/M3 to remain consistent with previously published results, and comparisons were made to reference literature.

Results: The study included 385 subjects and 624 nerve repairs. Overall, 82% meaningful recovery (MR) was achieved across sensory, mixed, and motor nerve repairs up to gaps of 70 mm. No related adverse events were reported. There were no significant differences in MR across the nerve type, age, time-to-repair, and smoking status subgroups in the upper extremity ($p > .05$). Significant differences were noted by the mechanism of injury subgroups between complex injures (74%) as compared to lacerations (85%) or neuroma resections (94%) ($p = .03$) and by gap length between the <15 mm and 50–70 mm gap subgroups, 91 and 69% MR, respectively ($p = .01$). Results were comparable to historical literature for nerve autograft and exceed that of conduit.

Conclusions: These findings provide clinical evidence to support the continued use of PNA up to 70 mm in sensory, mixed and motor nerve repair throughout the body and across a broad patient population.

1 | INTRODUCTION

Peripheral nerve damage due to traumatic injury is common and can result in loss of sensation and motor function impacting overall quality of life. Almost immediately after a nerve is severed, function directed by that nerve are lost unless proximal axon branches can be reconnected, which often requires appropriate surgical repair (Lundborg, 2000). While a tension-free direct repair with joints at extension is ideal, complex or extensive injuries may require a bridging material to support axonal regeneration across the nerve discontinuity for successful recovery (Lundborg, 2000; Mackinnon & Dellon, 1988).

Currently available bridging materials include nerve autografts, conduits, or processed nerve allografts (Dvali & Mackinnon, 2003; Safa & Buncke, 2016). Nerve autograft, preferred over a direct repair under tension, is a well-established method to manage nerve gap injuries (Safa & Buncke, 2016); however, there are drawbacks to this method. Nerve autografts require an additional surgical procedure, which increases costs, anesthesia time, surgical and healing complications (e.g., scarring, pain, and neuromas) (Ehretsman, Novak, & Mackinnon, 1999; Frykman & Gramyk, 1991; Ijpma, Nicolai, & Meek, 2006; Meek, Coert, & Robinson, 2005; Rappaport et al., 1993; Taras, Amin, Patel, & McCabe, 2013). Furthermore, tissue availability is limited and requires that a healthy, functional nerve be sacrificed to repair the damaged nerve. Conduits, hollow tubes made from various biological or synthetic materials, have been used clinically since the late 1990s. A recent systematic review found their outcomes to be highly variable and inconsistent from study to study with a recommendation for their use be limited to gaps <10 mm (Safa & Buncke, 2016). Recently, processed nerve allografts (PNAs) have been increasingly used as a viable option in clinical practice. These grafts possess many of the physiological characteristics of nerve autografts without the associated complications.

Avance® Nerve Graft (Axogen, Inc., Alachua, FL) is a decellularized, pre-degenerated, sterilized extracellular matrix (ECM) processed from donated human peripheral nerve tissue that serves as a scaffold for nerve regeneration. The benefits include a flexible, pliable, ECM that maintains the structure and laminin of native nerve, allows for revascularization and remodels into the patient's own tissue while supporting

axonal growth across the nerve discontinuity. These characteristics are considered to be ideal for nerve graft bridging materials (Millesi, 2007). Additionally, due to patented tissue processing methods, patient immunosuppressive therapy is not required.

In 2008, a multi-center observational registry study ("RANGER®") was initiated to collect utilization and outcome data on nerve injuries repaired with PNA. RANGER is currently the largest on-going collection of nerve repair data of its kind; it actively monitors and collects injury, repair, safety, and real world outcomes data for PNAs. Cumulative registry outcomes were initially described in a single study-wide publication (Brooks et al., 2012), with subsequent publications summarizing results in focused sub-group study populations. (Cho et al., 2012; Isaacs & Safa, 2017; Rinker et al., 2015; Rinker, Zoldos, Weber, et al., 2017; Safa, Shores, Ingari, et al., 2019) Additionally, a growing number of clinical studies have shown the use of PNA to be safe and effective option to repair nerve gap injuries. This listing is provided in Data S1. RANGER now includes over 1,600 nerve repairs. This update focuses on quantitative outcomes data of the expanded cumulative registry for injuries spanning 70 mm as compared to historical controls for nerve autograft and tube conduit.

2 | PATIENTS AND METHODS

RANGER is conducted under Institutional Review Board (IRB) approval and in accordance with Good Clinical Practice (GCP) standards. Between November 2008 and October 31, 2018 sites have enrolled subjects treated with PNA. As the registry is inclusive of nerve repairs in all regions of the body, specific follow-up time and assessments vary based on the associated nerve and distance for reinnervation. Thus treatment, rehabilitation regime, and follow-up were determined by each site's standard of care and the needs of the patient.

All patients enrolled were included in the utilization population and safety population (UP/SP). Analysis for efficacy included only subjects with sufficient follow-up data available to determine the outcome of the repair. These were categorized into the Outcomes Population (OP). To qualify, subjects had to have reported follow-up assessments at a time-point commensurate with the approximated distance for reinnervation, based on estimated 1–2 mm/day regeneration to the target zone of reinnervation (Brooks et al., 2012). Nerve repairs older than a year after initial injury were excluded from motor functional recovery analysis due to the effects of chronic muscle denervation. Patient demographics did not vary considerably from those included in Brooks et al. (Brooks et al., 2012); patients were generally healthy and without significant underlying illness or comorbidities.

Clinical evaluation followed the prespecified guidelines in the protocol and was in accordance with previously listed standards. Data were collected in an observational manner from electronic medical records (EMR) and managed by an independent contract research organization. Only authorized personnel at the study could access the database and all data underwent data monitoring for accuracy and completeness.

The incidence of adverse events (AEs) was assessed as a safety evaluation. The sites were instructed to report all events related to the repair. Safety was assessed by means of summarizing the incidence of AEs.

Response to treatment was evaluated for subjects reporting either qualitative and quantitative data. Response to treatment was defined as any reported improvement after repair collected from the medical record. In subjects reporting quantitative data, the Mackinnon-Dellon Modification of the Medical Research Council Classification (MRCC) sensory and motor scales (Mackinnon & Dellon, 1988) were then used. Meaningful recovery was defined to be S3 or M3 or greater to remain consistent with previously published results. PNA outcomes were compared to historical data for hollow tube conduit and/or nerve autograft and were summarized in each result section and served as comparative reference tables (see Data S2) for expected outcomes. For repairs reporting long term follow-up (12 months and 18 months for sensory and mixed/motor nerves, respectively), evaluation of higher thresholds of recovery, defined as S3+/M4 or greater, were also made to comparative subgroups of historical data reporting the same higher thresholds.

2.1 | Statistical analysis

Detailed evaluation methods are described in Brooks et al (Brooks et al., 2012). Subgroup analyses were also performed by nerve type, gap length, time to repair, age, mechanism of injury, and smoking status. The percentage meaningful recovery (MR rate) was calculated for the quantitative population/subgroups. Continuous variables were compared using Mann Whitney *U* test. Categorical variables were compared using Fisher's exact or exact Chi square test as appropriate. Unless specified otherwise, all statistical tests were two sided and performed using a significance (alpha) level of 0.05. *p* values were corrected for multiple comparisons using the Bonferroni method.

3 | RESULTS

3.1 | Subject and nerve injury characteristics

The UP/SP consisted of 1,041 subjects undergoing 1,630 repairs across 31 study centers. Nerve repairs occurred in the upper extremity, lower extremity, and head/neck regions of the body. As of the data cutoff, 691 subjects lost or were still in active post-operative care and 385 subjects completed follow-up with sufficient assessments to determine the outcome of the repair. The mean age was 42 ± 17 (6–83) years. Subject and traumatic injury characteristics are summarized in Tables 1 and 2.

3.2 | Efficacy outcomes: response to treatment and meaningful recovery

Response to treatment was defined as any improvement after repair based on either qualitative and/or quantitative assessments. The

TABLE 1 Subject characteristics

Parameter	Outcome population
Subjects (*n*)	385
Age (years)	
Mean ± SD	41.59 ± 16.73
Median	40.00
Std error	0.85
Coefficient of variation (%)	40.24%
(min, max)	(6.0, 83.0)
Under 18 years, n (%)	8 (2.1%)
18–29 years, n (%)	113 (29.4%)
30–49 years, n (%)	136 (35.3%)
50–64 years, n (%)	85 (22.1%)
65 or more years, n (%)	43 (11.2%)
Gender—*n* (%)	
Male	299 (77.7%)
Female	86 (22.3%)
Smoking history—*n* (%)	
Smoker	94 (24.4%)
Previous smoker	22 (5.7%)
Non-smoker	255 (66.2%)
Unknown	14 (3.6%)
Hand dominance—subject, *n* (%)	
Left	24 (6.2%)
Right	315 (81.8%)
Ambidextrous	2 (0.5%)
Unknown	42 (10.9%)
Missing	2 (0.5%)
Pertinent medical history—subject, *n* (%)	
Yes	204 (52.99%)
None	173 (44.94%)
Unknown	8 (2.08%)
Medical history—subject, *n* (%)	
Diabetes	28 (10.37%)
Difficult healing	1 (0.37%)
Hypertension	77 (28.52%)
Peripheral neuropathy	4 (1.48%)
Other medical history	160 (59.26%)

TABLE 2 Nerve injury characteristics

Population	Outcome population (N,S = 385), (N,R = 624)
Mechanism of nerve injury—*n* (%)[a]	
Amputation/replantation	27 (7.0%)
Avulsion	22 (5.7%)
Blunt laceration	11 (2.9%)
Crush/compression	49 (12.7%)
Gunshot/blast	37 (9.6%)
Iatrogenic	16 (4.2%)
Missing	2 (0.5%)
Other	14 (3.6%)
Saw laceration	107 (27.8%)
Sharp laceration	92 (23.9%)
Stretching	1 (0.3%)
Tumor	7 (1.8%)
Nerve injury area—*n* (%)[a]	
Head/neck	4 (1.0%)
Lower extremity	28 (7.3%)
Upper extremity	353 (91.7%)
Concomitant injuries—*n* (%)[b]	
Fracture	191 (28.4%)
Ligament	5 (0.7%)
Other	11 (1.6%)
Skin	8 (1.2%)
Tendon	247 (36.7%)
Vascular	211 (31.4%)

Abbreviations: N,S, number of subjects; N,R, number of repair.
[a]Subjects with more than one repair are reported under each category.
[b]Repairs with more than one concomitant injury were reported under each category.

overall subject response to treatment rate was 87%. Within this group, 475 repairs reported quantitative outcomes data which allowed for evaluation of meaningful recovery. This included 386 sensory, 77 mixed, and 12 motor nerve repairs. The mean gap was 24 ± 15(3–70) mm. The mean follow-up time was 417 (120–3,286) days. The median time to repair was 2 (0–4,452) days. Cumulative meaningful recovery was reported in 82% of these repairs.

By body region meaningful recovery was reported in 83, 53, and 100% in the upper extremity, lower extremity and head/neck respectively. The rate of meaningful recovery was significantly different between the upper and lower extremities (p = .01). While all six of the head and neck repairs reported meaningful recovery, comparisons were not conducted due to the small sample size. Outcomes were further evaluated by nerve function and compared to historical literature by body region for hollow tube conduit and/or nerve autograft. Table 3 summarizes PNA sensory and motor function to reference data. Rates of meaningful recovery of PNA were within the range of reference data for nerve autograft and exceed those of nerve conduit by body region. As such further subgroup analysis was conducted in both the upper and lower extremity when possible.

3.2.1 | Subgroup analysis

Factors found to influence the outcome of nerve repairs (Burnett & Zager, 2004; Chiriac, Facca, Diaconu, Gouzou, & Liverneaux, 2012; Frykman & Gramyk, 1991; Grinsell & Keating, 2014; He, Zhu, Zhu, et al., 2014; Kabak, Halici, Baktir, et al., 2002; Mauch, Bae,

TABLE 3 Comparisons of meaningful sensory and motor function of PNA to reference data

Sensory function	No repairs reporting MRCC scores for sensory function	Meaningful sensory ≥S3, *N*, %	Reference data [a]
All repairs	449	362, 81%	NA
Digital sensory repairs	356	299, 84%	Conduit: 44–75% Autograft: 70–90%
Upper extremity: Sensory nerve	19	13, 68%	NA
Upper extremity mixed nerve	55	39, 71%	Conduit: 8% Autograft: 71–85%
Lower extremity sensory nerve	3	3, 100%	NA
Lower extremity mixed nerve	14	6, 43%	Conduit: NA Autograft: 24–80%
Head neck	2	2, 100%	NA
Motor function	**No repairs reporting MRCC scores for motor function**	**Meaningful motor ≥M3, *N*, %**	**Reference data [a]**
All repairs	62	41, 66%	NA
Upper extremity	52	36, 69%	Conduit: 8% Autograft: 67%
Lower extremity	6	1, 17%	Conduit: NA Autograft: 14–86%
Head neck	4	4, 100%	NA

[a]Reference data source is provided in Data S1.

Shubinets, & Lin, 2019; Moore, Wagner, & Fox, 2015; Roganovic & Pavlicevic, 2006; Ruijs, Jaquet, Kalmijn, Giele, & Hovius, 2005; Weber, Breidenbach, Brown, Jabaley, & Mass, 2000; Zeeshan, Dembe, Seiber, & Lu, 2014) were also evaluated for MR by subgroup. Table 4 displays overall results for MR and by subgroup. Similarly, Table 5 displays results for MR by subgroups split into upper and lower extremities.

3.3 | Nerve type

While a significant number of nerve repairs have been added to the database since the initial interim analysis, outcomes by nerve type remained similar to Brooks et al with 84, 71, and 83% for sensory, mixed, and motor nerves, respectively. For upper extremities, there was no significant difference in the MR outcomes by nerve type indicating PNA performed consistently across nerve types (p = .56). As expected, outcomes between upper and lower extremity mixed nerve repairs were significantly different (79 and 44%, respectively, p = .01). These outcomes and differences among body region were comparable to those reported for upper and lower extremity autograft repair, see Table 3, especially for sciatic and peroneal nerve repairs.

When looking at higher thresholds of recovery, S3+/M4 or greater, only limited comparisons to reference data could be made due to the lack of studies reporting these granular levels outcomes in the historical literature. Weber et al reported results from a controlled study comparing conduit and nerve autograft for sensory gap repairs (Weber et al., 2000). Higher thresholds of sensory recovery were reported in 68% of conduits and 71% of autografts, as compared to 83% of PNA digital nerve repairs in this study. Ruijs et al. completed a large systemic review of median and ulnar nerve autograft repairs through 2004 (Ruijs et al., 2005). Higher thresholds were reported in 51% of autograft repairs as compared to 46% of the PNA upper extremity mixed nerve repairs. Table 6 summarizes PNA sensory and motor function at higher thresholds of recovery to reference data. Similarly, Table 7 displays results for higher thresholds by subgroups in the upper extremities.

3.4 | Nerve gap length

Repair outcomes were divided into four gap length groups, <15, 15–29, 30–49, and 50–70 mm. Overall, MR rates in the upper extremity ranged between 78 and 91% for the three gap length subgroups less than 50 mm and were not significantly different. Gaps <15 mm performed better than the 50–70 mm subgroup (p = .011). This was not significant between the 50–70 and 15–29 mm (p = .38) and 30–49 mm (>0.999) subgroups. The 50–70 mm subgroup was comprised of 43 repairs (16 sensory and 27 mixed), of which 29 were complex injuries, 10 were lacerations, and four were neuroma repairs. See Table 4. Outcomes from this long gap group were found to be in line with nerve autograft outcomes of similar gap lengths (Frykman & Gramyk, 1991; He et al., 2014; Millesi, 2007). There were no significant differences in the MR rates of lower extremities.

TABLE 4 Summary of nerve repairs in the OP, quantitative subpopulation, and subgroups with meaningful recovery

					Nerve type			Mechanism of injury			MR
Factor	*N*	Age (Yrs)	POI (days)	Gap length (mm)	Sensory	Mix.	Motor	Lac.	Neur.	Comp.	%
OP by repair	475	42 ± 17	97 ± 370	24 ± 15	386	77	12	290	38	147	82
Nerve type											
Sensory	386	42 ± 17	82 ± 309	21 ± 12	–	–	–	252	27	107	84
Mixed	77	40 ± 18	186 ± 608	39 ± 18	–	–	–	34	9	34	71
Motor	12	49 ± 17	48 ± 68	21 ± 9	–	–	–	4	2	6	83
Gap length (mm)[a]											
<15	133	41 ± 17	11 ± 34	–	127	3	3	109	4	20	91
15–29	168	44 ± 17	76 ± 269	–	145	18	5	110	8	50	85
30–49	114	42 ± 17	182 ± 459	–	83	27	4	47	22	45	78
50–70	43	35 ± 16	268 ± 792	–	16	27	0	10	4	29	60
Time to repair[b]											
Acute	373	41 ± 17	–	21 ± 13	321	45	7	261	1	111	81
Chronic	75	43 ± 15	–	34 ± 17	50	22	3	14	36	25	83
Delayed	26	40 ± 14	–	28 ± 17	14	10	2	15	1	10	85

					Nerve type			Mechanism of injury			MR
Factor	*N*	Age (Yrs)	TTR (days)	Gap length (mm)	Sensory	Mix.	Motor	Lac.	Neur.	Comp.	%
Age (years)											
Under 18 years	10	–	18 ± 41	24 ± 16	8	2	0	4	0	6	80
18–29	141[a]	–	70 ± 262	25 ± 16	113	26	2	86	10	45	84
30–49	171	–	110 ± 429	23 ± 15	143	25	3	105	16	50	78
50–64	98	–	156 ± 486	23 ± 12	77	15	6	49	10	39	91
65+	55	–	37 ± 99	23 ± 15	45	9	1	46	2	7	71
Mechanism of injury											
Laceration	290	43 ± 18	22 ± 118	19 ± 12	252	34	4	–	–	–	84
Neuroma	38	43 ± 14	764 ± 942	31 ± 13	27	9	2	–	–	–	95
Complex[c]	147	39 ± 16	81 ± 285	30 ± 17	107	34	6	–	–	–	73
Smoking history[d]											
Smoker	108	37 ± 13	109 ± 544	23 ± 15	84	21	3	–	–	–	79
Non-smoker	334	42 ± 17	87 ± 280	24 ± 15	282	44	8	–	–	–	82
Previous smoker	22	60 ± 13	162 ± 546	24 ± 16	14	8	0	–	–	–	82

Abbreviations: Comp., complex; Lac., lacerations; Mix., mixed; Neur., neuroma; TTR, Time to repair; Sens., sensory; Yrs, years; MR, meaningful recovery MRCC ≥ S3/M3.

[a]11 repairs reported unknown gap length was excluded from the subgroup analysis.

[b]One repair reported unknown pre-operative interval was excluded from the subgroup analysis.

[c]Complex injury includes gunshot/blast wound, crush/compression, amputations, and avulsion injuries.

[d]14 repairs reported unknown smoking history was excluded from the subgroup analysis.

Note: Age, pre-operative interval, follow-up days, and gap length are expressed as mean ± standard deviation.

3.5 | Time to repair

Time to repair was categorized as acute, chronic, or delayed based on the pre-operative interval, which demonstrated large within-group variability in general. In this study, most of the repairs were acute (n = 369) compared to chronic (n = 73) and delayed repairs (n = 26), with consistent MR rates of 81, 83, and 85%, respectively. Overall, these rates were not significantly different (p = .93).

3.6 | Mechanism of injury

Most of the injuries were either due the lacerations or complex mechanisms. Lacerations included sharp, saw, and blunt. Complex included amputations, avulsion, blast, gunshot, crush, and compression injuries. There was no statistical difference between laceration and neuroma repairs, 84 and 95% meaningful recovery (p = .269). In upper extremity, lacerations and neuroma resections did perform

TABLE 5 Summary of upper and lower extremity nerve repairs with meaningful recovery in the op, quantitative subpopulation, according to subgroups

					Nerve type			Mechanism of injury			
Factor	N	Age (Yrs)	POI (days)	Gap (mm)	Sens.	Mix.	Mot.	Lac.	Neur.	Com.	MR
Extremity type											
Upper	450	42 ± 17	87 ± 351	23 ± 13	381	61	8	286	36	128	83%[a]
Lower	19	38 ± 17	380 ± 709	50 ± 18	3	16	0	3	1	15	53%[a]
Nerve type—upper											
Sensory	381	42 ± 17	76 ± 297	21 ± 12	–	–	–	286	26	104	84%
Mixed	61	40 ± 18	158 ± 598	35 ± 16	–	–	–	32	8	21	79%[a]
Motor	8	42 ± 15	57 ± 74	20 ± 9	–	–	–	3	2	3	75%
Nerve type—lower											
Sensory	3	35 ± 8	721 ± 993	25 ± 13	–	–	–	1	0	2	100%
Mixed	16	38 ± 18	307 ± 659	55 ± 15	–	–	–	2	1	13	44%[a]
Motor	0	–	–	–	–	–	–	–	–	–	–
					Nerve type			Mechanism of injury			
Factor	N	Age (Yrs)	POI (days)	Gap (mm)	Sens.	Mix.	Mot.	Lac.	Neur.	Com.	MR
Gap length (mm)—upper											
<15	130	41 ± 17	9 ± 30	–	125	3	2	107	3	20	91%[b]
15–29	165	43 ± 16	77 ± 272	–	144	18	3	110	8	47	84%
30–49	106	42 ± 18	172 ± 441	–	81	22	3	47	22	37	78%
50–70	32	34 ± 14	225 ± 820	–	16	16	0	8	3	21	69%[b]
Gap length (mm)—lower											
<15	1	27	6	–	1	0	0	1	0	0	100%
15–29	0	–	–	–	–	–	–	–	–	–	–
30–49	7	40 ± 11	437 ± 803	–	2	5	0	0	0	7	71%
50–70	11	38 ± 20	388 ± 729	–	0	11	0	2	1	8	36%
Time to repair[c]—upper											
Acute	364	41 ± 17	–	21 ± 13	319	41	4	260	1	103	81%
Chronic	61	44 ± 15	–	31 ± 13	47	12	2	11	34	16	90%[a]
Delayed	24	38 ± 13	–	26 ± 16	14	8	2	15	1	8	83%
					Nerve type			Mechanism of injury			
Factor	N	Age (Yrs)	POI (days)	Gap (mm)	Sens.	Mix.	Mot.	Lac.	Neur.	Com.	MR
Time to repair[c]—lower											
Acute	5	26 ± 8	–	39 ± 22	1	4	0	1	0	4	60%
Chronic	12	39 ± 16	–	55 ± 15	2	10	0	2	1	9	42%[a]
Delayed	2	60 ± 6	–	47 ± 25	0	2	0	0	0	2	100%
Age (years)—upper											
Under 18 years	10	–	18 ± 41	25 ± 16	8	2	0	4	0	6	80%
18–29	131	–	47 ± 156	23 ± 15	110	19	2	85	8	38	85%
30–49	164	–	97 ± 413	22 ± 14	141	20	3	105	16	43	80%[a]
50–64	93	–	164 ± 498	22 ± 11	77	13	3	49	10	34	90%[b]
65+	52	–	31 ± 98	21 ± 11	45	7	0	43	2	7	73%[b]
Age (years)—lower											
Under 18 years	0	–	–	–	–	–	–	–	–	–	–
18–29	8	–	439 ± 870	50 ± 21	1	7	0	1	1	6	63%
30–49	7	–	511 ± 760	45 ± 15	2	5	0	0	0	7	43%[a]

(Continues)

TABLE 5 (Continued)

Factor	N	Age (Yrs)	POI (days)	Gap (mm)	Nerve type			Mechanism of injury			MR
					Sens.	Mix.	Mot.	Lac.	Neur.	Com.	
50–64	2	–	51 ± 38	48 ± 25	0	2	0	0	0	2	100%
65+	2	–	145 ± 0	70 ± 0	0	2	0	2	0	0	0%
Factor	**N**	**Age (Yrs)**	**POI (days)**	**Gap (mm)**	**Nerve type**			**Mechanism of injury**			**MR**
					Sens.	**Mix.**	**Mot.**	**Lac.**	**Neur.**	**Com.**	
Mechanism of injury—upper											
Laceration	286	42 ± 18	21 ± 118	19 ± 11	251	32	3	–	–	–	85%[a,b]
Neuroma	36	44 ± 13	797 ± 960	32 ± 12	26	8	2	–	–	–	94%[b]
Complex	128	39 ± 16	45 ± 121	28 ± 16	104	21	3	–	–	–	74%[b]
Mechanism of injury—lower											
Laceration	3	54 ± 23	99 ± 80	50 ± 35	1	2	0	–	–	–	33%[a]
Neuroma	1	23	227	50	0	1	0	–	–	–	100%
Complex	15	36 ± 14	456 ± 801	50 ± 16	2	13	0	–	–	–	53%

Abbreviations: Comp., complex; Lac., lacerations; Mix., mixed; Neur., neuroma; POI, pre-operative interval; Sens., sensory; Yrs, years; MR, meaningful recovery MRCC ≥S3/M3.

[a]Statistically significant between upper extremity and lower extremity meaningful recovery rate: $p > .05$.

[b]Statistically significant between upper extremity subgroups: $p > .05$.

[c]Acute = repaired within 21 days after injury; Delayed = repaired between 21–90 days after injury; Chronic = repaired 90 days after injury.

better than complex mechanisms, MR = 74% ($p = .027$) despite similar gaps between the neuroma resection and complex mechanisms. These outcomes were however found to be consistent to Reference Data on nerve autograft repairs after complex mechanisms with meaningful recovery between 42 and 77% indicating these injury patterns may play a larger role on the likelihood of recovery than the nerve bridging material used (He et al., 2014; Moore et al., 2015; Ruijs et al., 2005).

3.7 | Age

Subject age was analyzed to determine the influence on MR. Our current data showed similar functional recovery across different age groups (range 6–83 years), with MR rates between 78% and 84% for age subgroups under 50. Interestingly, there was a significantly higher MR rate in the 50–64 age subgroup (91%) compared to the 65+ age subgroup (71%) ($p = .014$). This difference however was not observed in the upper and lower extremity independently. Other factors were largely balanced among age subgroups.

3.8 | Smoking status

In this study, most subjects who supplied smoking status recovered regardless of smoking history. In the upper extremity, MR rates did trend higher for nonsmokers (82%) compared to current smokers (79%) but was not significant. Further evaluation looking at the potential effect of smoking among subgroups will be an area of interest as it is believed to be a factor effecting recovery.

3.9 | Safety outcomes: Revision rates and AEs

The overall subject revision rate was 2.98% in the Safety Population and 6.25% in the OP. There were 31 subjects with 39 repairs requiring a revision surgical procedure of the effected nerve with 10 of these revisions related to an adverse experience (AE).

There were 43 AEs reported in 39 subjects resulting in a 3.7% incidence rate by subjects and 2.7% by repair in the Safety Population and 6.9% by repair in the OP. Twenty-three of these where considered serious events. The most common reported AE was neuroma at the repair site with 1.2% incidence rate followed by infection at the repair site at 0.9%. None of the AEs were determined to be related to the product but instead to the circumstances surrounding the original injury. There were no communicable disease transmissions reported.

Comparisons of AE incidence rates were made to expected levels. Zeeshan et al. 2014 reported on AE incidence rates in the US healthcare system from 82,784 surgical hospitalizations (Zeeshan et al., 2014). Incidence rates from surgical procedures involving peripheral nerves and other tissues reported as concomitant injuries (i.e., joint, skin, fracture, muscle) ranged from 2.1 to 8.6%. These reported rates are in line with our study and demonstrates the use of PNAs as safe without posing additional patient risk.

4 | DISCUSSION

Utilization of processed nerve allograft has become an accepted alternative for nerve gap repair. RANGER has collected a repository of more than 1,600 repairs on the utilization, safety, and outcomes from a comprehensive registry study. To our knowledge, this is the largest

TABLE 6 Comparisons of higher thresholds of sensory and motor recovery in repairs reporting long-term follow-up to historical literature

Sensory function	PNA repairs[a]	PNA, Higher thresholds of recovery ≥S3+	Autograft or conduit, Higher thresholds of recovery ≥S3+
Digital nerves	291	83%	Autograft: 70% (Frykman & Gramyk, 1991; Weber et al., 2000) Conduit: 66% (Weber et al., 2000)
Upper extremity mixed nerve	41	56%	Autograft: 40% (Frykman & Gramyk, 1991; Ruijs et al., 2005) Conduit: 8% (Chiriac et al., 2012)
Lower extremity mixed nerve	9	56%	Autograft: 14% (Roganovic & Pavlicevic, 2006)
Motor function	**PNA repairs[a]**	**PNA, Higher thresholds of recovery ≥M4**	**Autograft or Conduit, Higher thresholds recovery ≥M4**
Upper extremity	39	46%	Autograft: 51–54% [7.26]
Lower extremity	6	17%	Autograft:15% (Roganovic & Pavlicevic, 2006)

[a]PNA repairs included subjects from the primary analysis reporting at least 12 months of follow-up for sensory repairs and 18 months follow-up for mixed motor repairs.

TABLE 7 Subgroup assessment of higher thresholds of meaningful recovery in upper extremity nerve repairs reporting long-term follow-up

Subgroup	Number of repairs[a]	Repairs reporting higher thresholds (% MRCC ≥ S3+ or M4)
Gap length (mm)		
<15	113	88%
15–29	139	84%
30–49	76	68%
50–70	25	56%
Time to repair		
Acute	300	78%
Chronic	51	78%
Delayed	18	89%
Age (years)		
Under 18	8	100%
18–29	111	76%
30–49	126	83%
50–64	84	80%
65+	41	63%
Mechanism of injury		
Laceration	239	81%
Neuroma	30	87%
Complex	101	69%

[a]PNA repairs included subjects from the primary analysis reporting at least 12 months of follow-up for sensory repairs and 18 months follow-up for mixed motor repairs.

database of peripheral nerve repair available, providing clinicians and healthcare providers with real world clinical evidence.

The use of the processed nerve allograft is safe with no reported related adverse events and a low subject revision rate. Additionally, adverse experiences reported in the medical record, regardless of product relatedness, were also collected to prevent underreporting. These overall AE incidence rates were in line with the rates expected from US surgical procedures indicating that Avance did not pose additional patient risk.

Results gathered in the RANGER study indicate that a high percentage of nerve repairs utilizing processed nerve allograft (≥82%) achieved MR with 84%, 71%, and 83% in sensory, mixed, and motor nerves. Upper extremity nerve repairs did have a significantly higher MR percentage (83%) compared to lower extremity nerve repairs (53%) ($p < 0.05$). Comparisons in these body regions were also consistent with nerve autograft (see Data S2) (Frykman & Gramyk, 1991; He et al., 2014; Mauch et al., 2019; Safa & Buncke, 2016). In the upper extremity, digital nerve repairs reported 84% sensory recovery and upper extremity mixed/motor nerves repairs reported 69% motor recovery. This is comparable to autograft reference data for upper extremity sensory and motor function respectively (see Data S2) (Frykman & Gramyk, 1991; He et al., 2014; Mauch et al., 2019; Safa & Buncke, 2016).

This study also evaluated several factors considered to impact outcomes in the upper and lower extremities. There were no significant differences in MR across the nerve type, age, time-to-repair, and smoking status subgroups in the upper extremity ($p > .05$). In the mechanism of injury subgroup, lacerations and neuroma resections reported significantly higher outcomes compared to complex injuries such as amputation, avulsion, gunshot injures. In the gap length subgroup, the short gap (<15 mm) subgroup reported significantly higher outcomes compared to the longest gap (50–70 mm) subgroup. Of note, the 50–70 mm subgroup was comprised of significantly more complex injury patterns than the short gap group ($p > .05$), which may explain the differences observed between these two groups and not the other gap length groups. This however, was in line with expected outcomes reported with nerve autograft for similar subgroups (Frykman & Gramyk, 1991; Kabak et al., 2002; Mauch et al., 2019; Moore et al., 2015; Safa & Buncke, 2016) (see Data S2).

In a recent meta-analysis, PNA were found to be comparable to nerve autografts and superior to conduits for repair of sensory injuries (Mauch et al., 2019). In our study, short gap lengths (<15 mm), consisting of mostly sensory nerves reported 91% MR. Furthermore, when including gap lengths between 15 and 29 mm, the combined MR for gaps <30 mm was 88% for sensory and 71% for motor function. In gaps 30–70 mm, MR was 75% for sensory and 67% for motor

function throughout the body. These subgroups were not significantly different except when comparing the <15 mm and 50–70 subgroup categories. Evaluation of the 50–70 mm group found it was predominantly complex mixed nerve injuries. Although research on peripheral nerve repairs with PNA in 50+ mm gap lengths is limited, several other published studies have reported successful outcomes (Ducic, Fu, & Iorio, 2012; Fleming, Bharmal, & Valerio, 2014; Safa & Buncke, 2016; Salomon, Miloro, & Kolokythas, 2016; Vögelin & Juon, 2013; Zuniga, Williams, & Petrisor, 2017). Similarly, previous studies with nerve autografts for long-gap repairs (50+ mm) reported MR rates between 64 and 80% (Amillo & Mora, 1999; Bertelli, Soldado, Lehn, & Ghizoni, 2016; Flores, 2015; Gesslbauer et al., 2017; Gezercan et al., 2016; Kallio & Vastamäki, 1993). These results are aligned with the allograft MR rates when assessed by mechanism of injury. The results also suggest that complex injuries introduce additional variables that may influence recovery. Additional clinical data is needed to assess the role mechanism of injury and gap length play on the likelihood of a successful outcome in both nerve allograft and autograft.

Limitations of the study include a flexible study design, to allow for comprehensive collection of all nerve reconstructions, that resulted in a heterogenic dataset and a lack of comparable literature using higher thresholds of recovery. This is a common limitation in observational studies due to variability of patients, nerve injuries, sites, and surgeons. Sites used standardized case report forms (CRFs) to reduce potential bias, minimize reporting errors, and ensure consistency of the data collected. Additionally, a detailed data management plan specified that all data captured undergo quality-control checks via monitoring of electronic medical records. This standardization controls for heterogenicity and will allow for more future focused subgroup analysis.

In this study, limited comparisons of PNA to nerve autograft could be made at higher thresholds of recovery due to the lack of comparable literature. The authors encourage the completion of more contemporary systematic reviews from observational data and the publication of controlled quantitative outcomes data with nerve autograft using these higher thresholds of recovery. This data would allow for further comparisons with PNA and would assist in powering future prospective studies to evaluate new technologies in peripheral nerve gap repair.

The results of the RANGER study to date show overall favorable results for nerve repair and regeneration using the processed nerve allograft and provide support for its continued use. Nerve allografts have been gaining popularity in the clinic over recent years and other publications reporting outcomes with PNA have shown successful recovery throughout the body. Outcomes were similar to historical literature with nerve autograft and exceeded that of conduit (Frykman & Gramyk, 1991; Mauch et al., 2019; Means, Rinker, Higgins, et al., 2016; Safa & Buncke, 2016).

5 | CONCLUSION

The RANGER registry has provided real world evidence to support the use of processed nerve allografts up to 70 mm throughout the body as a successful intervention, with regard to both safety and meaningful recovery, for peripheral nerve reconstruction.

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REFERENCES

Amillo, S., & Mora, G. (1999). Surgical management of neural injuries associated with elbow fractures in children. *Journal of Pediatric Orthopaedics*, *19*(5), 573–577.

Bertelli, J. A., Soldado, F., Lehn, V. L. M., & Ghizoni, M. F. (2016). Reappraisal of clinical deficits following high median nerve injuries. *The Journal of Hand Surgery*, *41*(1), 13–19.

Brooks, D., Weber, R. V., Chao, J. D., Rinker, B. D., Zoldos, J., Robichaux, M. R., … Buncke, G. (2012). Processed nerve allografts for peripheral nerve reconstruction: A multicenter study of utilization and outcomes in sensory, mixed, and motor nerve reconstructions. *Microsurgery*, *32*, 1–85.

Burnett, M., & Zager, E. L. (2004). Pathophysiology of peripheral nerve injury: A brief review. *Neurosurgical Focus*, *16*(5), E1.

Chiriac, S., Facca, S., Diaconu, M., Gouzou, S., & Liverneaux, P. (2012 May). Experience of using the bioresorbable copolyester poly(DL-lactide-ε-caprolactone) nerve conduit guide Neurolac™ for nerve repair in peripheral nerve defects: Report on a series of 28 lesions. *The Journal of Hand Surgery, European Volume*, *37*(4), 342–349. https://doi.org/10.1177/1753193411422685

Cho, M. S., Rinker, B. D., Weber, R. V., Chao, J. D., Ingari, J. V., Brooks, D., … Buncke, G. M. (2012 Nov). Functional outcome following nerve repair in the upper extremity using processed nerve allograft. *The Journal of Hand Surgery*, *37*(11), 2340–2349.

Ducic, I., Fu, R., & Iorio, M. L. (2012). Innovative treatment of peripheral nerve injuries: Combined reconstructive concepts. *Annals of Plastic Surgery*, *68*(2), 180–187. https://doi.org/10.1097/SAP.0b013e3182361b23

Dvali, L., & Mackinnon, S. (2003). Nerve repair, grafting, and nerve transfers. *Clinics in Plastic Surgery*, *30*, 203–221.

Ehretsman, R. L., Novak, C. B., & Mackinnon, S. E. (1999). Subjective recovery of nerve graft donor site. *Annals of Plastic Surgery*, *43*(6), 606–612.

Fleming, M. E., Bharmal, H., & Valerio, I. (2014). Regenerative medicine applications in combat casualty care. *Regenerative Medicine*, *9*, 179–190.

Flores, L. P. (2015). Comparative study of nerve grafting versus distal nerve transfer for treatment of proximal injuries of the ulnar nerve. *Journal of Reconstructive Microsurgery*, *31*(09), 647–653.

Frykman, G., & Gramyk, K. (1991). In R. Gelberman (Ed.), *Results of nerve grafting, in operative nerve repair and reconstruction*. Philadelphia: JB Lippincott.

Gesslbauer, B., Furtmüller, G. J., Schuhfried, O., Roche, A. D., Sporer, M., & Aszmann, O. C. (2017). Nerve grafts bridging the thenar branch of the median nerve to the ulnar nerve to enhance nerve recovery: A report

of three cases. *The Journal of Hand Surgery, European Volume*, *42*(3), 281–285.

Gezercan, Y., Menekşe, G., Ökten, A. İ., Arslan, A., Özsoy, K. M., Ateş, T., … Güzel, A. (2016). The outcomes of late term surgical treatment of penetrating peripheral nerve injuries. *Turkish Neurosurgery*, *26*(1), 146–152.

Grinsell, D., & Keating, C. P. (2014). Peripheral nerve reconstruction after injury: A review of clinical and experimental therapies. *BioMed Research International*, *2104*, 698256–698213. https://doi.org/10.1155/2014/698256

He, B., Zhu, Z., Zhu, Q., Zhou, X., Zheng, C., Li, P., … Zhu, J. (2014). Factors predicting sensory and motor recovery after the repair of upper limb peripheral nerve injuries. *Neural Regeneration Research*, *9*(6), 661–672. https://doi.org/10.4103/1673-5374.130094

Ijpma, F. F., Nicolai, J. P., & Meek, M. F. (2006). Sural nerve donor-site morbidity: Thirty-four years of follow-up. *Annals of Plastic Surgery*, *57*(4), 391–395.

Isaacs, J., & Safa, B. (2017). A preliminary assessment of the utility of large-caliber processed nerve allografts for the repair of upper extremity nerve injuries. *The Hand*, *12*(1), 55–59. https://doi.org/10.1177/1558944716646782

Kabak, S., Halici, M., Baktir, A., Türk, C. Y., & Avşarogullari, L. (2002). Results of treatment of the extensive volar wrist lacerations: 'The spaghetti wrist'. *European Journal of Emergency Medicine*, *9*(1), 71–76.

Kallio, P. K., & Vastamäki, M. (1993). An analysis of the results of late reconstruction of 132 median nerves. *The Journal of Hand Surgery*, *18*(1), 97–105.

Lundborg, G. (2000). A 25-yr perspective of peripheral nerve surgery: Evolving neuroscientific concepts and clinical significance. *Journal of Hand Surgery*, *25*, 391–414.

Mackinnon, S. E., & Dellon, A. L. (1988). *Results of nerve repair and grafting, in surgery of peripheral nerve*. New York: Thieme Medical.

Mauch, J. T., Bae, A., Shubinets, V., & Lin, I. C. (2019 Apr). A systematic review of sensory outcomes of digital nerve gap reconstruction with autograft, allograft, and conduit. *Annals of Plastic Surgery*, *82*(4S Suppl 3), S247–S255. https://doi.org/10.1097/SAP.0000000000001851

Means, K. R., Rinker, B. D., Higgins, J. P., Payne, S. H. Jr., Merrell, G. A., & Wilgis, E. F. (2016). A multicenter prospective randomized pilot study of outcomes for digital nerve repair in the hand using hollow conduit compared with processed nerve allograft. *The Hand*, *11*(2), 144–151. https://doi.org/10.1177/1558944715627233

Meek, M. F., Coert, H., & Robinson, P. H. (2005). Poor results after nerve grafting in the upper extremity: Quo vadis? *Microsurgery*, *25*(5), 396–402.

Millesi, H. (2007). Bridging defects: Autologous nerve grafts. *Acta Neurochirurgica*, *100*, 37–38.

Moore, A. M., Wagner, I. J., & Fox, I. K. (2015 Feb). Principles of nerve repair in complex wounds of the upper extremity. *Seminars in Plastic Surgery*, *29*(1), 40–47. https://doi.org/10.1055/s-0035-1544169

Rappaport, W. D., Valente, J., Hunter, G. C., Rance, N. E., Lick, S., Lewis, T., & Neal, D. (1993). Clinical utilization and complications of sural nerve biopsy. *American Journal of Surgery*, *166*, 252–256.

Rinker, B. D., Ingari, J. V., Greenberg, J. A., Thayer, W., Safa, B., & Buncke, G. (2015). Outcomes of short-gap sensory nerve injuries reconstructed with processed nerve allografts from a multicenter registry study. *Journal of Reconstructive Microsurgery*, *31*(5), 384–390. https://doi.org/10.1055/s-0035-1549160

Rinker, B. D., Zoldos, J., Weber, R. V., Ko, J., Thayer, W., Greenberg, J., … Buncke, G. (2017). Use of processed nerve allografts to repair nerve injuries greater than 25 mm in the hand. *Annals of Plastic Surgery*, 78(6S Suppl 5), S292–S295. https://doi.org/10.1097/SAP.0000000000001037

Roganovic, Z., & Pavlicevic, G. (2006). Difference in recovery potential of peripheral nerves after graft repairs. *Neurosurgery*, *59*(3), 621–633.

Ruijs, A. C., Jaquet, J. B., Kalmijn, S., Giele, H., & Hovius, S. E. (2005). Median and ulnar nerve injuries: A meta-analysis of predictors of motor and sensory recovery after modern microsurgical nerve repair. *Plastic and Reconstructive Surgery*, *116*(2), 484–494 discussion 495-6.

Safa, B., & Buncke, G. (2016). Autograft substitutes: Conduits and processed nerve allografts. *Hand Clinics*, *32*(2), 127–140.

Safa, B., Shores, J. T., Ingari, J. V., Weber, R. V., Cho, M., Zoldos, J., … Buncke, G. M. (2019). Recovery of motor function after mixed and motor nerve repair with processed nerve allograft. *Plastic and Reconstructive Surgery—Global Open*, *7*(3), e2163. https://doi.org/10.1097/GOX.0000000000002163

Salomon, D., Miloro, M., & Kolokythas, A. (2016). Outcomes of immediate allograft reconstruction of long-span defects of the inferior alveolar nerve. *Journal of Oral and Maxillofacial Surgery*, *74*(12), 2507–2514.

Taras, J. S., Amin, P., Patel, N., & McCabe, L. A. (2013). Allograft reconstruction for digital nerve loss. *The Journal of Hand Surgery*, *38*(10), 1965–1971. https://doi.org/10.1016/j.jhsa.2013.07.008

Vögelin, E., & Juon, B. (2013. Chapter 7–3). Nerve allografts and vein grafts in nerve reconstructions. In L. B. Dahlin & G. Leblebicioglu (Eds.), (pp. 271–278). Zurich (Switzerland): Palme Publications.

Weber, R. A., Breidenbach, W. C., Brown, R. E., Jabaley, M. E., & Mass, D. P. (2000 Oct). A randomized prospective study of polyglycolic acid conduits for digital nerve reconstruction in humans. *Plastic and Reconstructive Surgery*, *106*(5), 1036–1045.

Zeeshan, M. F., Dembe, A. E., Seiber, E. E., & Lu, B. (2014). Incidence of adverse events in an integrated US healthcare system: A retrospective observational study of 82,784 surgical hospitalizations. *Patient Safety Surgery*, *8*, 23.

Zuniga, J. R., Williams, F., & Petrisor, D. (2017). A case-and-control, multisite, positive controlled, prospective study of the safety and effectiveness of immediate inferior alveolar nerve processed nerve allograft reconstruction with ablation of the mandible for benign pathology. *Journal of Oral and Maxillofacial Surgery*, *75*(12), 2669–2681. https://doi.org/10.1016/j.joms.2017.04.002

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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