WFH COMPREHENSIVE CARE SUMMIT

Musculoskeletal health after gene therapy for Hemophilia A: a three-year follow-up study

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Disclosures for: Gabriela G Yamaguti-Hayakawa

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Musculoskeletal (MSK) health is **an important and unmet need** in hemophilia

Severe hemophilia A
↓
FVIII< 1IU/dL

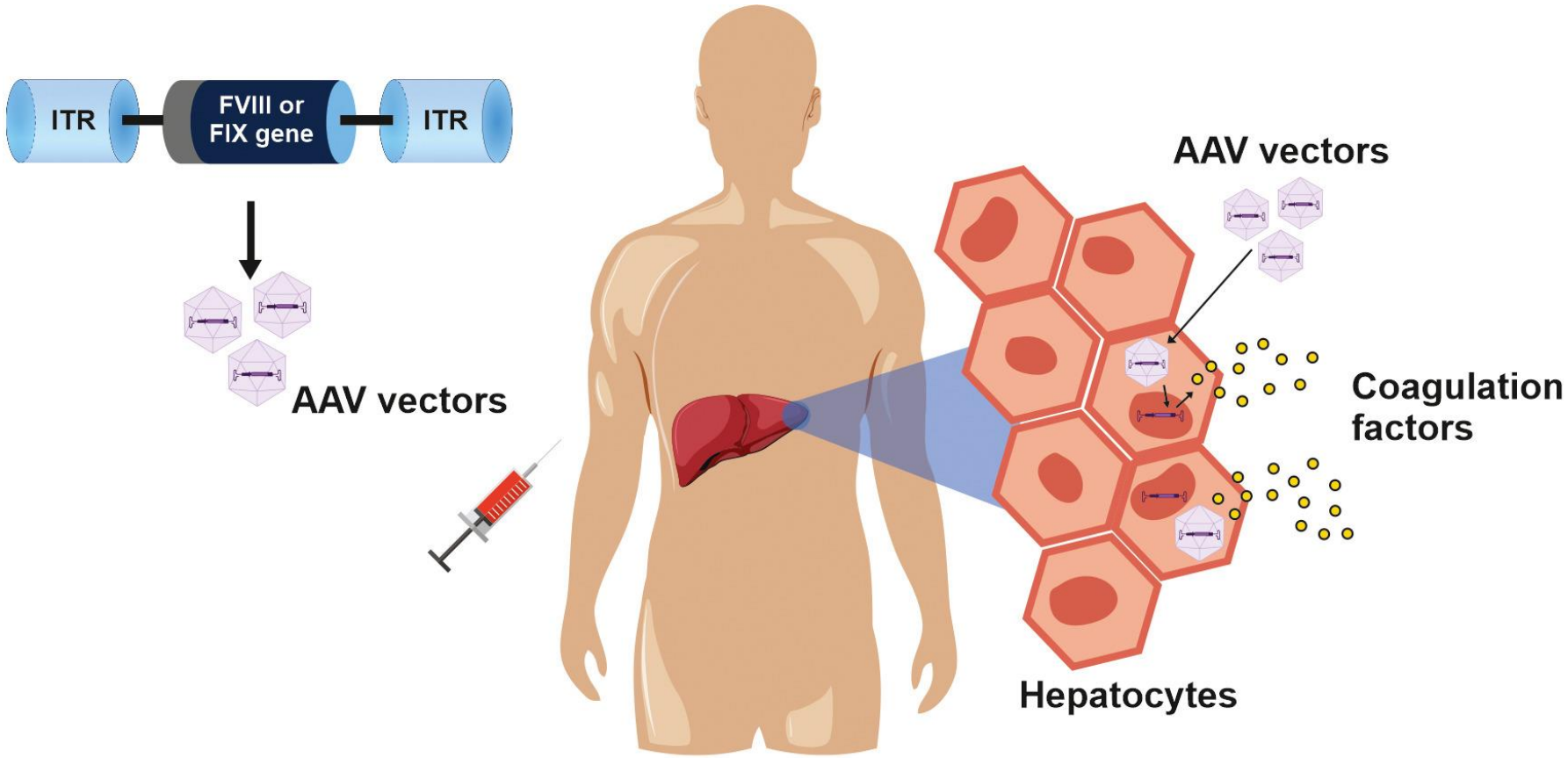
Hemophilic arthropathy results from recurrent hemarthrosis[1,2]

Synovitis +
Cartilage damage +
Bone lesion

Once installed, **arthropathy progresses** even under intensive factor replacement[2]

1. Gualtierotti R et al, J Thromb Haemost, 2021; 2. Oldenburg J, Blood, 2015;

Gene therapy results in stable FVIII expression in many patients



How does MSK health behave after gene therapy?

Yamaguti-Hayakawa GG, Ozelo MC. Exp Biol Med, 2022

16 patients with severe hemophilia A
Single infusion of $6x10^{13}$ vg/kg of valoctocogene roxaparvovec
from August to November, 2019

HJHS
MSK physical evaluation

FISH + HAL
Functionality evaluation

HEAD-US
Ultrasound joint evaluation

Baseline, Year 1, Year 2, Year 3

HJHS: Hemophilia Joint Health Score; HAL: Haemophilia Activities List; FISH: Functional Independence Score in Hemophilia; HEAD-US: Hemophilia Early Arthropathy Detection with Ultrasound

Clinical characteristics

	n=16
Age (years) – median (range)	**26.5** (19-41)
Masculine – n (%)	12 (100)
Race/ethnicity – n (%)	
White	8 (50)
Black	5 (31.3)
Indigenous	3 (18.8)
BMI (kg/m²) – mean (range)	**26.1** (16.2-34.5)
Comorbidities – n (%)	
Previous hepatitis C	**1 (6.2)**
Previous hepatitis B	**1 (6.2)**
Previous inhibitor	0
HIV infection	0

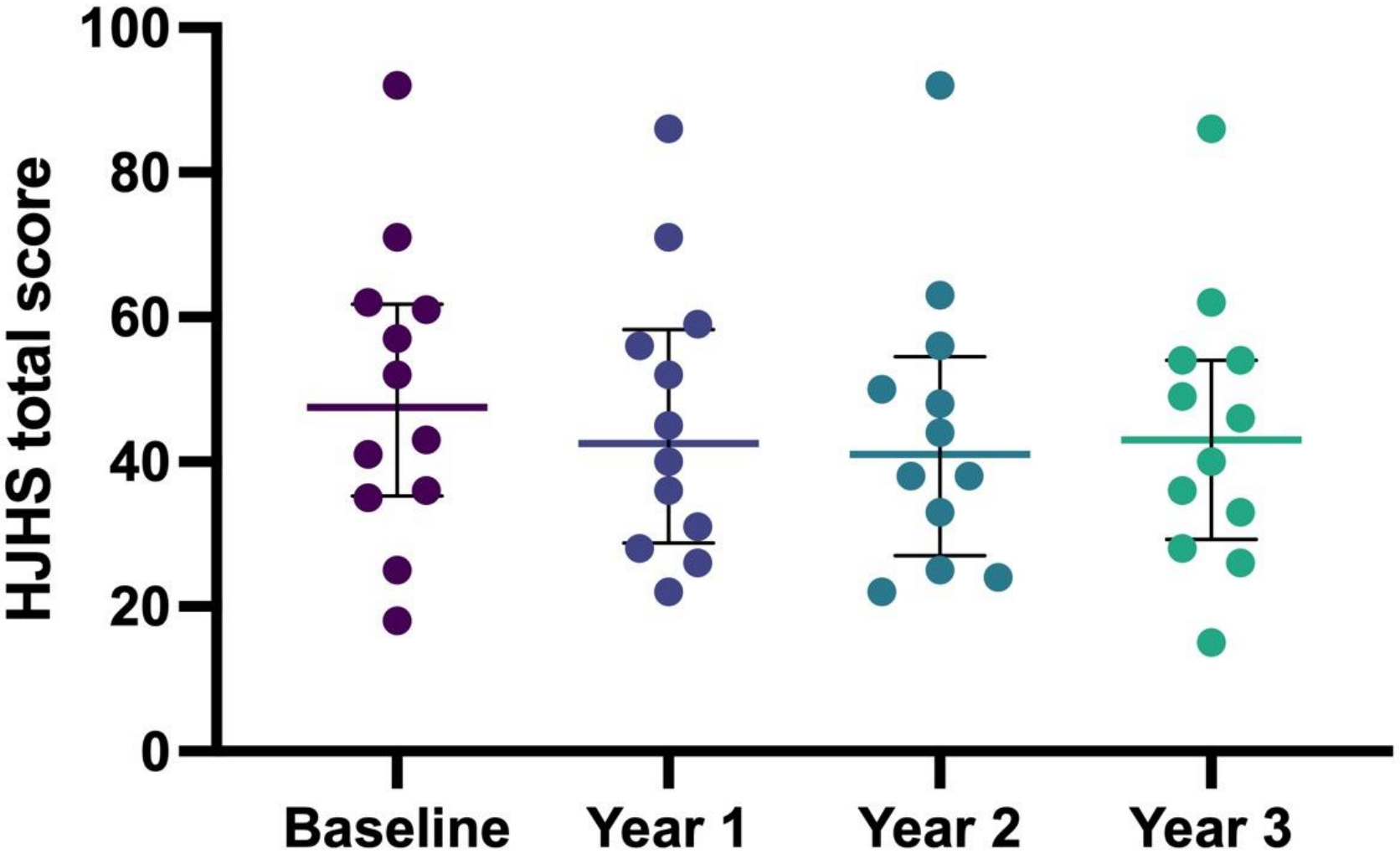
BMI: body mass index; HIV: human immunodeficiency virus

MSK health and FVIII consumption at baseline

	n=16
Target joints (n) – median	0
Annual FVIII comsumption (IU/kg/year) Median (range)	**3,200** (1,300-6,800)
Annual bleeding rate (episodes/year) Median (range)	0.5 (0-5)
Annual joint bleeding rate (episodes/year) Median (range)	0 (0-2)
HJHS – median (IQR)	47 (25.5-61.7)
HAL – median (IQR)	82.8 (70.4-99)
FISH – median (IQR)	28 (22-32)
HEAD-US – median (IQR)	25.5 (14-36.7)

MSK: musculoskeletal health; HJHS: Hemophilia Joint Health Score; HAL: Haemophilia Activities List; FISH: Functional Independence Score in Hemophilia; HEAD-US: Hemophilia Early Arthropathy Detection with Ultrasound

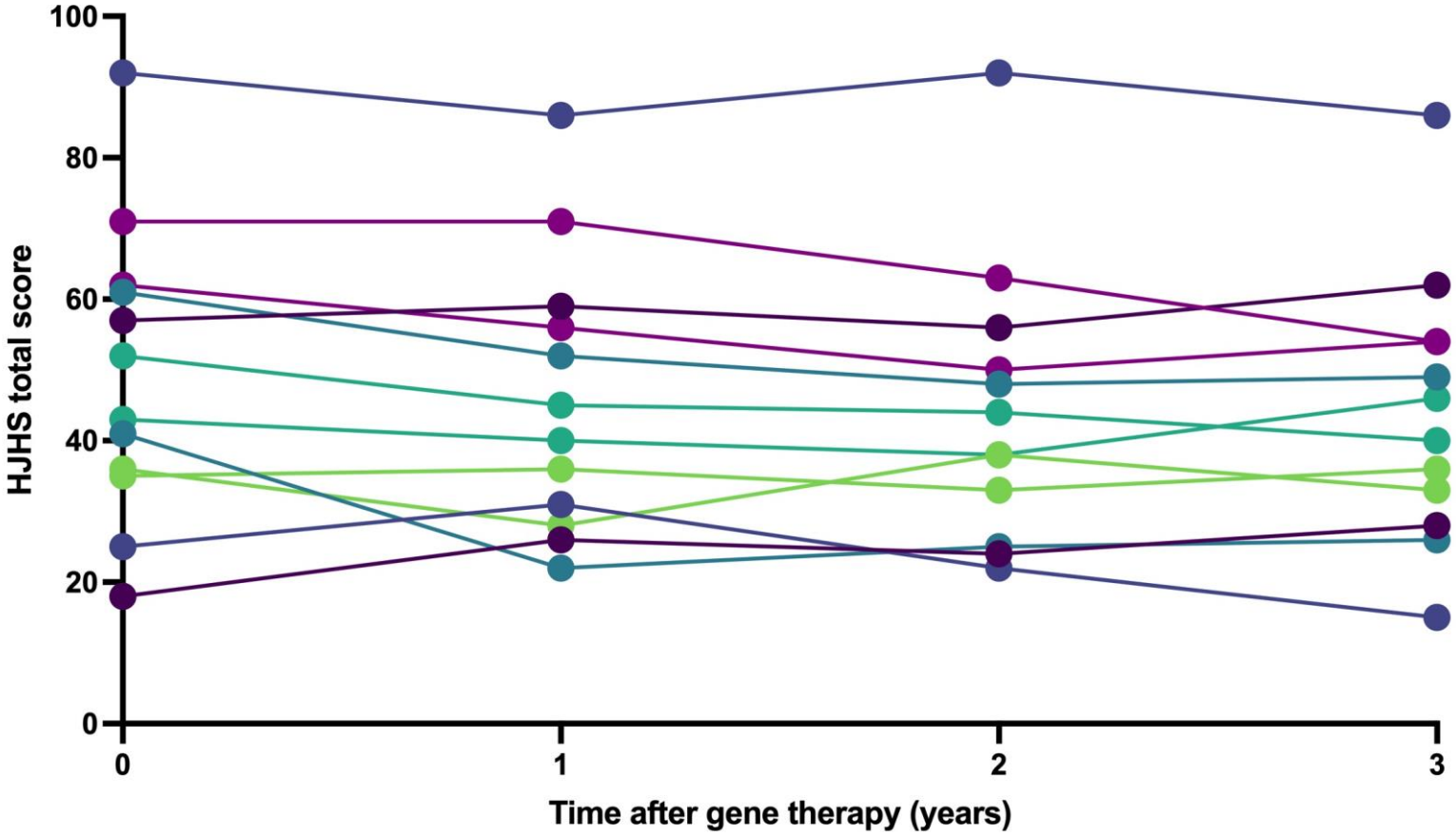
Joint physical exam – HJHS (n=12)

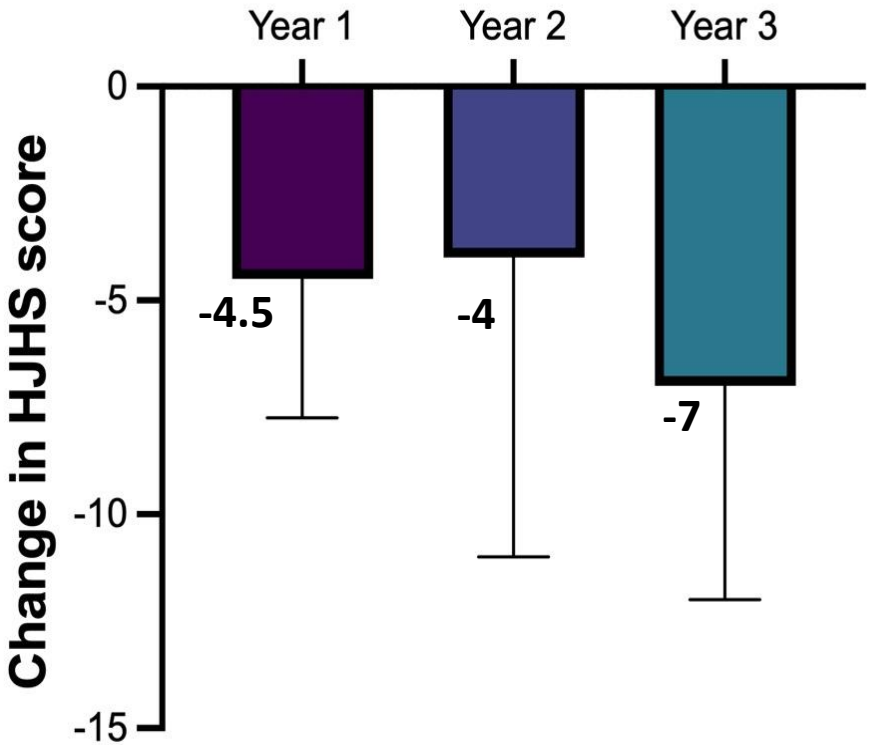


No difference between HJHS scores at baseline and years 1-3

Friedman 2-way analysis of variance by ranks

Joint physical exam – HJHS (n=12)



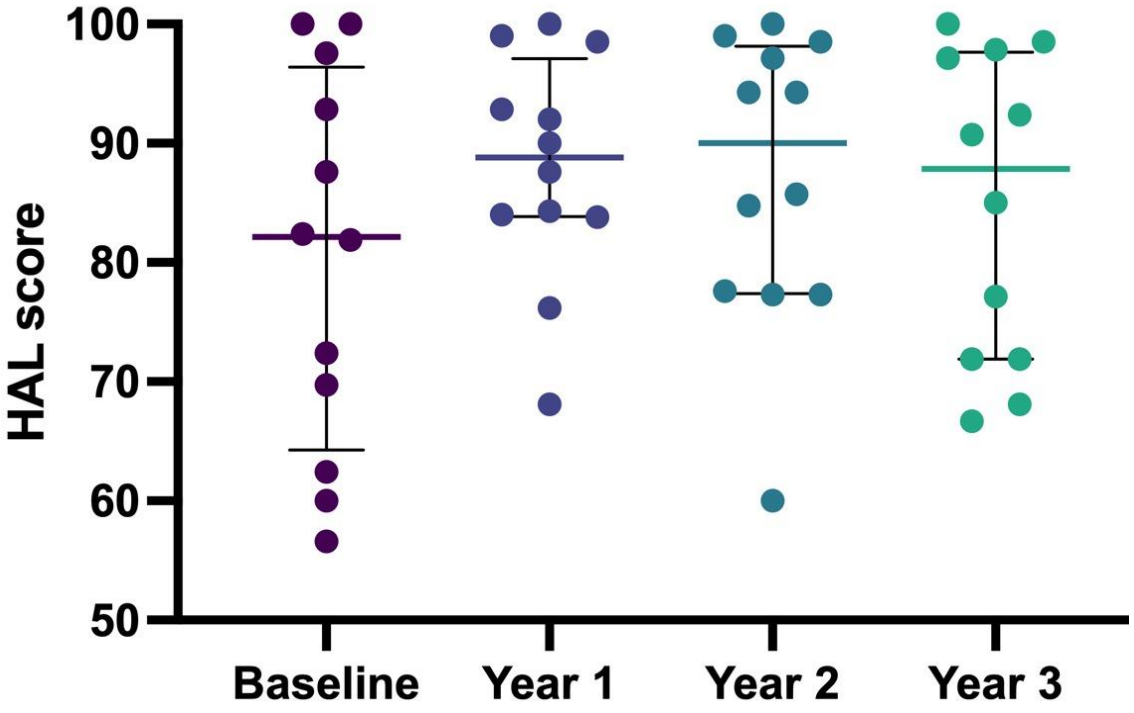


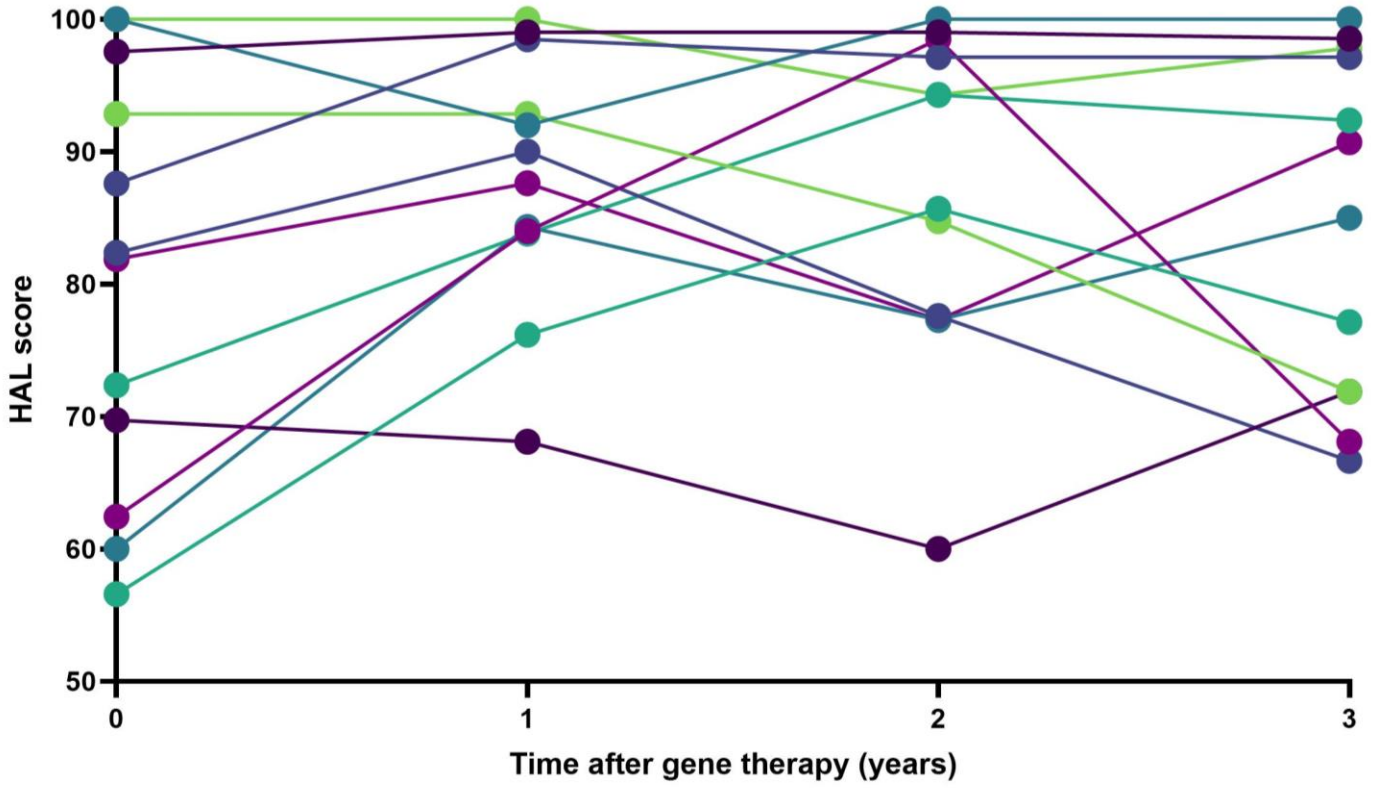
Comparing baseline to Year 3:

3 patients (**25%**) with **stable** HJHS scores

7 patients (**58%**) with **improved** HJHS scores

Functionality – HAL (n= 12)

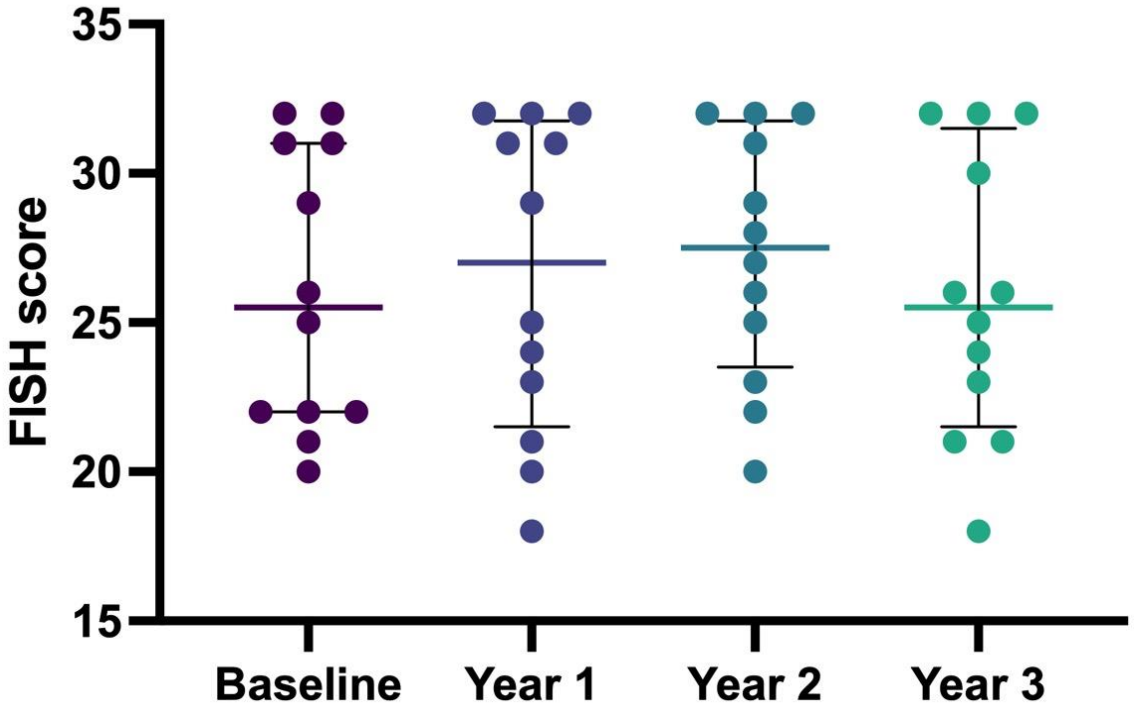


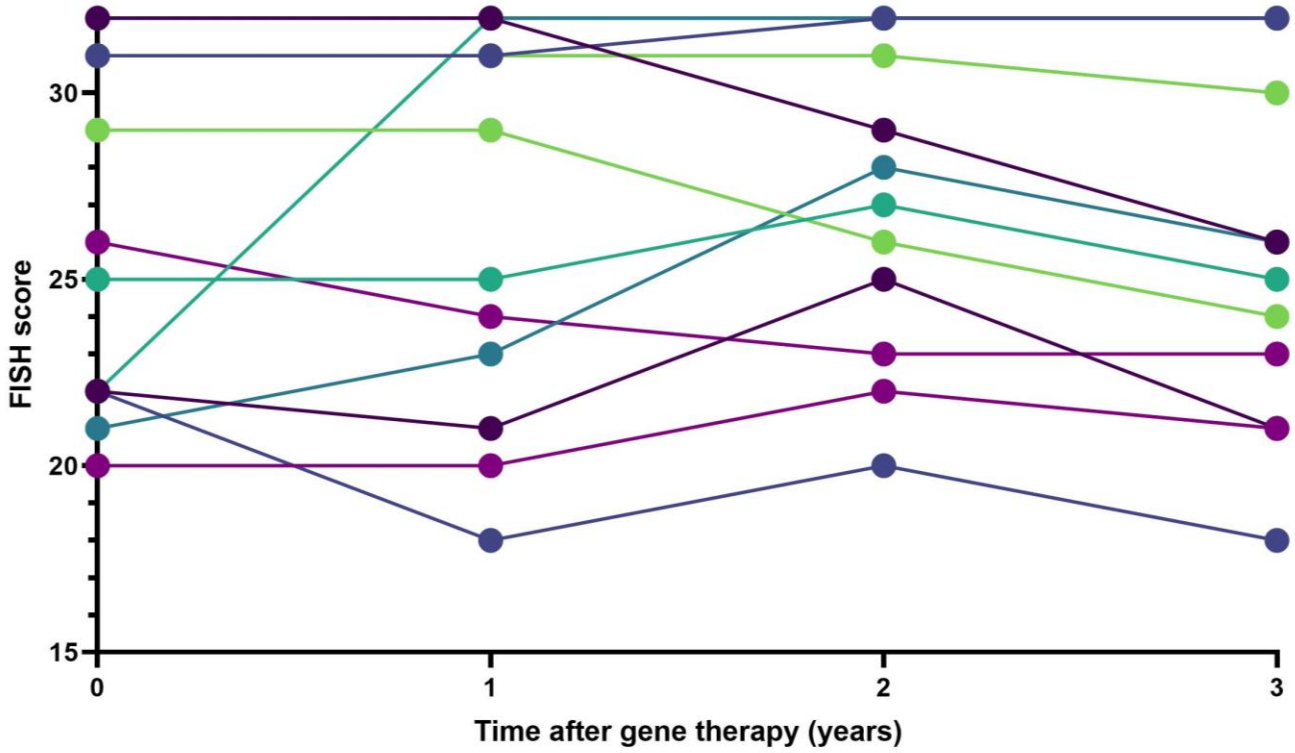


No difference between HAL scores
at baseline and years 1-3

Friedman 2-way analysis of variance by ranks

Functionality – FISH (n= 12)

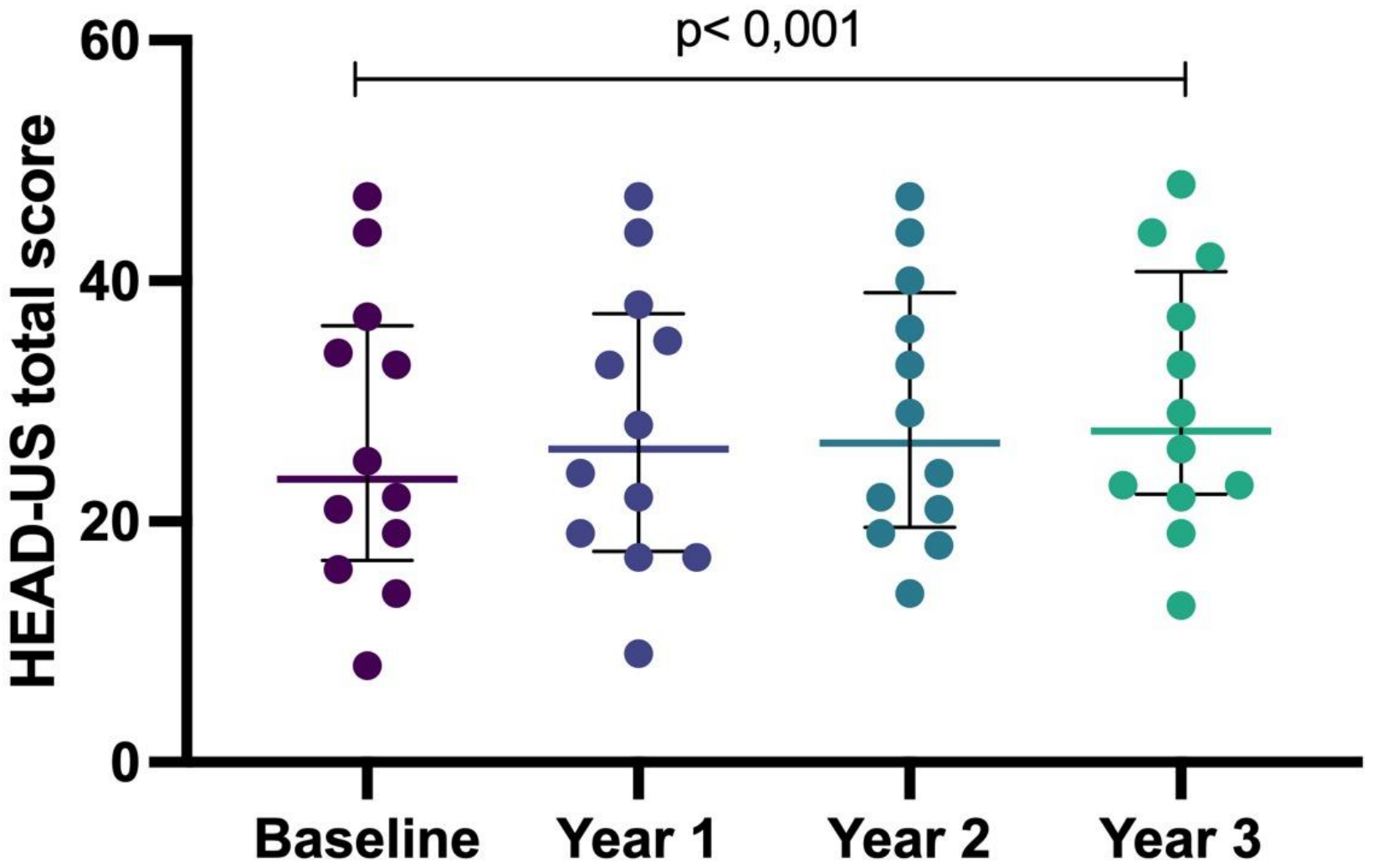




No difference between FISH scores
at baseline and years 1-3

Friedman 2-way analysis of variance by ranks

Ultrasound evaluation - HEAD-US (n=12)

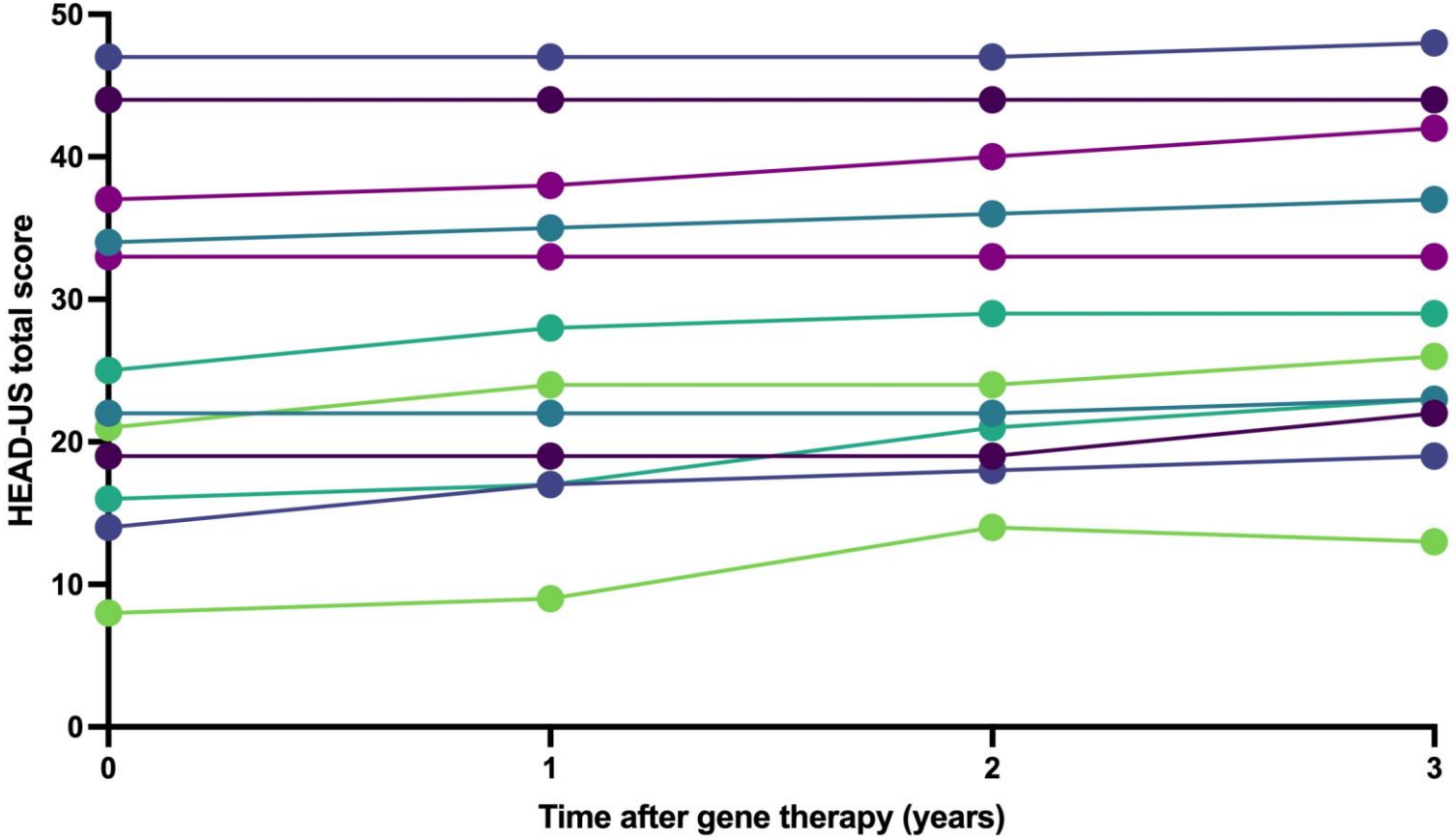


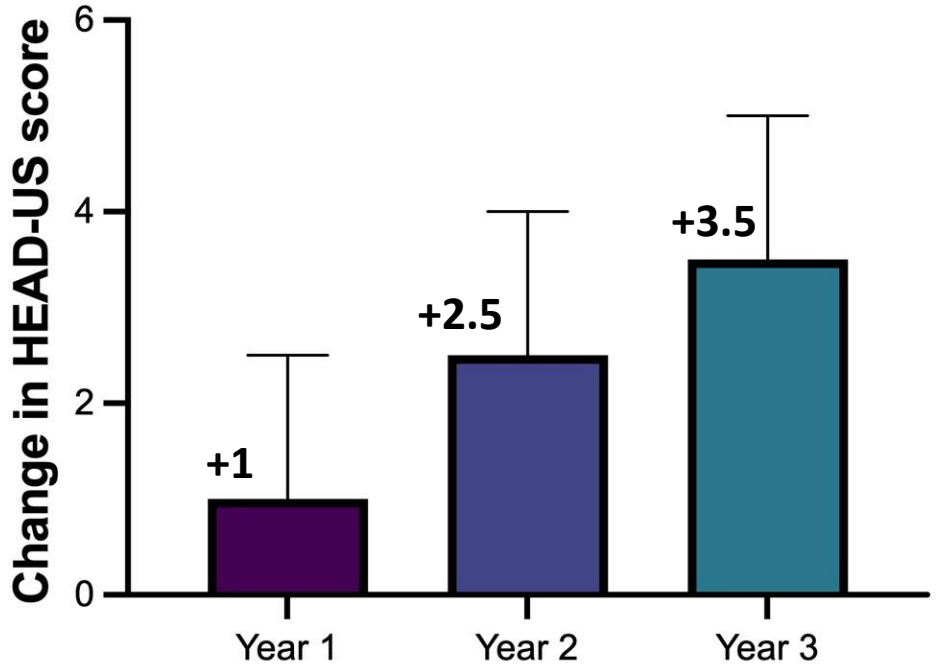
Baseline
Median (IQR)
23.5 (16.8-36.3)

Year 3
Median (IQR)
27.5 (22.3-40.8)

Friedman 2-way analysis of variance by ranks, *post-hoc* analysis with Wilcoxon signed rank test

Ultrasound evaluation - HEAD-US (n=12)



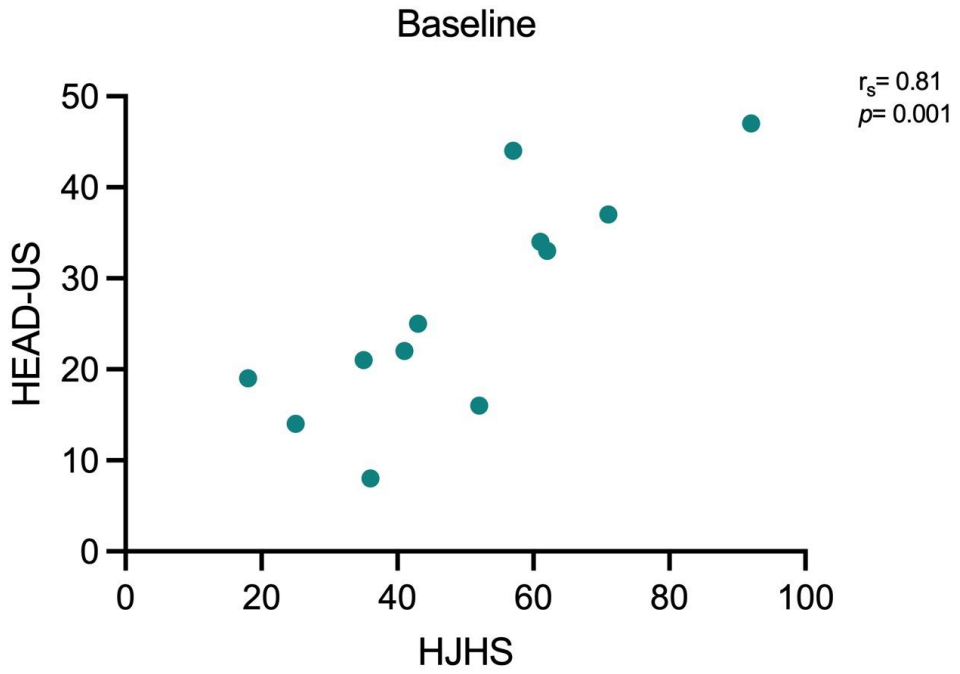


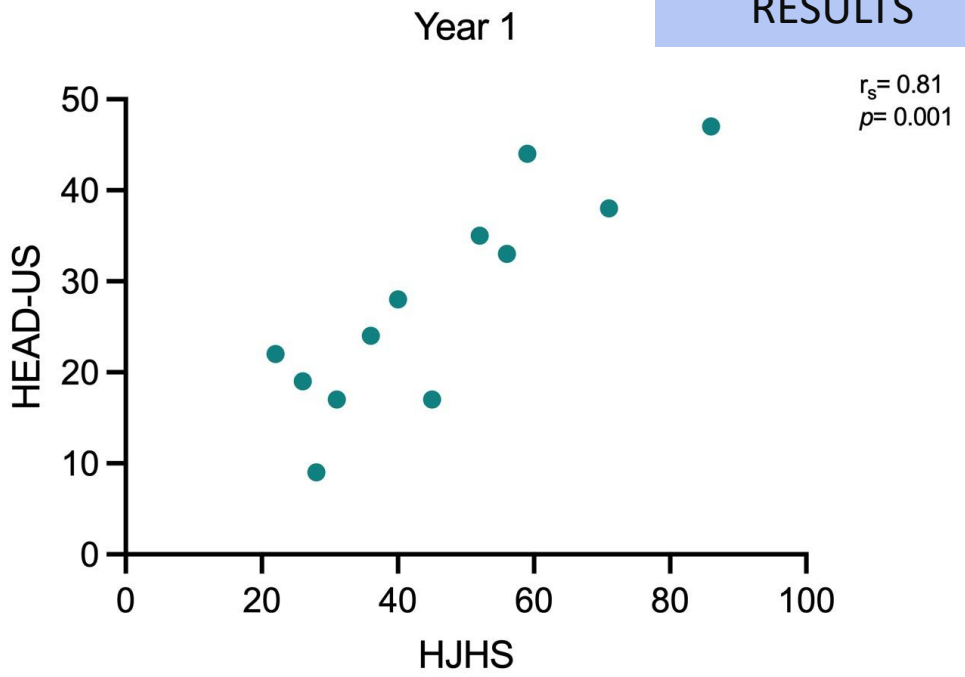
At Year 3:

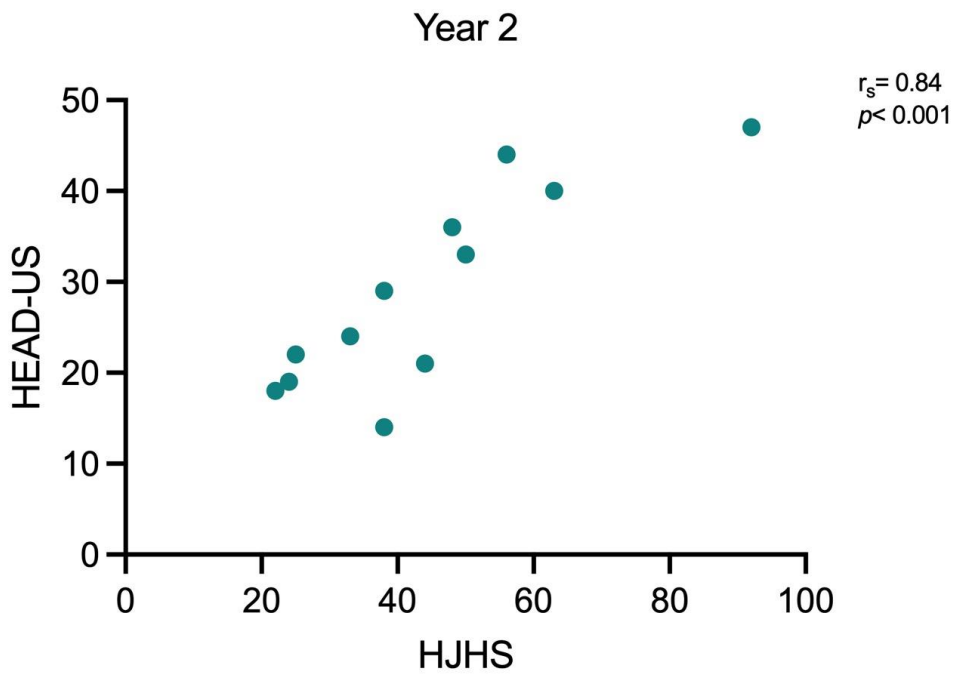
4 (**33%**) patients with **stable** HEAD-US scores

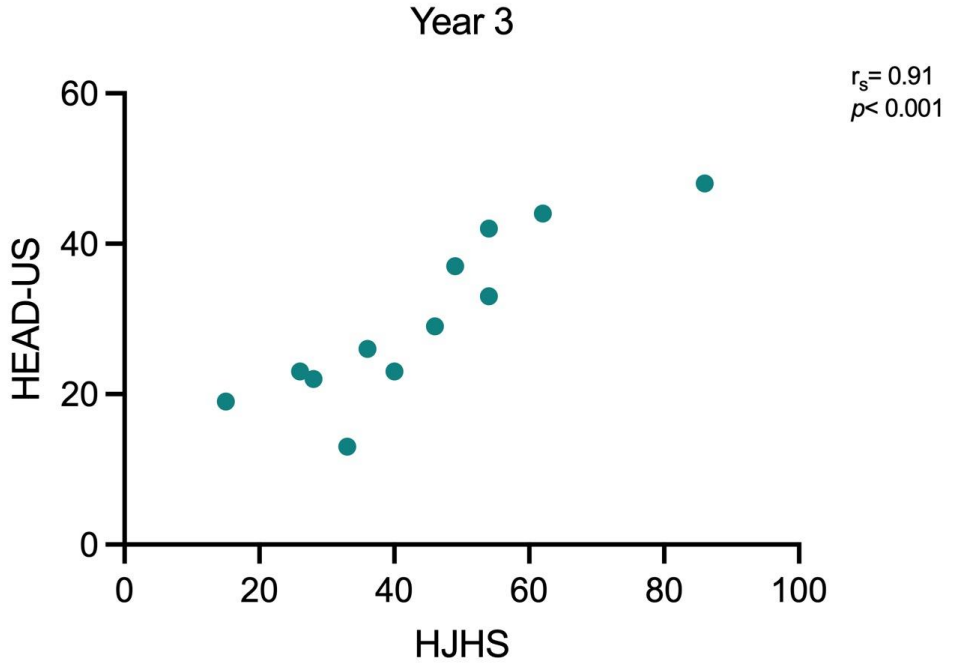
8 (**67%**) patients with **worsened** HEAD-US scores

Strong correlation between HJHS and HEAD-US at all time points (n= 12)







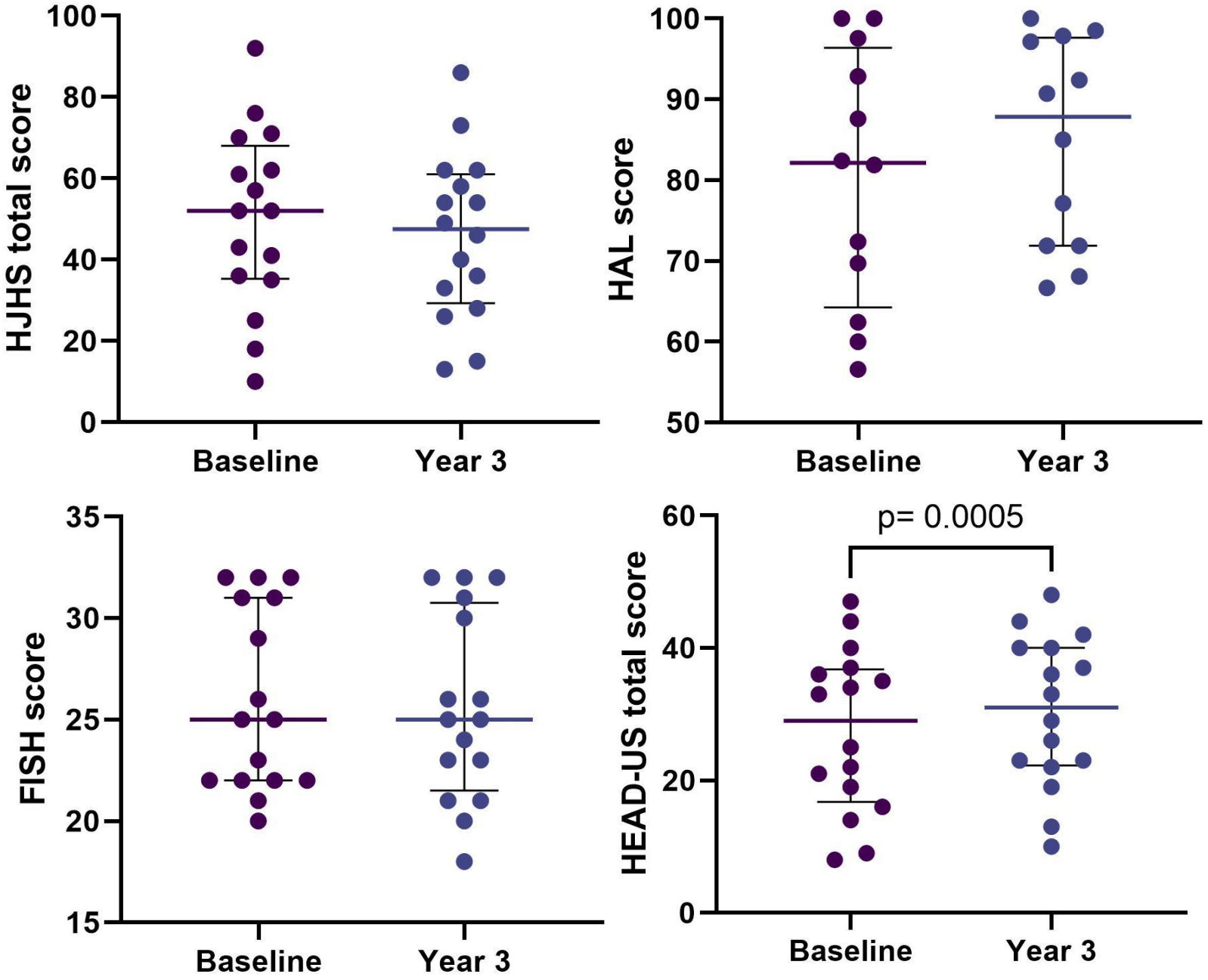


Baseline *vs.* Year 3

(n= 16)

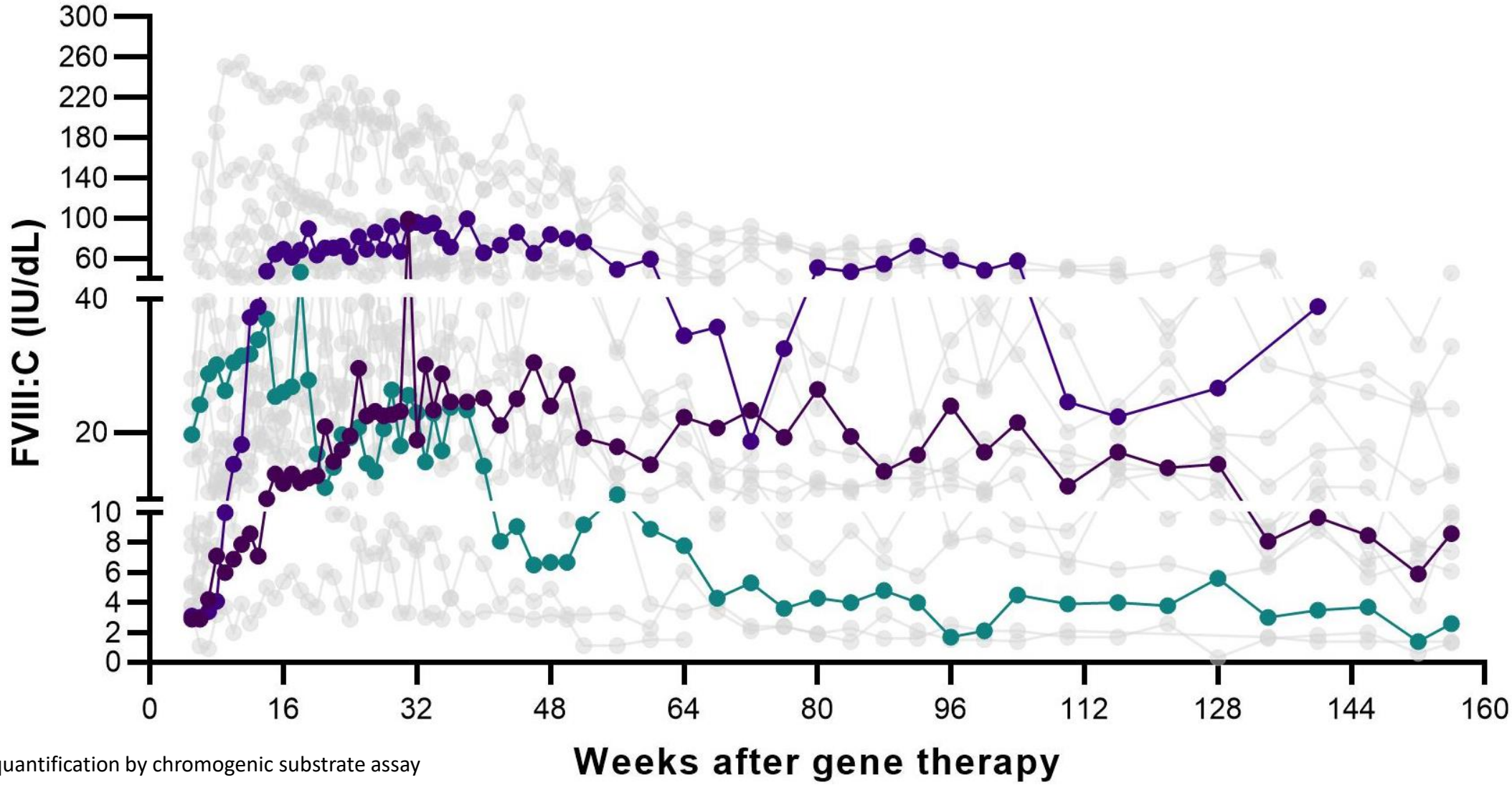
No difference for HJHS, HAL and FISH

Higher HEAD-US score at Year 3 compared to baseline



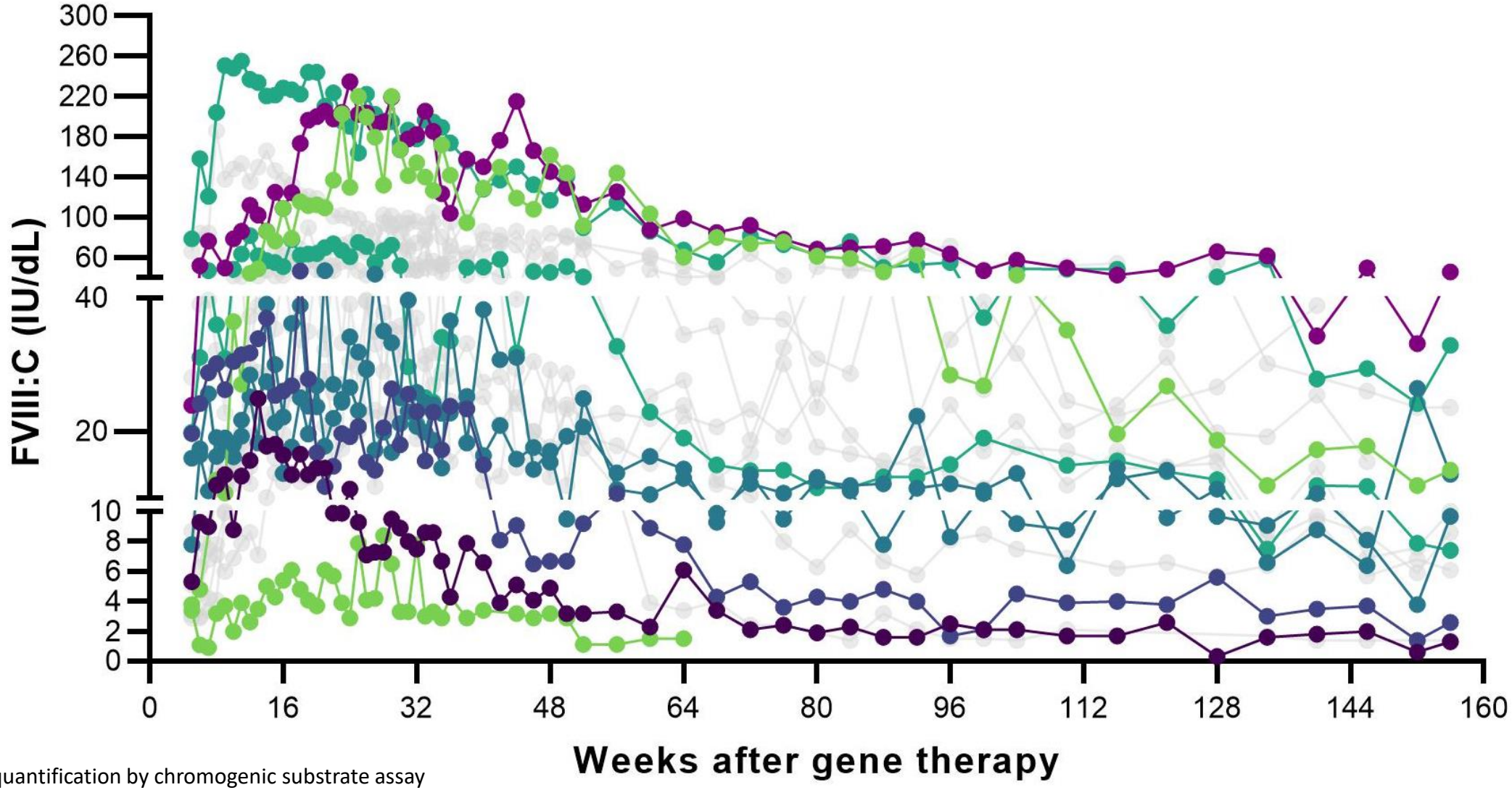
Wilcoxon paired test

FVIII:C in worsened HJHS scores at Year 3 (n=3 , 18.7%)



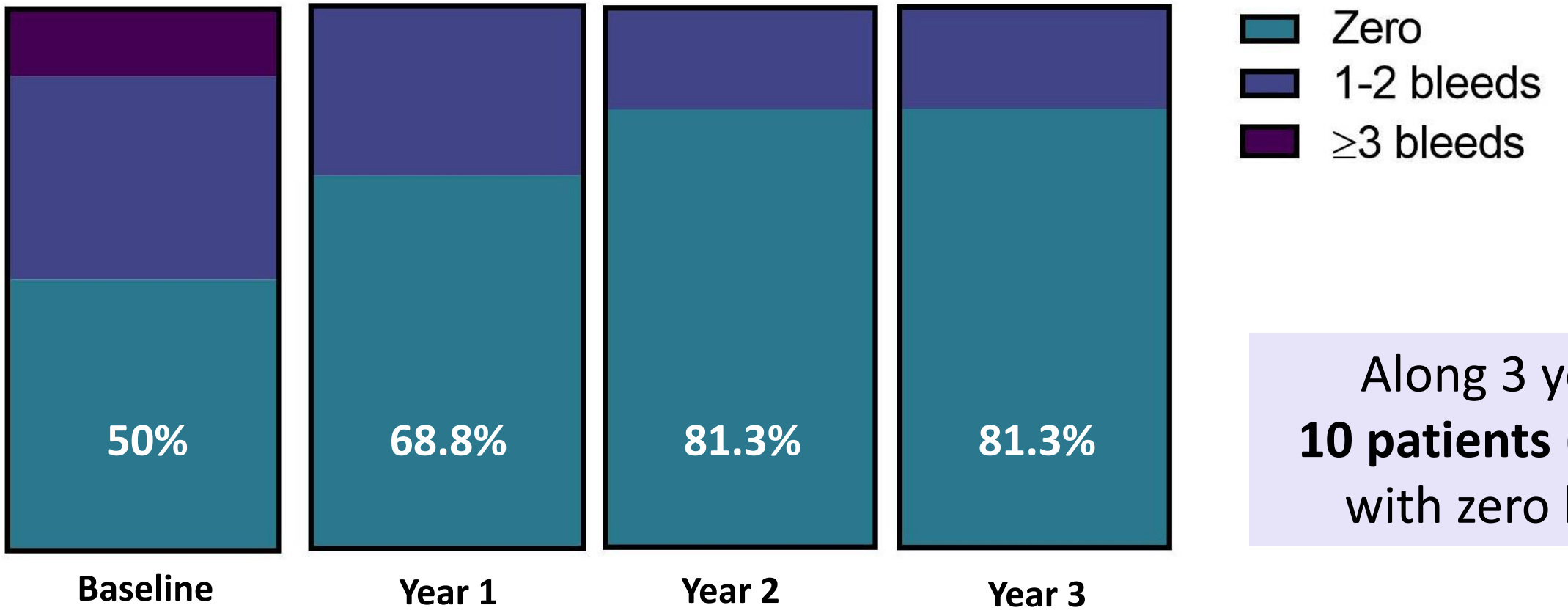
FVIII:C quantification by chromogenic substrate assay

FVIII:C in worsened HEAD-US scores at Year 3 (n= 9, 56.3%)



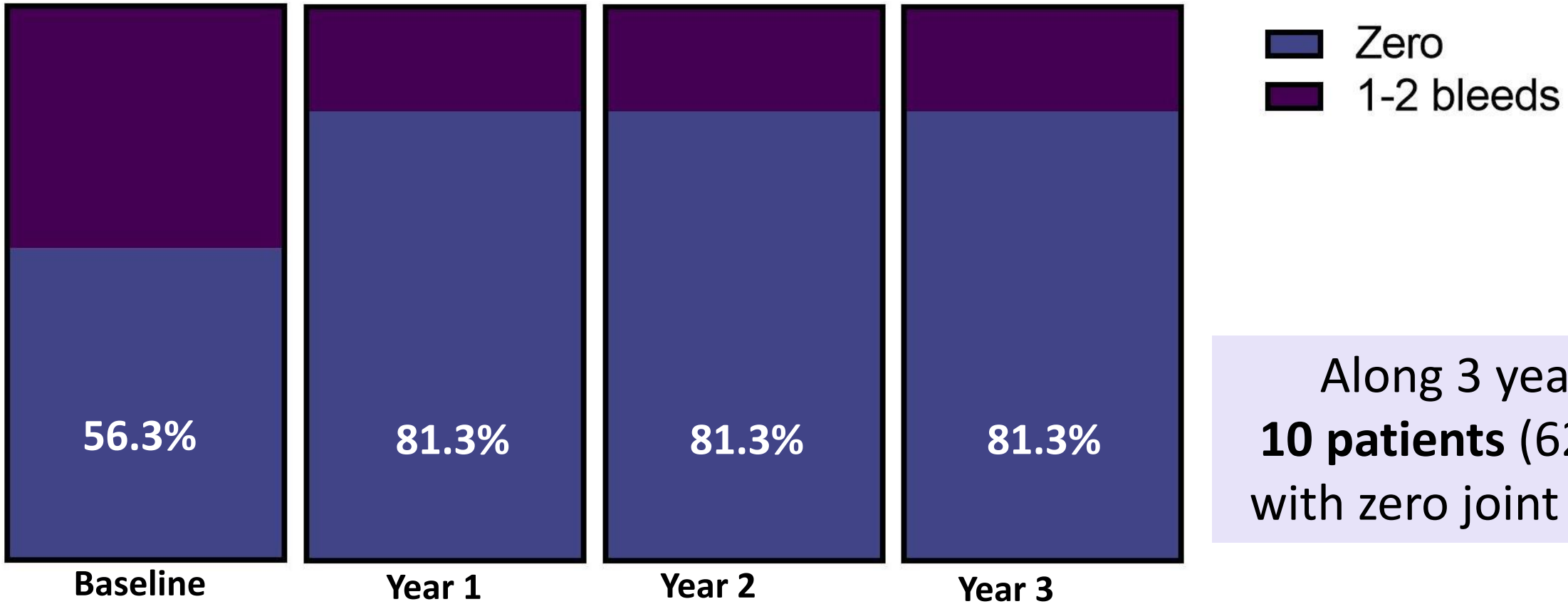
FVIII:C quantification by chromogenic substrate assay

Annualized bleeding rate (n= 16)



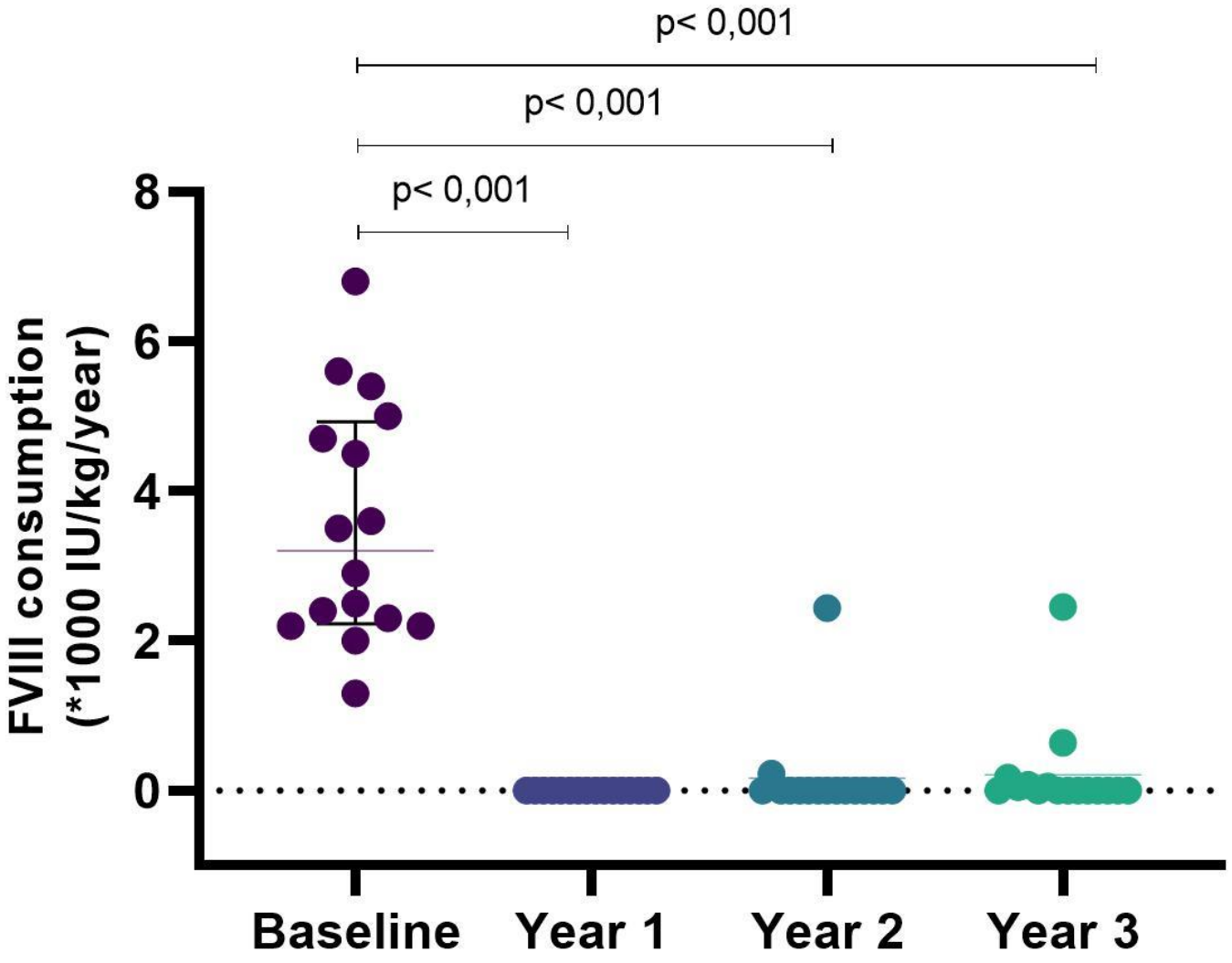
Along 3 years,
10 patients (62.5%)
with zero bleed

Annualized Joint Bleeding Rate (n= 16)



Along 3 years,
10 patients (62.5%)
with zero joint bleed

FVIII consumption (n= 16)



96.1% decrease
in mean annual rFVIII

15 (93.8%) patients
are off FVIII
prophylaxis at Year 3

Friedman 2-way analysis of variance by ranks, *post-hoc* analysis with Wilcoxon signed rank test

Strengths and limitations

STRENGHTS

- **First data on MSK health** after gene therapy
- **Significative number** of patients treated with gene therapy
- Three-year follow-up

LIMITATIONS

- **Small cohort**
- **US as an imaging tool**
  - HEAD-US and ceiling effect
- **Corticosteroid use**
- COVID-19 pandemic

Conclusion

- **81.3%** patients presented with stable or improved HJHS scores
- **56.3%** presented with worsened HEAD-US scores
  - No correlation with FVIII:C – is progression of arthropathy an independent process?
  - No changes in functionality
- **62.5%** patients with zero bleed during 3 years of follow-up
- **Significative decrease** in FVIII consumption

What would the progression of arthropathy be without gene therapy?

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CAPES

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