

Characterizing Improvements in Physical Functioning with PROMIS-PF and In-trial Exit Interviews: A Mixed-methods Analysis to Understand the Meaningful Changes Experienced by Patients on Vimseltinib in the MOTION Trial

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Introduction

- Tenosynovial giant cell tumor (TGCT) is a locally aggressive neoplasm of the synovium of joint, bursa, and tendon sheath, and is associated with joint destruction, inflammation, pain, and swelling.¹
- Patients with TGCT experience many impacts on their physical functioning associated with pain, stiffness, and limited range of motion. The impacts on physical functioning vary across individuals and depend on tumor location.
- Although mean change scores on clinical outcome assessments often establish statistically significant changes in clinical trials, it is challenging to characterize improvements using change scores from multi-item measures, such as the Patient-Reported Outcomes Measurement Information System — Physical Functioning (PROMIS-PF).

Objectives

- The objective of this analysis was to characterize the improvements in physical functioning that responding patients treated with vimseltinib experienced in the MOTION trial.

Methods

Study Design

- The MOTION trial was a phase 3, randomized, placebo-controlled, double-blind study of vimseltinib to assess its efficacy and safety in patients with TGCT (MOTION; ClinicalTrials.gov ID: NCT05059262).²
- At trial baseline and their Week 25 visit, patients completed a custom PROMIS-PF form and Patient Global Impression of Change (PGIC) items.
- Cross-sectional, trial embedded exit interviews were conducted within 28 days prior to unblinding. Patients were cognitively debriefed on the PROMIS-PF to evaluate the relevance and comprehension of the measure. Patients also described the changes they experienced in physical functioning during the trial and what changes represented a meaningful change.
- Qualitative and quantitative mixed methods were used to characterize the improvements in physical functioning among patients on vimseltinib who met/exceeded the meaningful change threshold (≥ 3 points) on PROMIS-PF (n=36).

Measure

- The PROMIS-PF includes 15 items from the PROMIS-PF item bank assessing physical functioning, with specific items for tumors located in the upper-extremity (11 items) and lower-extremity (13 items) (Figure 1).³
 - The PROMIS-PF Total Score was calculated using item-response theory (IRT) so that all patients had scores, measured as T-scores with a mean of 50 and SD of 10, on the same latent physical functioning trait. Higher scores indicate better physical functioning.
- PROMIS-PF has demonstrated content validity and psychometric properties in patients with TGCT.^{4,5}

Figure 1. Items on PROMIS-Physical Functioning Upper and Lower Extremity Forms

UPPER EXTREMITY	LOWER EXTREMITY
<div>1. Are you able to go for a walk of at least 15 minutes?</div> <div>2. Are you able to dress yourself, including tying shoelaces and buttoning up your clothes?</div> <div>3. Does your health now limit you in going OUTSIDE the home, for example to shop or visit a doctor's office?</div> <div>4. Does your health now limit you in doing heavy work around the house like scrubbing floors, or lifting or moving heavy furniture?</div> <div>5. Are you able to push open a heavy door?</div> <div>6. Are you able to lift 10 pounds (5 kg) above your shoulder?</div> <div>7. Are you able to carry a heavy object (over 10 pounds/5 kg)?</div> <div>8. Does your health now limit you in doing moderate work around the house like vacuuming, sweeping floors or carrying in groceries?</div> <div>9. Does your health now limit you in lifting or carrying groceries?</div> <div>10. Are you able to carry a laundry basket up a flight of stairs?</div> <div>11. Are you able to exercise for an hour?</div>	<div>1. Are you able to go for a walk of at least 15 minutes?</div> <div>2. Are you able to dress yourself, including tying shoelaces and buttoning up your clothes?</div> <div>3. Does your health now limit you in going OUTSIDE the home, for example to shop or visit a doctor's office?</div> <div>4. Does your health now limit you in doing heavy work around the house like scrubbing floors, or lifting or moving heavy furniture?</div> <div>5. Are you able to push open a heavy door?</div> <div>6. Are you able to carry a heavy object (over 10 pounds/5 kg)?</div> <div>7. Does your health now limit you in doing moderate work around the house like vacuuming, sweeping floors or carrying in groceries?</div> <div>8. Does your health now limit you in lifting or carrying groceries?</div> <div>9. Are you able to go up and down stairs at a normal pace?</div> <div>10. Are you able to carry a laundry basket up a flight of stairs?</div> <div>11. Are you able to stand for one hour?</div> <div>12. Does your health now limit you in bending, kneeling, or stooping?</div> <div>13. Are you able to exercise for an hour?</div>
PHYSICAL FUNCTIONING	

Methods (cont.)

Analysis

- Audio transcripts were coded and analyzed using ATLAS.ti version 22.0.
- Individual item response patterns for all responding patients were calculated. In addition, the mean item change score and standard error for each item, the proportion of responders improving on each item, and the proportion of responders improving on each item over placebo were calculated. The number and percentage of items that improved was calculated for each patient, and their overall PROMIS-PF Baseline, Week 25, and change scores are presented.

Results

- A total of 36 out of 83 patients (43%) in the vimseltinib treatment group were PROMIS-PF responders (change of ≥ 3 points on PROMIS-PF Total Score at Week 25) (Figure 2).
 - On average, these patients improved on every PROMIS-PF item and had more than a 1 category improvement in 12 of the 15 items (item change range: 0.7–2.3) (Figure 3).
 - Between 47% and 100% of the patients improved on each PROMIS-PF item (Figure 2).
 - The heat map of responses provides information, by tumor location, on what aspects of physical functioning changed, and by how much, for each patient (Figure 2).
- A total of 29 of the 36 PROMIS-PF responders completed exit interviews at Week 25 of the trial and provided qualitative information on their experience with changes in physical functioning.
 - During the exit interviews, many of the patients reported specifically on improvements in walking, climbing stairs, exercising, completing chores and housework, squatting, kneeling, getting out of the house (i.e., driving, using buses, going to specific events, work) and many other activities (Figure 4).
 - The most useful qualitative data came from responses to a question simply asking participants to describe the changes they experienced in their physical functioning in the trial, rather than questions that asked them to describe what would constitute a meaningful change.

Figure 2. Individual Item Responses on PROMIS-Physical Functioning Items for All 36 Vimseltinib PROMIS-Physical Function Responders

	Upper Extremity Patients			Lower Extremity Patients																																				Average Change in Item Score	% Tx Responders Improved on Item	Percent Responders Improved Over Placebo		
	Hand	Shoulder	Hip								Knee																								Ankle									
			Pt 1	Pt 2	Pt 3	Pt 4	Pt 5	Pt 6	Pt 7	Pt 8	Pt 9	Pt 10	Pt 11	Pt 12	Pt 13	Pt 14	Pt 15	Pt 16	Pt 17	Pt 18	Pt 19	Pt 20	Pt 21	Pt 22	Pt 23	Pt 24	Pt 25	Pt 26	Pt 27	Pt 28	Pt 29	Pt 30	Pt 31	Pt 32	Pt 33	Pt 34	Pt 35	Pt 36						
Lift 10 lbs Over Shoulders ^a																																							2.3	100%	67%			
Change Lightbulb Overhead ^a																																							2.3	100%	100%			
Up and Down Stairs ^a																																							1.4	88%	64%			
Carry heavy object 10+ lbs ^a																																							1.4	75%	55%			
Exercise 1 hr ^a																																							1.3	86%	56%			
Moderate Work ^a																																							1.2	75%	50%			
Bend/Kneel/Stoop ^a																																							1.2	67%	29%			
Lifting/Carrying Groceries ^a																																							1.1	72%	50%			
Walk 15+ min ^a																																							1.1	64%	47%			
Heavy Work ^a																																							1.1	64%	31%			
Carry Laundry Up Stairs ^a																																							1.0	67%	49%			
Stand for 1 hr ^a																																							1.0	64%	31%			
Health Limits Going OUTSIDE Home ^b																																							0.8	58%	38%			
Heavy door ^a																																							0.8	56%	31%			
Dress Yourself ^a																																							0.7	47%	40%			
# Items Improved	11	10	9	13	12	12	9	7	13	12	11	11	11	10	10	9	9	9	9	9	9	8	8	8	8	7	7	6	6	6	6	2	9	6	5									
# PF Items in Score	11	11	11	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13						
% Items improved	100%	91%	82%	100%	92%	92%	69%	54%	100%	92%	85%	85%	85%	77%	77%	69%	69%	69%	69%	69%	69%	62%	62%	62%	62%	62%	54%	54%	46%	46%	46%	46%	15%	69%	46%	38%								
Baseline PROMIS-PF Score	28	34	27	39	38	36	41	34	33	37	39	32	28	31	37	37	42	37	33	40	40	40	34	42	34	43	40	45	37	40	44	42	51	41	38	39								
Week 25 PROMIS-PF Score	46	47	40	49	49	52	47	37	62	43	45	42	39	36	51	44	50	45	41	51	56	44	38	47	40	51	44	52	40	43	48	47	62	47	41	42								
Individual PROMIS-PF Change Score	18	13	13	10	11	16	6	3	29	6	6	10	11	5	14	7	8	8	8	11	16	4	4	5	6	8	4	7	3	3	4	5	11	6	3	3								
Shaded squares represent individual patients' changes in response to PROMIS-PF items from Baseline to Week 25. Green represents an improvement, no shading represents no change, red represents worsening. Darker shading means greater change in the direction indicated.																																												
4 category improvement3 category improvement2 category improvement1 category improvementno change1 category worseningItem not used for PROMIS-PF total score based on tumor location.																																												

Abbreviations: PF = Physical Functioning; PROMIS-PF = Patient-Reported Outcomes Measurement Information System Physical Functioning; PT = patient; Tx = treatment. Response options for PROMIS-PF items: ^aWithout any difficulty, with a little difficulty, with some difficulty, with much difficulty, unable to do; ^bNot at all, very little, somewhat, quite a lot, cannot do; PROMIS-PF Total Scores are T-scores with a mean of 50 and standard deviation of 10; Higher scores on PROMIS-PF indicate better physical functioning.

Limitations

- Not all patients who were PROMIS-PF responders were interviewed.
- As patients completed the PROMIS-PF measure throughout the clinical trial, the examples they provided during the interviews may have been more closely related to aspects of physical functioning covered by the PROMIS-PF items familiar to them; they may have been less likely to identify other physical functioning concepts.

Conclusions

- Many patients with TGCT on vimseltinib experienced clinically meaningful changes across a broad array of physical functioning items.
- Through the approach presented here, the nature and extent of these individual and average patient improvements can now be more clearly communicated with physicians and patients.
- It is often challenging to characterize the specific improvements contributing to total scores that patients have experienced using multi-item measures such as the PROMIS-PF.
 - The method presented here is applicable across disease areas.
 - It provides clinically useful and easily digestible information for physicians and patients considering treatment.

Figure 3. Mean Item Change Scores (Standard Errors) for PROMIS-Physical Function Responders

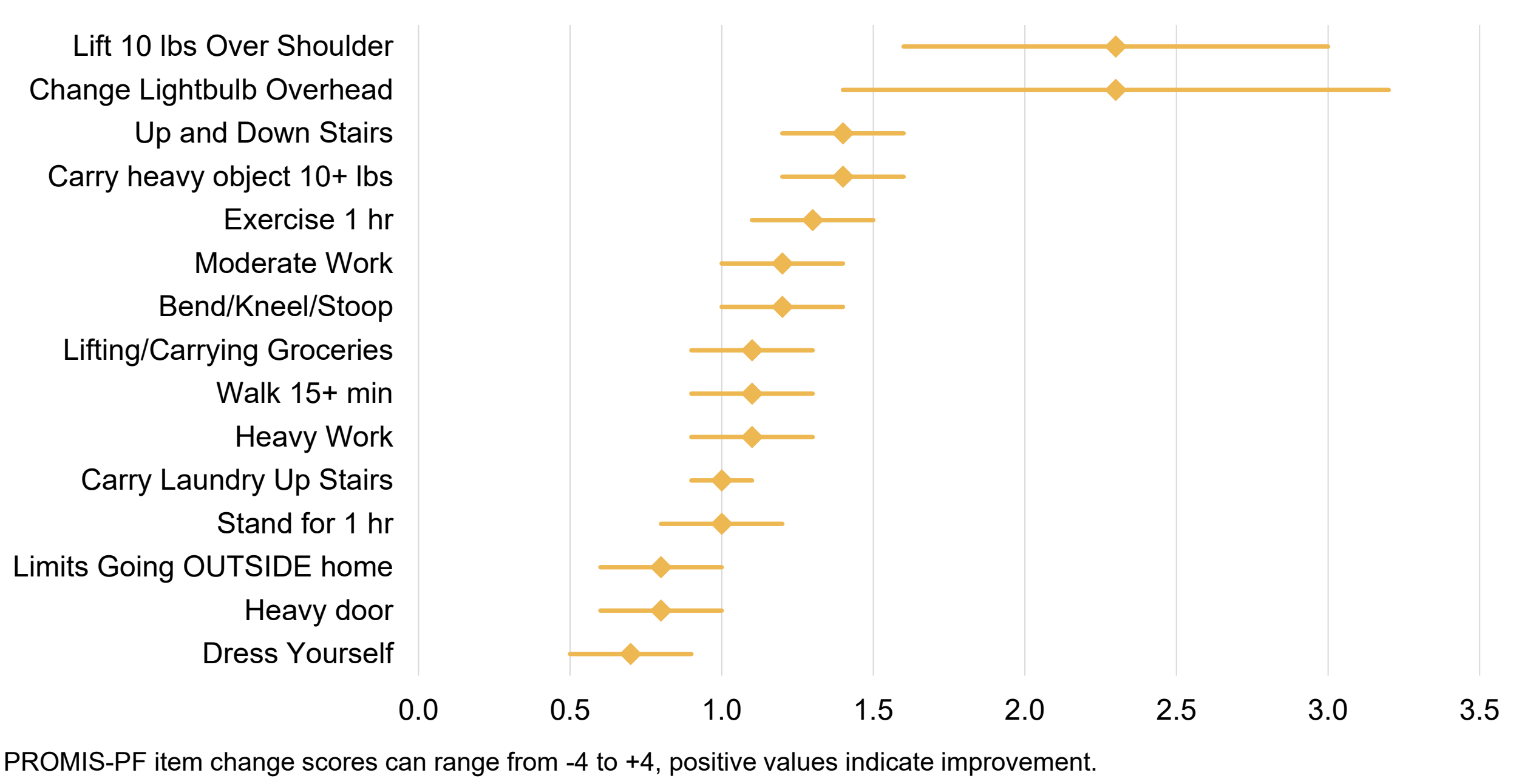


Figure 4. Quotes by PROMIS-PF Responders Describing the Changes in Physical Functioning They Experienced during the MOTION Trial

Pt 2-Hand: Because my wrist was swollen earlier, and when I did this movement to tie the laces, my hand rotated and touched my wrist, and at that point, because of the swelling, I could not complete the movement, so I had some problems... Now that the wrist is not swollen anymore, the situation improved. I think that this is the activity with the biggest success

Pt 6-Hip:...this treatment automatically made it so that I feel better physically, since I can take walks for an hour, an hour and fifteen minutes, even one and a half hour. I can resume my daily activities at home, do the housework, vacuum, I can move around without any problem, there you go.

Pt 9-Knee: Going out for big walks. Don't have to sit down every ten seconds. Can carry things up the stairs. I'm running. Before, I would do like a crab walk. You know the crabs, how they walk up and down, walk, whatever. I'll do a crab walk up and down the stairs just to get up there. It's stupid because you see me, you know I go to the gym and to see me do that, it's like, that's weird. Why is he doing that? Did we do a hard leg session or what? Why is he doing that? But it's because of this stupid knee. Anyway. You should see it. I'm running up three or four stairs up at one go now, like running up the stairs.

Pt 10-Knee: I'm able to run about with my son a lot more. He's two, turning three in February, so he's still very little, still wanting to do all that stuff with his dad. I've been enjoying been able to actually do them things with him. Gives me an opportunity to go back into work and look at retraining. And it obviously gives me a positive outlook for the future with my son and being able to go out and play football with him when he's a bit older and do all them things a dad should do that I wouldn't have otherwise been able to.

Pt 11-Knee: I notice it especially when I go up and down the stairs. And in and out of the car, for example. Then I must bend my knee. Before, I always had to push the seat back in the car. But I don't have to do that as much anymore. To get more space when I get out. But now I can do this without any problem.

Pt 12-Knee: I can stand for longer than before. And when I sit down, I do it better.

Pt 15-Knee: Yes, I have to admit that there are have been many changes. From when I started, up to now, I walk normally, the knee is not swollen at all, I also restarted a light activity of walking, going on walks outside, so it changed very much for the better.

Pt 18-Knee: ...and with that, with the swelling going away, it's meant that the mobility of my knee has come back, so I can do really normal things like sit in buses and fold my legs and do a squat occasionally and be able to—like that was unimaginable. For about five years, I couldn't do a squat and raise myself up with just my knee going down and across, so that's been fantastic, just being able to do normal things.

Pt 22-Knee: Being able to walk without fear and without pain gives you a lot of freedom and you get a lot of autonomy.

Pt 23-Knee: Yes, the only fact of being able to do some exercise, yes for me it is. Maybe not for another person, but for me it is. I notice I have improved my way of walking since I don't experience any pain, I can put my foot properly on the ground and as I put the foot properly, my knees doesn't hurt nor my hip.

Pt 26-Knee: I can walk and run for a long time without any repercussion, without fearing being in any pain or having a synovial effusion the next week, well, the next day, or even the very evening. It's really completely different now.

Pt 28-Knee: It's completely different now. I don't feel anything anymore. I can bend my knee. It's fantastic. ...I recovered some flexibility, I can bend it almost normally. ...It's just when I squat that I still feel a little discomfort. The amplitude is not maximal. And it's much less swollen. I feel that my knee is much less swollen.

Pt 34-Ankle: I can walk and run for a long time without any repercussion, without fearing being in any pain or having a synovial effusion the next week, well, the next day, or even the very evening. It's really completely different now.

Abbreviations: PF = physical functioning; Pt = patient

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