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Patient satisfaction with extended-interval warfarin monitoring

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Abstract Extended-interval monitoring of warfarin has been proposed to reduce follow-up burden and improve patient satisfaction. We aimed to make an initial assessment of anticoagulation satisfaction before and after an extended-interval warfarin monitoring intervention. We conducted a translational prospective single-arm pilot study of extended-interval warfarin monitoring in five pharmacist-managed anticoagulation clinics. Patients meeting CHEST guideline criteria for extended-interval warfarin monitoring began progressive extended-interval follow-up (6, 8, and 12 weeks thereafter). The Duke Anticoagulation Satisfaction Scale (DASS) was administered at baseline and at end-of-study or study removal (in patients no longer appropriate for extended interval follow-up). Forty-six patients had evaluable pre- and post-intervention DASS survey data. Mean age of patients was 66.5 years, 74 % were non-Hispanic whites, and 48 % were men. Patients completed a mean ± SD of 34 ± 22 weeks of follow-up. Mean ± SD total DASS score at baseline was 45.2 ± 14.2 versus 49.1 ± 14.9 at end-of-study (mean change, +3.9 [95 % CI −0.6–8.4; $p = 0.09$]), indicating no benefit—and trending toward decrement—to anticoagulation satisfaction. Change in anticoagulation satisfaction varied substantially following extended-interval monitoring, with no evidence of improved satisfaction. Plausible reasons for patients not preferring extended-interval monitoring include increased anxiety and disengagement from self-management activities, both potentially related to less frequent feedback and reassurance during extended interval-monitoring. Additional research is needed to identify who is likely to benefit most from extended-interval monitoring. Anticoagulation satisfaction should be considered with clinical factors and shared-decision making when implementing extended-interval warfarin monitoring.

Keywords Anticoagulation · Warfarin · Interval · Monitoring · Patient satisfaction

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Introduction

For many decades, warfarin has been the mainstay for treatment and prevention of thromboembolic events in the US [1]. However, warfarin has a complex interaction profile requiring intensive monitoring, thus increasing treatment burden [2]. In part because of this high treatment burden, recent CHEST guidelines now give preference to

newer oral anticoagulants, which have generally similar or better safety and efficacy profiles, but require less monitoring than warfarin [3]. Nevertheless, these newer agents are not well studied in many patient populations and some patients and providers may prefer to continue using warfarin given the decades of experience with this agent. Thus, other strategies have been suggested to improve the experience with long-term warfarin use [4]. For example, extended-interval follow-up—that is, monitoring international normalized ratio (INR) up to every 12 weeks rather than the conventional 4 weeks—has been proposed as an alternative strategy in patients with a history of stable therapeutic INRs while taking warfarin [4, 5]. Several recent studies have suggested that this approach to warfarin monitoring has similar outcomes to conventional 4-week monitoring [5–7]. However, whether this approach reduces patient-perceived burden and is preferred by patients is not known.

We previously reported on the real-world feasibility of extended-interval warfarin monitoring per CHEST guideline criteria in the Feasibility of Extended-Interval Follow-up for Patients Receiving Warfarin (FADE-OUT) study [8]. In this pre-specified secondary analysis, we aimed to perform an initial assessment of the impact of extended-interval warfarin monitoring on anticoagulation satisfaction. We hypothesized that anticoagulation-related satisfaction would improve following extended-interval warfarin monitoring.

Methods

Study population and design

The design and principal results of FADE-OUT have been published previously [8]. Briefly, FADE-OUT was a prospective, single-arm intervention translational pilot study, enrolling patients from five University of Florida Ambulatory Care Research Network outpatient anticoagulation clinics, that investigated the feasibility of extended-interval follow-up for patients taking warfarin in a real-world setting. Patients were eligible for the study if they met CHEST criteria for considering extended-interval follow-up—that is, they required at least 6 months of anticoagulation and were on a stable dose of warfarin for the 12 weeks prior to enrollment. Patients were excluded from the study if they had a recent thromboembolic event, short life expectancy, recent diagnosis of cancer, or were actively receiving cancer treatment. This study was approved by the University of Florida Institutional Review Board. Informed consent was obtained from all individual participants included in the study.

Patients meeting study criteria were transitioned from usual care (warfarin monitoring at intervals up to ~4 weeks) to extended-interval follow-up. The interval of warfarin monitoring was initially extended to 6 weeks, then 8 weeks, and then every 12 weeks thereafter. Patients were maintained on extended-interval monitoring for a maximum of 68 weeks or until they were no longer suitable for extended-interval follow-up. The 68-week maximum allowable follow-up period accounted for scheduling study visits within a ±1 week scheduling window. If a patient's next scheduled visit would have exceeded 68 total weeks, the present visit was counted as their last study visit and they were considered a study completer. Their care following the last visit was continued as determined by the treating practitioner.

At each study visit patients were considered suitable to continue extended-interval warfarin monitoring if they met the following criteria: (1) therapeutic INR or INR ≤0.3 away from goal; (2) no change in warfarin dose required; (3) no need for shorter follow-up interval due to other reasons (e.g., new medication started with potential for a significant interaction). Patients who did not meet the criteria for extended-interval follow-up at or before the week 26 study visit were permitted to enter a "second-chance" study phase provided that they did not require a warfarin dose change and their INR excursion was caused by a reversible and transient factor. The "second-chance" study phase proceeded by confirming the patient's INR had returned to goal range in 1–2 weeks with subsequent follow-up intervals of 4, 8, and then 12 weeks thereafter. Patients were removed from the study early if they were deemed unsuitable for continuing extended-interval follow-up. Reasons included warfarin dose change, out of range INR, missed appointments, patient desire for more frequent monitoring, bleeding event that investigators determined to require more frequent patient monitoring, and at the discretion of the study investigators if the patient's INR was not expected to return to or remain in therapeutic range (e.g., new continuing drug interaction).

Data collection

Demographic and anticoagulation related factors were collected at baseline and at study end, including age, sex, race, ethnicity, employment status, use of adherence aids, indication for anticoagulation, weeks with stable INR, total weekly warfarin dose, specific warfarin regimen, total duration of warfarin therapy, history of bleeding event in the past year, and reported servings of vitamin K containing food per week.

Anticoagulation satisfaction was measured using the Duke Anticoagulation Satisfaction Scale (DASS) [9]. The DASS is a validated instrument designed to assess

satisfaction with anticoagulation. The instrument is comprised of 25 questions, each scored on a 1–7 point ordinal scale where "not at all" = 1, "a little" = 2, "somewhat" = 3, "moderately" = 4, "quite a bit" = 5, "a lot" = 6, and "very much" = 7. Of the 25 questions, six are worded in a positive position (e.g., "Overall, how satisfied are you with your anti-clot treatment?") and are therefore reverse coded. Across all questions a higher score indicates lower anticoagulation satisfaction. The sum of all the responses is the total DASS score, which can range from 25 to 175. The total score is broken down into three subscales which measure limitations, hassles, and psychological impact in relation to anticoagulation therapy. In the present study patients completed the DASS survey at baseline and again at the end of the study or discontinuation of extended-interval warfarin monitoring, whichever occurred first. Study data were managed using the electronic REDCap data-capturing application hosted by the University of Florida [10].

Outcomes and statistical analysis

The primary outcome of this pre-specified secondary analysis was the change in total DASS score from baseline to final study visit. Secondary outcomes included change in sub-scale scores and identification of patient characteristics associated with changes in DASS score. Descriptive statistics were used to characterize the study population. The paired t-test was used to assess the change in total DASS score and change in sub-scale scores. Analysis of variance was used for bivariate analyses. Pearson correlation coefficients were calculated for associations between change in DASS scores and continuous variables. We considered a $p < 0.05$ as statistically significant and did not adjust for multiple comparisons. We analyzed the data using SAS version 9.3 (SAS Institute, Cary, NC).

Results

Of the 47 patients with complete evaluable clinical data in FADE-OUT, 46 patients had at least partially complete pre- and post-intervention DASS survey data (i.e., for at least one sub-scale), and 36 had complete pre- and post-intervention DASS survey data. The baseline characteristics for the 46 patients with evaluable DASS scores for at least one sub-scale are summarized in Table 1 and these data did not differ appreciably from those with complete DASS data (data not shown). Patients with complete pre- and post-intervention DASS survey data for at least one sub-scale ($n = 46$) completed 34 ± 22 weeks (mean ± SD) of follow-up. No major bleeding or thrombotic events occurred during the study. Complete pre- and post-intervention limitation sub-scale scores were available for 44 patients, complete pre- and post-intervention hassles sub-scale scores were available for 44 patients, and complete pre- and post-intervention psychological impact sub-scale scores were available for 39 patients.

Substantial variation was observed in change in DASS total score and subscale scores following the intervention (Fig. 1). The mean ± SD total DASS score was 45.2 ± 14.2 at baseline and 49.1 ± 14.9 at study-end (mean change +3.9 [95 % CI −0.6–8.4; $p = 0.09$]; range −36 to +38), indicating a non-significant worsening of anticoagulation satisfaction. Table 2 summarizes baseline, end-of-study and change in DASS subscale scores. Only the change in psychological impact subscale score was statistically significant (+2.6 [95 % CI 0.6–4.5; $p = 0.01$]).

No baseline patient factors were significantly associated with mean change in total DASS score (Tables 3, 4). Total number of years taking warfarin at baseline trended toward an inverse association with the hassles sub-scale score ($r = -0.27$; $p = 0.07$). Total number of medications at baseline trended toward an association with increased mean psychological impact sub-scale score ($p = 0.089$), whereas, total number of medications used at the end of the study was significantly associated with increased mean psychological impact sub-scale score ($p = 0.026$). Interestingly, no association was observed between change in total DASS score (or sub-scale scores) and the length of extended-interval monitoring completed.

Discussion

This is the first study, to our knowledge, to examine the impact of extended-interval warfarin monitoring on anticoagulation satisfaction. We expected that anticoagulation satisfaction would improve in patients following extended-interval monitoring, particularly if it was successfully continued over time. To the contrary, we found that anticoagulation satisfaction, as measured by the DASS survey, did not change, and may have marginally worsened following extended-interval follow-up. The magnitude of change observed here was small though consistent with results from a previous study deemed to show modest, but clinically significant change in total DASS scores [11]. These findings do not support the notion that extending monitoring intervals for vitamin K antagonists generally leads to improved patient satisfaction, for example, from decreased follow-up burden.

Three questions in the DASS survey demonstrated the most marked change: "how much do you feel reassured because of your anti-clot treatment?", "overall, how much has anti-clot treatment had a positive impact on your life?",

Table 1 Baseline characteristics of participants with evaluable pre- and post-intervention DASS survey data (n = 46)

Characteristic	Mean ± SD or n (%)
Age (years)	66.5 ± 12.5
Male	22 (47.8)
Number of medications taken daily	6.9 ± 4.6
Race/ethnicity	
White (non-Hispanic)	34 (74)
Black (non-Hispanic)	10 (22)
Other	2 (4)
Indications for chronic warfarin[a]	
Non-valvular atrial fibrillation or flutter	27 (58.7)
Prevention of recurrent DVT	13 (28.3)
Prevention of recurrent PE	10 (21.7)
Other	7 (15.2)
Anticoagulation-related factors	
Weeks with stable INR/warfarin dose	32.9 ± 28.1
Total weekly dose (mg)	38.4 ± 17.5
Duration of chronic warfarin use (years)	6.66 ± 6.05
Any hospitalization in past year for bleeding event	2 (4.4)
Patient reported planned servings of vitamin K containing foods per week	3.88 ± 3.90

DVT deep venous thromboembolism, *INR* international normalized ratio, *PE* pulmonary embolism

[a] Six patients in study had multiple indications

and "overall, how satisfied are you with your anti-clot treatment?" Mean score for each of the three questions increased (worsened satisfaction) by ≥0.5, contributing to decreased anticoagulation satisfaction on the psychological impact subscale. Conversely no single question demonstrated a mean decrease (improved satisfaction) of ≥0.2. One plausible explanation for the change seen in these questions, based on the nature of the intervention (i.e., less monitoring) is that patients felt less engaged with their treatment. Less frequent feedback and patient-provider interaction may have resulted in reduced patient perception of benefit from anticoagulation and reduced self-management activities. Greater patient engagement in INR monitoring seems to positively affect patient satisfaction with anticoagulation therapy as evidenced by previous studies showing improved anticoagulation satisfaction (as measured by the DASS survey) in patients who self-monitor their INR [11–13]. Alternatively or concurrently, the less frequent follow-up may have resulted in increased anxiety with extended-interval monitoring owing to less frequent confirmation that their INR was in range and their warfarin dose was appropriate [14].

Interestingly, we found that change in DASS score was neither associated with duration of extended-interval follow-up nor completion of all study visits (and, as a corollary, more stable INR control throughout follow-up). We suspected that patients achieving successful, long-term extended-interval monitoring would have benefited most with regard to enhanced satisfaction, given the reduced follow-up burden over time. However, our findings did not support this supposed benefit of extended-interval monitoring [15]. Indeed, as another recent study suggests, there may be little association between INR control and overall quality-of-life [16]. Secondly, we observed no obvious or strong associations between baseline characteristics and change in total DASS score. However, we did find several potential relationships between baseline characteristics and change in DASS subscale scores worthy of future study. A greater number of years taking warfarin at baseline was nonsignificantly associated with decreased hassle from extended-interval monitoring. This finding needs confirmation in larger studies, but may reflect a greater comfort level with extending INR monitoring intervals among patients with greater experience with warfarin [17, 18]. Additionally, taking a greater number of medications may be associated with greater adverse psychological impact, possibly because patients with numerous medications may be more concerned with drug–drug interactions and an extended follow-up interval may magnify these concerns. However, these relationships were generally weak and statistically nonsignificant or only marginally significant and, because of multiple comparisons, may be spurious. Thus, more studies are required to clarify which patients may benefit from extended-interval warfarin monitoring, and whether any baseline characteristics might be used to predict benefit.

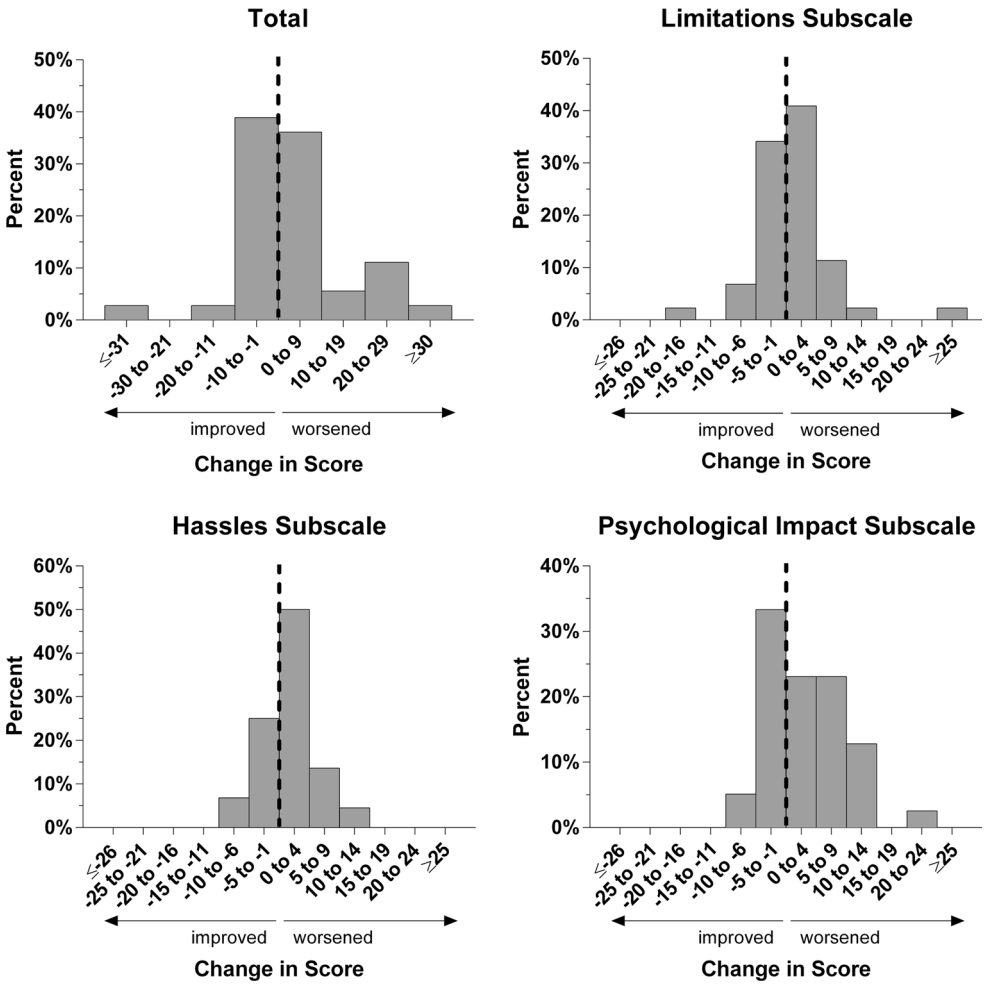

Fig. 1 Distribution of change in total DASS and subscale scores; the *hashed black line* represents no change in DASS score

Table 2 Pre- and post-extended-interval monitoring DASS scores

DASS score	N	Baseline	End of study	Difference (95 % CI)	p-value
Total	36	45.2 ± 14.4	49.1 ± 15.2	3.9 (−0.6–8.4)	0.09
Limitations	44	15.5 ± 6.88	16.0 ± 7.12	0.5 (−1.5–2.4)	0.61
Hassles	44	13.1 ± 5.08	13.8 ± 5.44	0.8 (−0.6–2.2)	0.27
Psychological impact	39	16.0 ± 5.51	18.6 ± 6.46	2.6 (0.6–4.5)	0.01

Data represent mean ± SD unless specified otherwise

Whether our findings apply more broadly to anticoagulants beyond warfarin is not known. Data from the Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY) study suggest that health-related quality of life remains stable over at least 1 year during treatment with both warfarin (with conventional 4-week follow-up) or dabigatran (with extended follow-up upto every 3 months), with no appreciable differences between treatments [19]. However, a slight majority of patients in the RE-LY trial had not previously used vitamin K antagonists. Previous work suggests that patients initially treated with newer oral anticoagulants, compared to warfarin, may have the potential for better relative quality-of-life, at least initially [20]. This is consistent with the comparison of rivaroxaban to enoxaparin/warfarin for deep vein thrombosis which showed a modest benefit of rivaroxaban on the Anti-Clot Treatment Scale [21]. Therefore, the lack of benefit or even detriment to anticoagulation satisfaction seen in our study may reflect that warfarin-treated patients have become accustomed to consistent and frequent follow-up. This reliance might be expected given the heavy emphasis on maintaining a therapeutic INR in warfarin management clinics and the related counseling and monitoring. We cannot say whether less frequent monitoring as

Table 3 Relationship between baseline characteristics and change in DASS total and subscale scores

Baseline characteristic	Total		Limitations		Hassles		Psychological	
	r	p-value	r	p-value	r	p-value	r	p-value
Age (baseline)	−0.041	0.811	0.001	0.995	−0.149	0.335	0.062	0.708
Years on warfarin (baseline)	−0.256	0.132	−0.158	0.304	−0.274	0.072	−0.059	0.721
Weeks with stable INR/warfarin dose (baseline)	−0.126	0.465	−0.107	0.488	−0.055	0.723	−0.121	0.462
Number of medications (baseline)	0.263	0.139	0.166	0.305	0.022	0.893	0.288	0.089
Number of medications (end of study)	0.216	0.228	0.114	0.476	−0.113	0.481	0.370	0.026
Number of weeks of extended-interval monitoring completed	−0.200	0.242	−0.169	0.272	−0.237	0.121	−0.182	0.269

Change in DASS score is calculated as post-intervention score minus pre-intervention score (i.e., a positive value indicates worsening of anticoagulation satisfaction. Thus, a positive r-value indicates a linear relationship between increasing values of the baseline characteristic and *worsening* of anticoagulation satisfaction; conversely, a negative r-value indicates a linear relationship between increasing values of the baseline characteristic and *improvement* of anticoagulation satisfaction

Table 4 Change in mean total DASS Score according to pertinent categorical variables

Variable	Mean change ± SD	p-value
Sex		0.166
Female	6.8 ± 14.0	
Male	0.6 ± 12.0	
Same dose each day of the week (baseline)		0.980
Yes	4.0 ± 13.6	
No	3.8 ± 13.5	
Employed (baseline)		0.315
Yes	8.7 ± 13.2	
No	2.9 ± 13.5	
Completed study		0.862
Yes	2.8 ± 13.2	
No	4.0 ± 13.5	

Change in DASS score is calculated as post-intervention score minus pre-intervention score, (i.e., a positive value indicates worsening of anticoagulation satisfaction)

a result of switching from warfarin to newer oral anticoagulants affects satisfaction.

Presumably, given the informed consent process, patients at baseline were inclined to participate in extended-interval follow-up for some perceived benefit. Indeed, a previous study of home INR monitoring suggests that 76 % of patients would be willing to pay some amount of money to reduce the frequency of their anticoagulation clinic visits [13]. However, based on the findings of our study it is unlikely that the majority of patients became meaningfully more satisfied with anticoagulation, despite less frequent follow-up visits. Furthermore, whether patients will routinely and voluntarily report dissatisfaction with extended-interval warfarin monitoring is not known. Despite the numerous patients with worse anticoagulation satisfaction following extended-interval monitoring, only one patient withdrew participation because of a request for more frequent monitoring [8]. Thus, additional assessments may be needed to ascertain the true patient perceived benefit—if any—of extended-interval monitoring.

To place our findings into the larger context of choosing an oral anticoagulant agent there are two major considerations for patients which are potentially indicated for both warfarin and newer oral anticoagulants: monitoring and safety/efficacy. First, newer oral anticoagulants (i.e., apixaban, dabigatran, edoxaban, and rivaroxaban) do not require routine laboratory monitoring. However, data has demonstrated that continued patient monitoring improves patient adherence [22]. Moreover, an observational study of patients with non-valvular atrial fibrillation demonstrated that as adherence to dabigatran decreases the combined outcome of all-cause mortality and stroke increases (hazard ratio 1.13, 95 % CI 1.07–1.19 per 10 % decrease in proportion of days covered) [23]. Therefore, the proposed benefit of less frequent monitoring should be considered carefully. In terms of safety and efficacy, the newer oral anticoagulants are generally non-inferior or superior to warfarin [24–31]. Of particular importance to patients with non-valvular atrial fibrillation is a consistent lower risk for intracranial bleeding with newer agents [24–27]. Therefore, because we do not expect that extending the interval of warfarin monitoring would improve patient perception of anticoagulation to a large (or any) extent, safety and efficacy should remain the primary determinants in choosing anticoagulation therapy. However, when deciding to switch patients from warfarin to newer agents, an individualized approach should be taken which considers the patient's time in therapeutic range [32].

The major strengths of this study are that it reports on an important outcome to patients—satisfaction—and that its pragmatic design reflects a "real world" population implementing and adhering to the CHEST guideline recommendations regarding extended-interval monitoring.

However, this study has important limitations. First, the small sample size may limit generalizability and the precision of the results. The reason(s) for incomplete survey data from 11 FADE-OUT participants are not fully known and we cannot say with any certainty whether total DASS score changes would have been qualitatively similar among these patients and those who completed the full survey. Second, our pragmatic implementation intervention did not include a control group and is therefore potentially prone to bias. Consequently, these results should be taken with a degree of caution and need to be confirmed in larger studies with more robust bias controls. Finally, all patients took the baseline survey under the same clinical scenario, that is, while having a stable INR for $\geq$12 weeks thus qualifying for extended-interval follow-up; however, patients took the exit survey under varied clinical scenarios. Specifically, some patients completed all study visits without a significant INR excursion and ended their study participation after more than 1 year of follow-up. Others were removed from the study early, per protocol, because they were no longer suitable candidates for extended-interval warfarin monitoring. Although we did not find any association between change in DASS score and duration of time between DASS survey administrations, we cannot say with certainty whether these varied scenarios affected results.

Conclusions

The current study does not support improved anticoagulation satisfaction with less frequent warfarin monitoring. Indeed, a trend toward decreased satisfaction was found following extended-interval warfarin monitoring. However, we observed considerable variation in patient response, suggesting that extended-interval warfarin monitoring is preferred by some patients but not by others. Further studies are needed to confirm the findings from this study and to identify patient characteristics predictive of improved anticoagulation satisfaction. At present, clinicians should use shared decision-making prior to initiating extended-interval warfarin monitoring, with continual reassessment of patient preferences and attitudes in conjunction with clinical appropriateness.

Compliance with ethical standards

Conflict of interest Dr. Marc S. Zumberg reports being the medical director for NCF diagnostics and DNA technology.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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