Combined Analysis of the HER2DX Genomic Tool in Adjuvant APT and ATEMPT Trials

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BACKGROUND

In the phase 2 APT trial, adjuvant paclitaxel and trastuzumab (TH) was associated with excellent long-term outcomes for patients with small, node-negative HER2+ breast cancer. In the randomized phase 2 ATEMPT trial, adjuvant trastuzumab emtansine (T-DM1) also demonstrated outstanding outcomes in patients with stage 1 HER2+ breast cancer. HER2DX risk-score was associated with survival outcomes in both trials, separately.

METHODS

We conducted a retrospective analysis combining patients included in the APT (n=406) and ATEMPT (n=497) trials with available HER2DX data. The co-primary endpoints of the study were associations of HER2DX with relapse-free interval (RFI) and invasive disease-free survival (iDFS).

		Overall (n=471)
Study, n (%)	APT ATEMPT	284 (60.3) 187 (39.7)
Clinical tumor stage, n (%)	T1 T2	440 (93.3) 31 (6.6)
Clinical nodal stage, n (%)	N0 N1mic	462 (98.1) 9 (1.9)
Hormone receptor, n (%)	Negative Positive	136 (28.9) 335 (71.1)
Treatment, n (%)	TH T-DM1	324 (68.8) 147 (31.2)
HER2DX risk groups (original cut-off 50), n (%)	Low High	445 (94.5) 26 (5.5)
HER2DX risk groups (cut-off 32), n (%)	Low High	385 (81.7) 86 (18.3)
HER2DX pCR score groups, n (%)	Low Med High	45 (9.6) 86 (18.3) 340 (72.2)

Table 1 – Clinicopathologic characteristics and HER2DX scores for the patients included in the pooled analysis of APT/ATEMPT

The HER2DX risk-score was evaluated i) as a continuous variable (0 - 100), ii) using the predefined cut-off (50), and iii) using an exploratory optimal cut-off (32) derived by maximizing the log-rank statistic for the recurrence-free interval endpoint in the APT trial. The Kaplan-Meier method and stratified Cox models were used to estimate hazard ratios (HRs) to evaluate the association between HER2DX and survival outcomes.

RESULTS

Overall, 471 patients receiving TH (n=324) or T-DM1 (n=147) were included in the analysis, most having stage I (n=432) and HR+ disease (n=335) (**Table 1**). The median follow-up was 6.7 years (10.8 and 5.8 for APT and ATEMPT, respectively).

The median HER2DX risk-score was 13.9 (IQR 4.7-27.0), with 5.5% and 18.3% of the patients having HER2DX high-risk disease according to the predefined and optimal cut-offs, respectively. Most tumors showed a high expression of HER2 (55.6%), a high expression of proliferation signatures (55.6%), IgG signatures (52.9%), and luminal signatures (42.9%). (**Figure 1**)

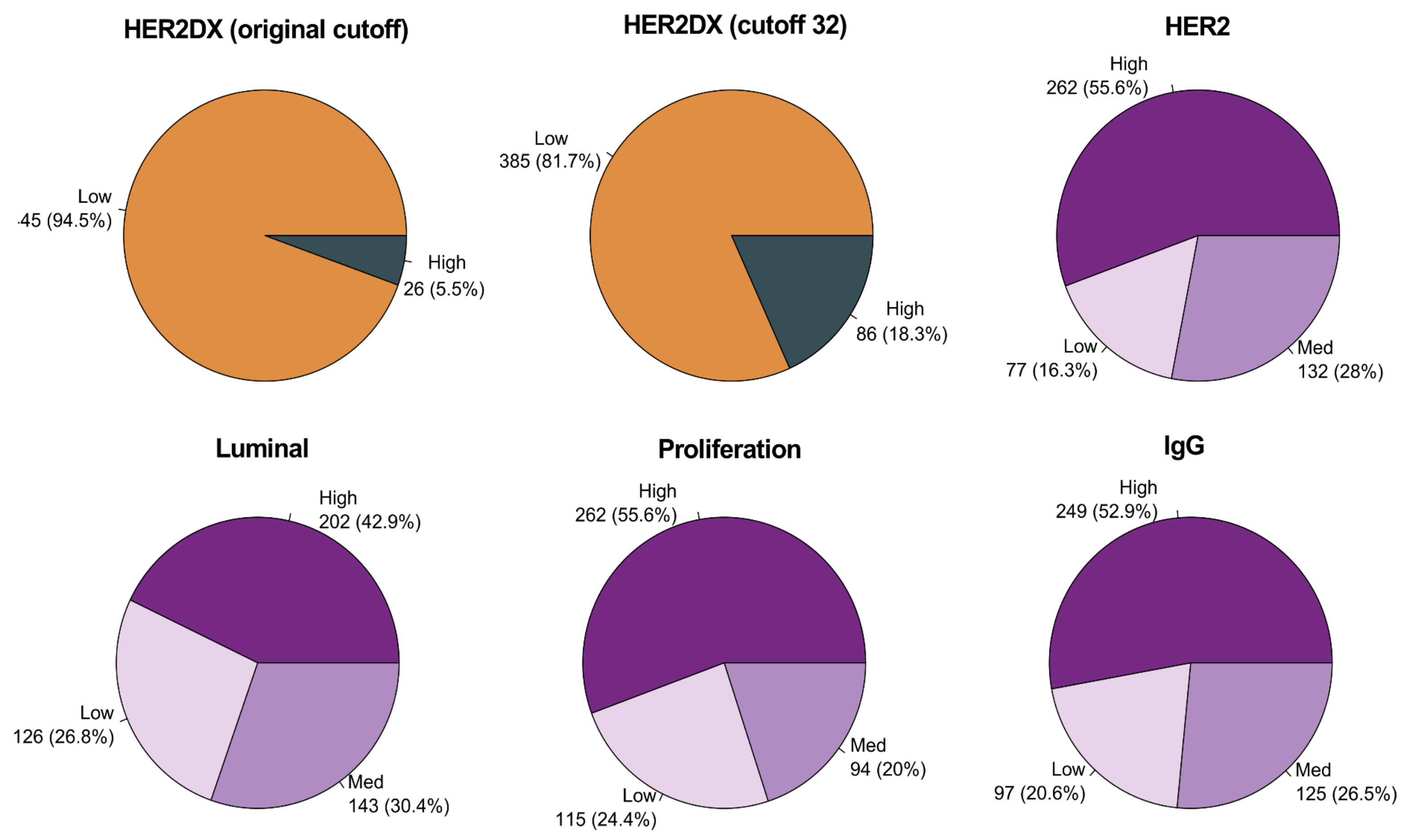

Figure 1 – HER2DX risk scores and expression of HER2, luminal, proliferation and IgG signatures among patients in APT/ATEMPT with available HER2DX data

HER2DX risk score as a continuous variable was found significantly associated with RFI (HR per 10-units: 1.39, 95%CI: 1.09-1.78; p=0.009) **but not with iDFS** (HR per 10-units: 1.18, 0.98-1.42; p=0.09).

Using the predefined cut-off (50), patients with HER2DX high-risk disease had higher RFI risk (HR: 7.33, 2.29-23.47, p<0.001), but the effect on iDFS was non-significant (HR: 2.78, 0.97-7.95, p=0.057) (**Figure 2, A-B**). The optimal cut-off (32) identified patients with low-risk disease (RFI at 7 years of 98.2%; 95% CI: 96.7%-99.6%) from those with high-risk (RFI at 7 years of 88.7%; 95% CI: 80.4%-97.8%) [delta of 9.5%], with a significant difference in both iDFS and RFI. (**Figure 2, C-D**)

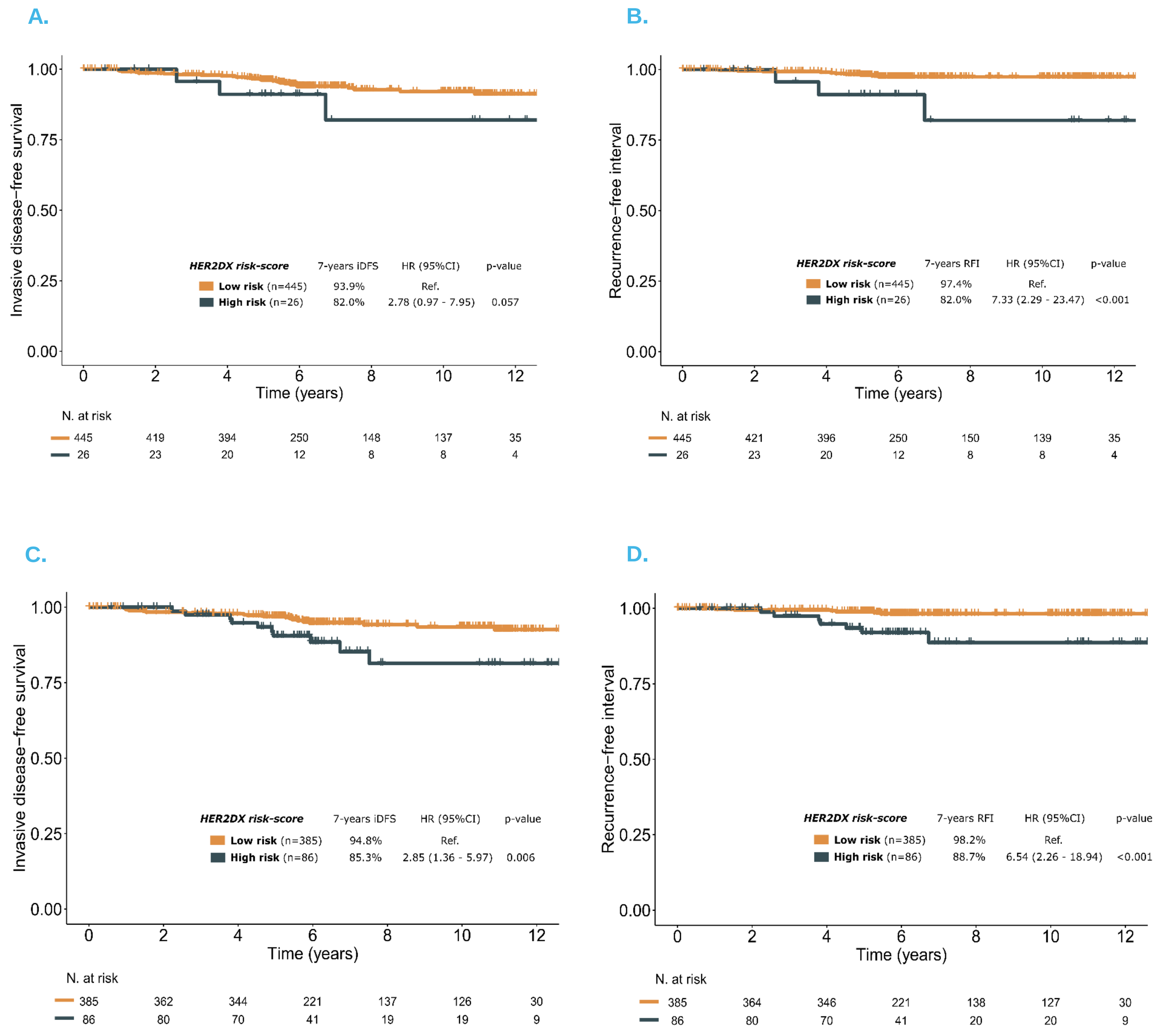

Figure 2 – 7-year iDFS and 7-year RFI by HER2DX score using the pre-defined risk score cutoff (50, curves A and B) or an exploratory optimal cutoff (32, curves C and D)

In the multivariable analysis, HER2DX group-risk maintained statistical significance after adjusting by HR status and tumor stage in RFI (HR: 6.87, 2.22-21.27, p<0.001) **and iDFS** (HR: 2.81, 1.26-6.23, p=0.01) (**Table 2**). Tumor size and HR expression were not found associated with RFI nor with iDFS (**Figure 3**).

n=471	iDFS (multivariable analysis)			RFI (multivariable analysis)		
	HR	95% CI	p-value	HR	95% CI	p-value
HER2DX risk-group						
Low-risk	Ref.	-	-	Ref.	-	-
High-risk	2.81	1.26 – 6.23	**0.01**	6.87	2.22 – 21.27	**<0.001**
Tumor stage						
T1	Ref.	-	-	Ref.	-	-
T2	1.01	0.32 – 3.22	0.99	0.85	0.16 – 4.54	0.85
HR status						
Negative	Ref.	-	-	Ref.	-	-
Positive	0.86	0.40 – 1.84	0.71	1.17	0.36 – 3.81	0.80

Table 2 – Multivariable analysis of iDFS and RFI in APT/ATEMPT by HER2DX score

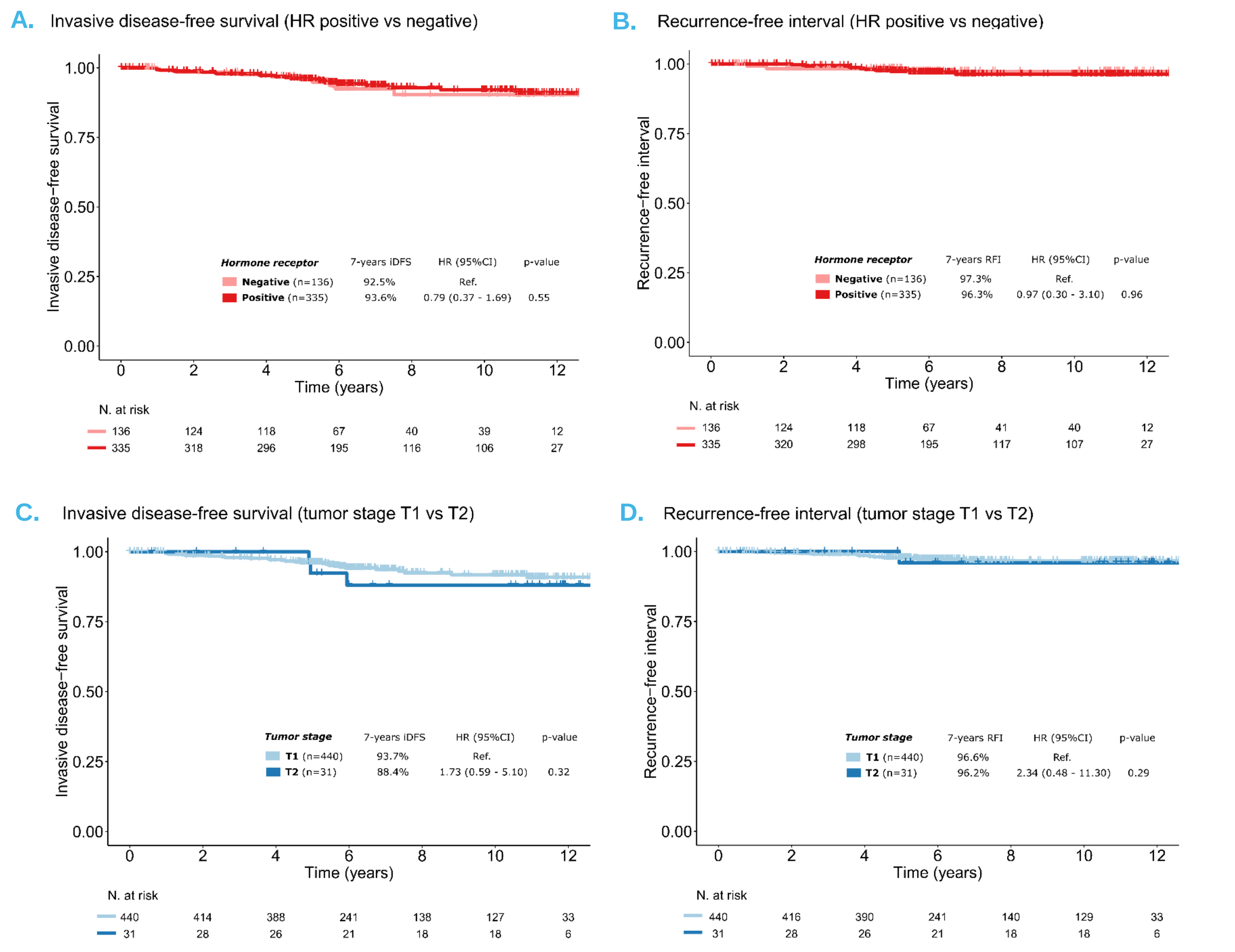

Figure 3 – iDFS and RFI by HR status (A-B) and tumor size (C-D) in the pooled analysis

SCAN ME

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PRESENTER'S DISCLOSURES: PT has served as advisor/consultant for AstraZeneca, Daiichi Sankyo, Gilead, Eli Lilly and Roche.

CONCLUSION

The HER2DX score is associated with the risk of recurrence among patients with small, node negative HER2+ breast tumors, and, if validated, may help in tailoring treatments for this disease.