Supplementary Online Content

Wolf RM, Channa R, Abramoff MD, Lehmann HP. Cost-effectiveness of autonomous point-of-care diabetic retinopathy screening for pediatric patients with diabetes. *JAMA Ophthalmol.* Published online September 3, 2020. doi:10.1001/jamaophthalmol.2020.3190

eAppendix. Peds Automated DR Screening

This supplementary material has been provided by the authors to give readers additional information about their work.

Summary

Base Rates

Table 1

Type 1	**Auto**	**ECP**	**Difference**		**Incremental Cost–Effectiveness Ratio**
Cost	$8.52	$7.91	Δ Cost	$0.61	$31*
TP	.026	.006	Δ Effectiveness	0.020	
Type 2					
Cost	$10.85	$8.20	Δ Cost	$2.65	$95
TP	.038	.010	Δ Effectiveness	0.028	

*per extra DR detected by Autonomous, above ECP

Sensitivity Analysis Summary

There is little uncertainty that alters the conclusion that Autonomous is more cost effective. ICER diagram is Figure 29.

Table 2

	Threshold	**Base Case**	**Comment**
Type 1/True Positives			
Sens Autonomous	.19	.87	DNAC*
Sens ECP	None	.35	DNAC
Probability of Going to ECP upon referral	.87	.2	DNAC
Relative Odds of Keeping ECP Appointment	23	76	DNAC
Type 1/Out of Pocket Costs			
Autonomous out of pocket	None	$0	ECP strategy always cheaper on average.
ECP out of pocket	$53	$35	Autonomous is preferred if ECP out of pocket cost is higher, due to greater

			sensitivity (cECP threshold is higher as Aut sensitivity improves, and lower, as Aut spec improves)
DR Rx out of pocket	$61	$94	Autonomous cheaper at lower DR Rx cost
DR prevalence	.076	.09	If DR prevalence can be driven lower, Autonomous is preferred.
Sensitivity Autonomous	.76	.87	If Aut sens drops below .76, Aut is cheaper
Specificity Autonomous	.93	.91	If Aut specificity were a little higher, it would be cheaper on average
Sensitivity of ECP	.23	.35	ECP loses its cost advantage if its sensitivity drops below .23
Specificity ECP	.83	.95	ECP specificity is already above threshold, where it is cheaper on average
Diagnosability of Autonomous	.98	.96	If Aut diagnosability is improved a bit more, Aut becomes cheaper on average.
Probability of keeping ECP Apointment	.22	.20	Base value is just at threshold, above which Autonomous is preferred.
Relative Odds of Keeping ECP Appointment	26	76	DNAC

2-way analyses	
cECP and sensAutonomous	If Autonomous had lower sensitivity, ECP becomes cheaper, on average. "X" represents base case.
sens Aut and pECPscreened	As the sensitivity of Aut goes down, ECP becomes cheaper on average, especially if cECP goes down as well.
cECP and spec Aut	As the specificity of Aut goes up, the threshold on cECP goes down. But if spec Aut is less than .90 or so, ECP remains cheaper on average.

DR prevalence vs pECPScreened	As the prevalence of DR goes up, the threshold for families keeping their ECP appointment at which Autonomous becomes cheaper on average also goes up. See ICER graph (Figure 29).
DR Prevalence vs cost of ECP	As the prevalence of DR prevalence rises, the threshold for cECP at which Autonomous becomes cheaper on average goes up as well, until a prevalence of about .13, at which point ECP remains cheaper on average for all cECPs.

Type 2/True Positives			
DR Prevalence	None	.137	DNAC
Sens Autonomous	None	.87	DNAC
Probability of Going to ECP upon referral	.87	.20	DNAC
Relative Odds of Keeping ECP Appointment	23	76	DNAC
Type 2/Out of pocket costs			
Autonomous out of pocket	None	$0	DNAC
ECP out of pocket	None	$35	DNAC
DR Treatment	$0	$94	DNAC
DR prevalence	None	.137	DNAC
Sensitivity Aut	.54	.87	DNAC
Spec Aut	None	.91	DNAC
Sens ECP	.001	.35	DNAC
Spec ECP	.42	.95	DNAC
Relative Odds of Keeping ECP Appointment	23	76	DNAC

2-way analyses	
sensECP and prev	The higher the prevalence, the lower the threshold
specAut and prev	the higher the prevalence, the higher the threshold

*DNAC= Does not affect conclusion

The Tree

Figure 1

Graphic of tree in calculation:

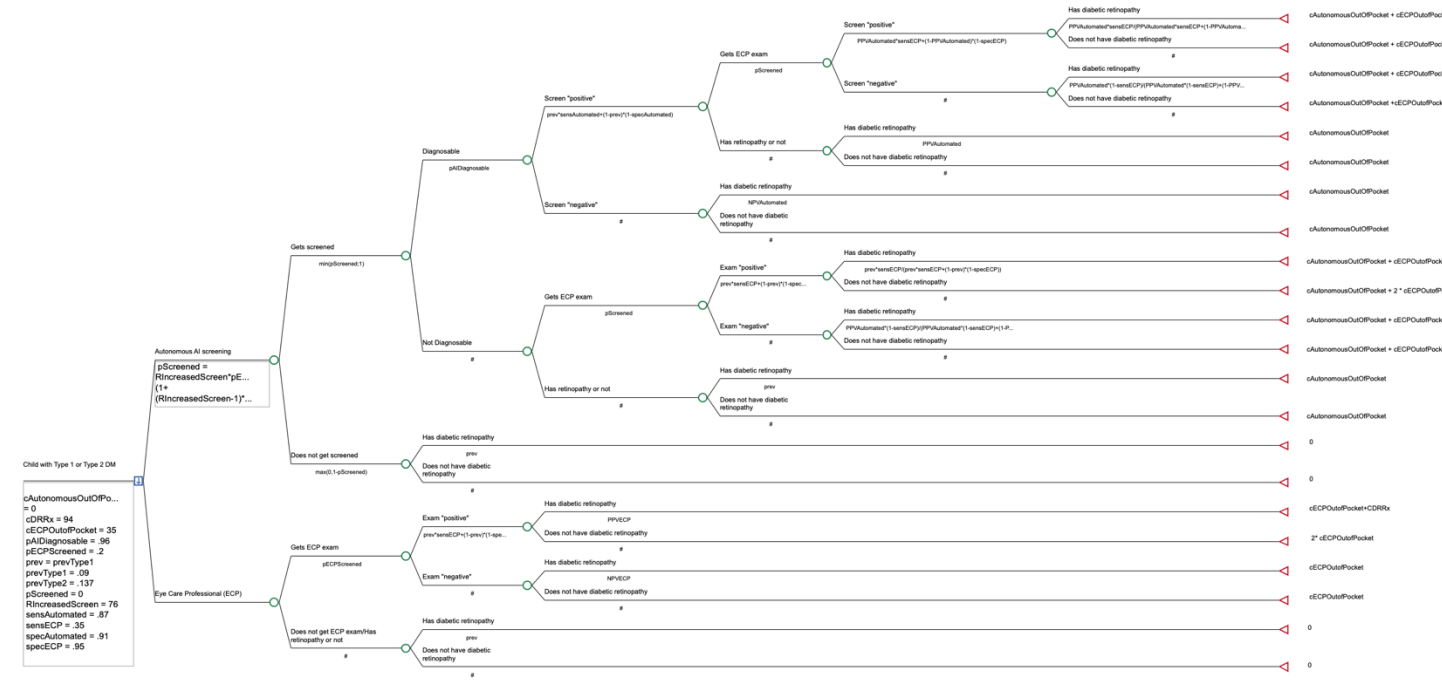

Figure 2

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The Variables

Cost of missed retinopathy: (going blind)

Name	Description	Definition	Low
cAutomatedOutOfPocket	Out of pocket cost for the automated screen	0	0
cECPOutofPocket	Out of pocket cost for the ophtho visit	35	0
cDRRx	Out of pocket cost for treating retinopathy	94	0
pECPScreened	Probability of a patient going for expert-based screening	.20	0.15
pPositiveAutonomousScreen	Probability that a positively-screened patient will followup with Ophthalmology	.95	0
pAIDiagnosable	Probability that image can be obtained and classified	.96	.8
prev	Prevalence of retinopathy in the population	.09	0.056
RIncreasedScreen	Relative odds of getting screened, with respect to	76	0.5
sensAutomated	Sensitivity of the automated screen	.87	0.001
sensECP	Sensitivity of the Expert exam	.35	0.001
specAutomated	Specificity of the automated screen	.91	0.001
specECP	Specificity of the Expert screen	.9	0.001

Type 1 DM

Base case for True Positive (DR Identified) and Patient Cost: [PedsRetinaScreening.JAMAO.15June2020.Type1CEA.png]

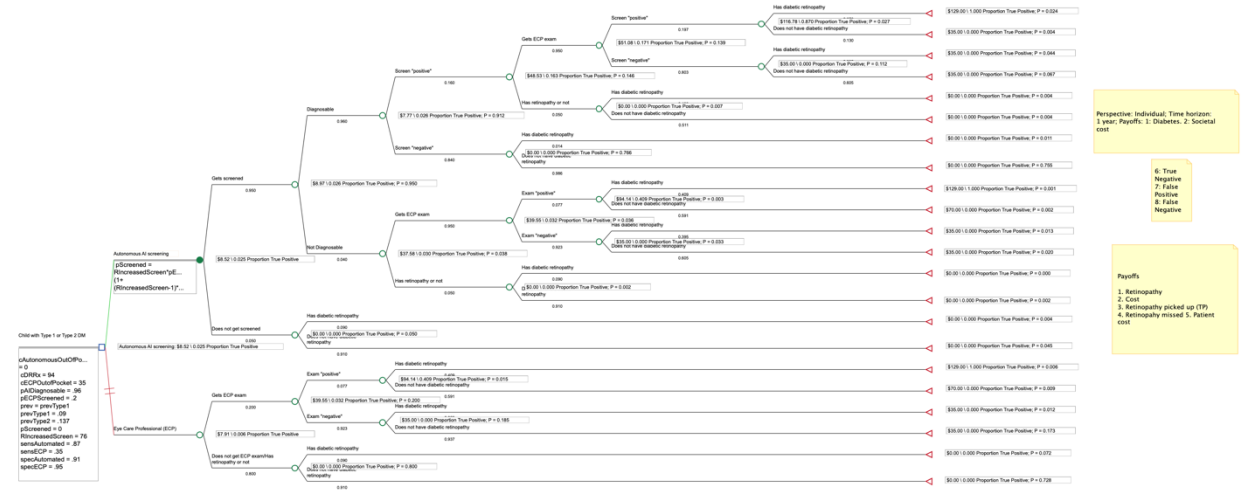


Figure 3

For legibility:

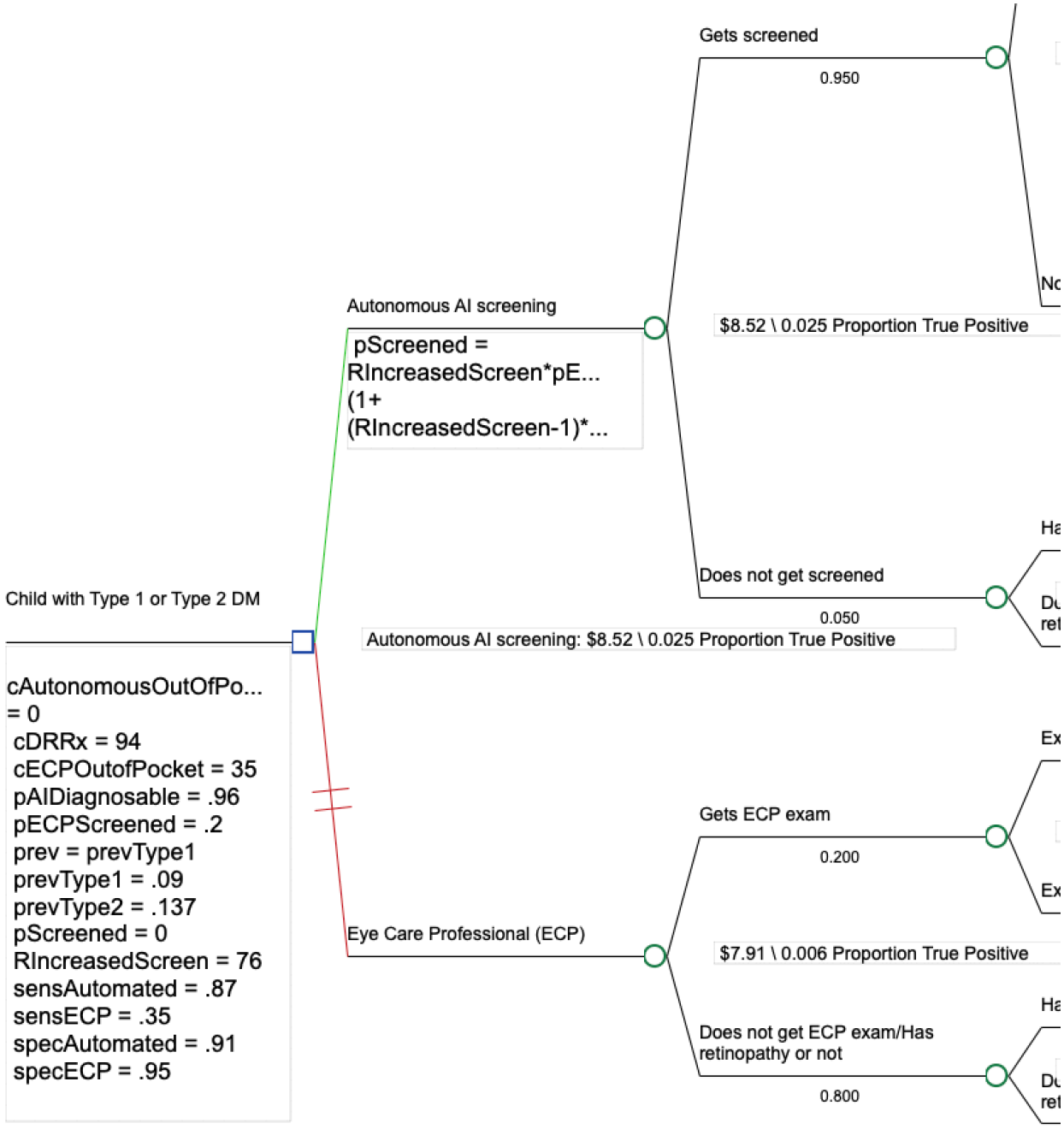


Figure 4

Base Case Results, Type 1 and Type 2

6/15/20

PedsRetinaScreening.JAMAO.15June2020.trex

cDRRx	Payoff 3	Payoff 7	Payoff 3	Payoff 7	Payoff 3	Payoff 7	Payoff 3	Payoff 7

Raw	Type 1					Type 2			
	Autonomous		ECP			Autonomous		ECP	
	DR	No DR	DR	No DR		DR	No DR	DR	No DR
Exam +	0.026	0.011	0.006	0.009		0.038	0.01	0.01	0.009
Exam −	0.064	0.899	0.084	0.901		0.099	0.853	0.127	0.854
	0.09	0.91	0.09	0.91		0.137	0.863	0.137	0.863

Rates	Type 1					Type 2			
	Autonomous		ECP			Autonomous		ECP	
	DR	No DR	DR	No DR		DR	No DR	DR	No DR
Exam +	0.289	0.012	0.067	0.010		0.277	0.012	0.073	0.010
Exam −	0.711	0.988	0.933	0.990		0.723	0.988	0.927	0.990
	1	1	1	1		1	1	1	1

LR+	23.9	6.7	23.9	7.0
LR-	1.4	1.1	1.4	1.1

Payoff 5

Cost

Raw	Type I	Type II

	Autonomous	ECP	
Total	8.52	7.91	

Autonomous	ECP
10.85	8.2

CEA

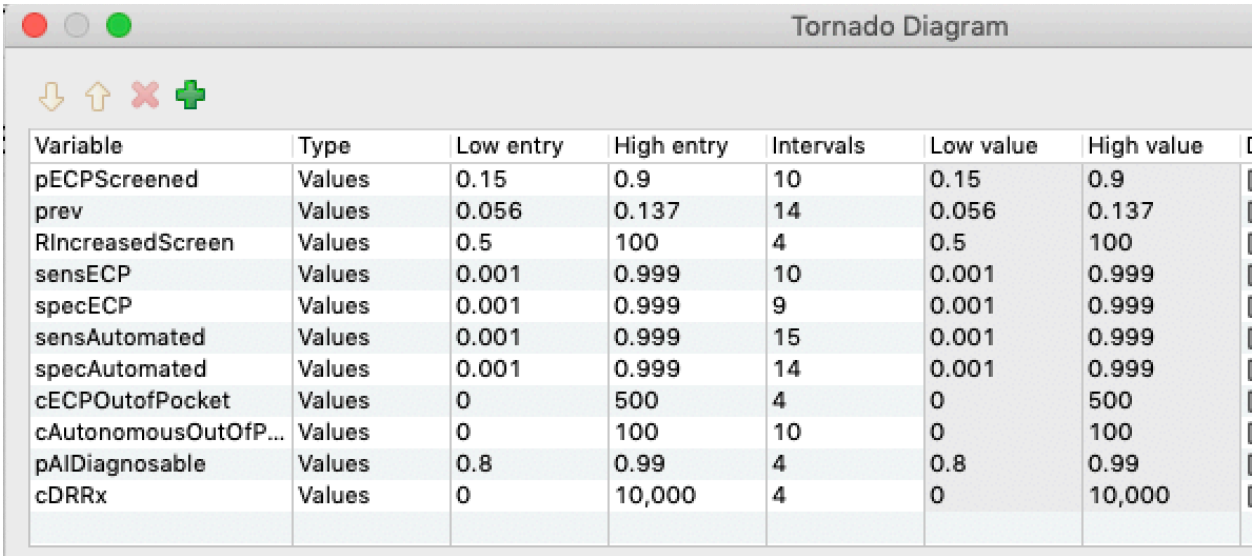
	Type 1		ICER Ratio
TP	Δ Cost	0.61	$31
	Δ Effectiveness	0.02	

Type 2		
Δ Cost	2.65	95
Δ Effectiveness	0.028	

Sensitivity Analysis Type 1 DM: True Positives

Here, expected value reflects true positives detected, so *higher* expected values are preferred.

Tornado Diagram



Variable	Type	Low entry	High entry	Intervals	Low value	High value
pECPScreened	Values	0.15	0.9	10	0.15	0.9
prev	Values	0.056	0.137	14	0.056	0.137
RIncreasedScreen	Values	0.5	100	4	0.5	100
sensECP	Values	0.001	0.999	10	0.001	0.999
specECP	Values	0.001	0.999	9	0.001	0.999
sensAutomated	Values	0.001	0.999	15	0.001	0.999
specAutomated	Values	0.001	0.999	14	0.001	0.999
cECPOutofPocket	Values	0	500	4	0	500
cAutonomousOutOfP...	Values	0	100	10	0	100
pAIDiagnosable	Values	0.8	0.99	4	0.8	0.99
cDRRx	Values	0	10,000	4	0	10,000

Figure 5

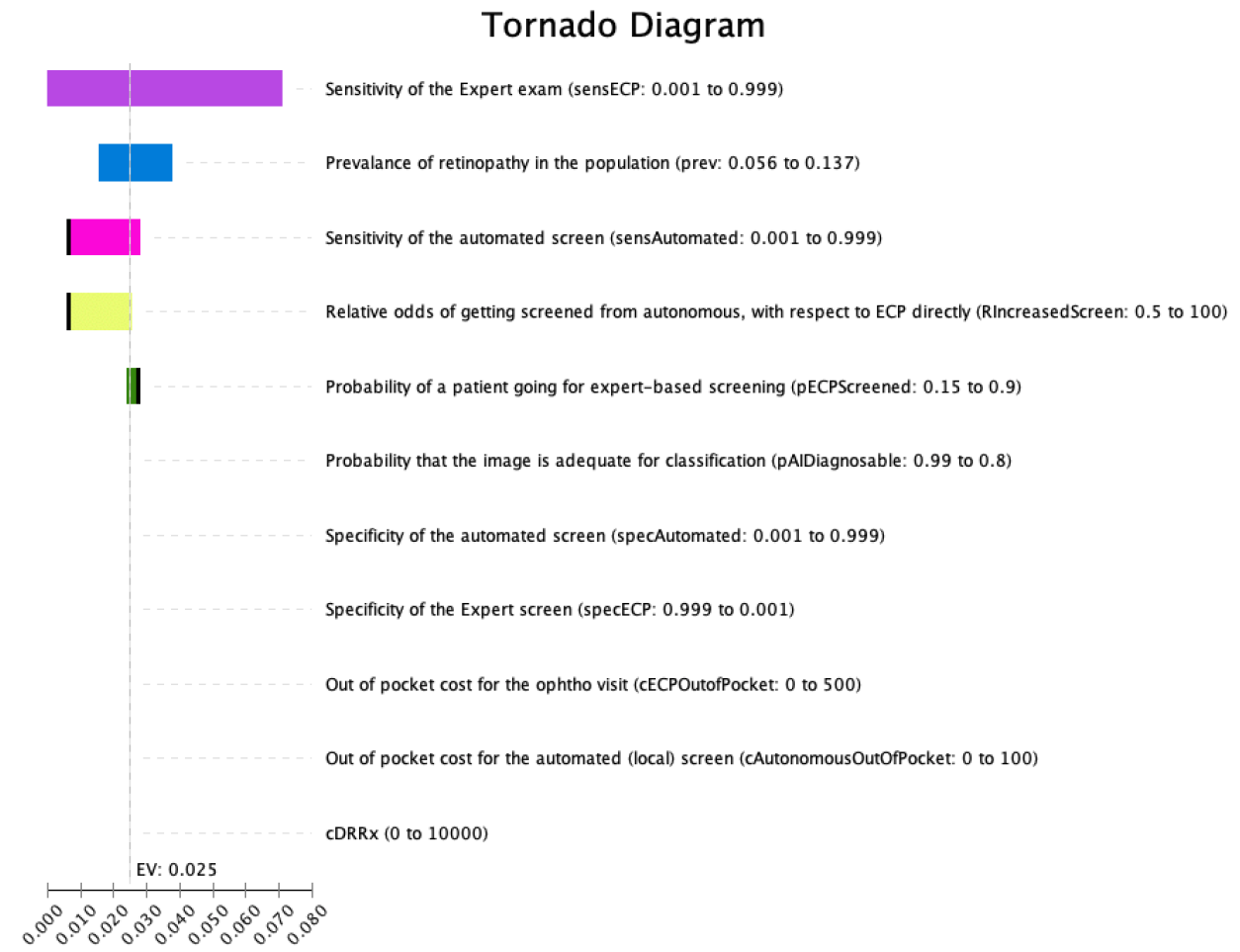


Figure 6

Prevalence

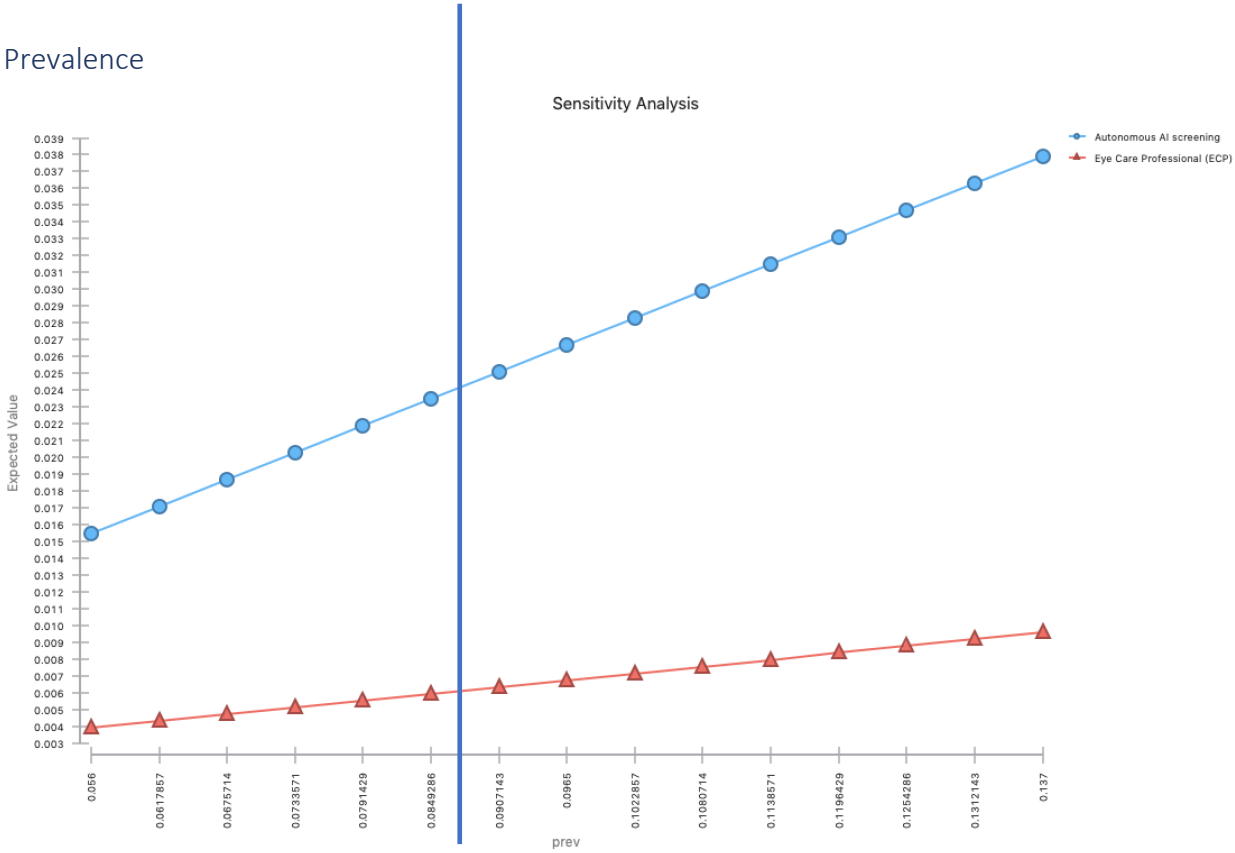


Figure 7

There is no threshold for prevalence; Autonomous always identifies more TPs.

Sensitivity of Autonomous

The vertical blue line, here and later, identifies the base case value (on the x-axis).

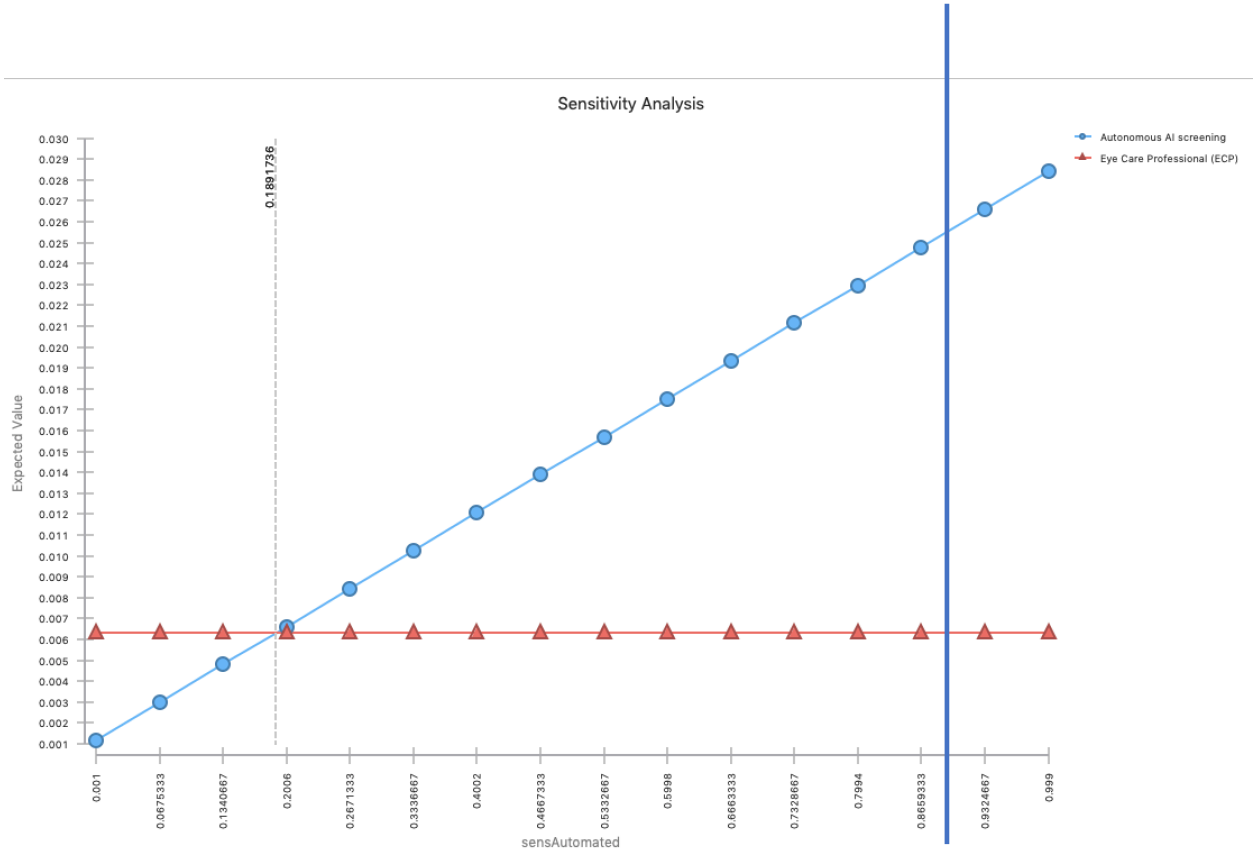


Figure 8

Autonomous detects more cases of DR above a sensitivity of .19, significantly below the base-case sensitivity of .87. Higher sensitivity means that more tests are positive. The number of TPs identified in the ECP-only strategy is unaffected by the sensitivity of the AI-based test.

Sensitivity of the ECP

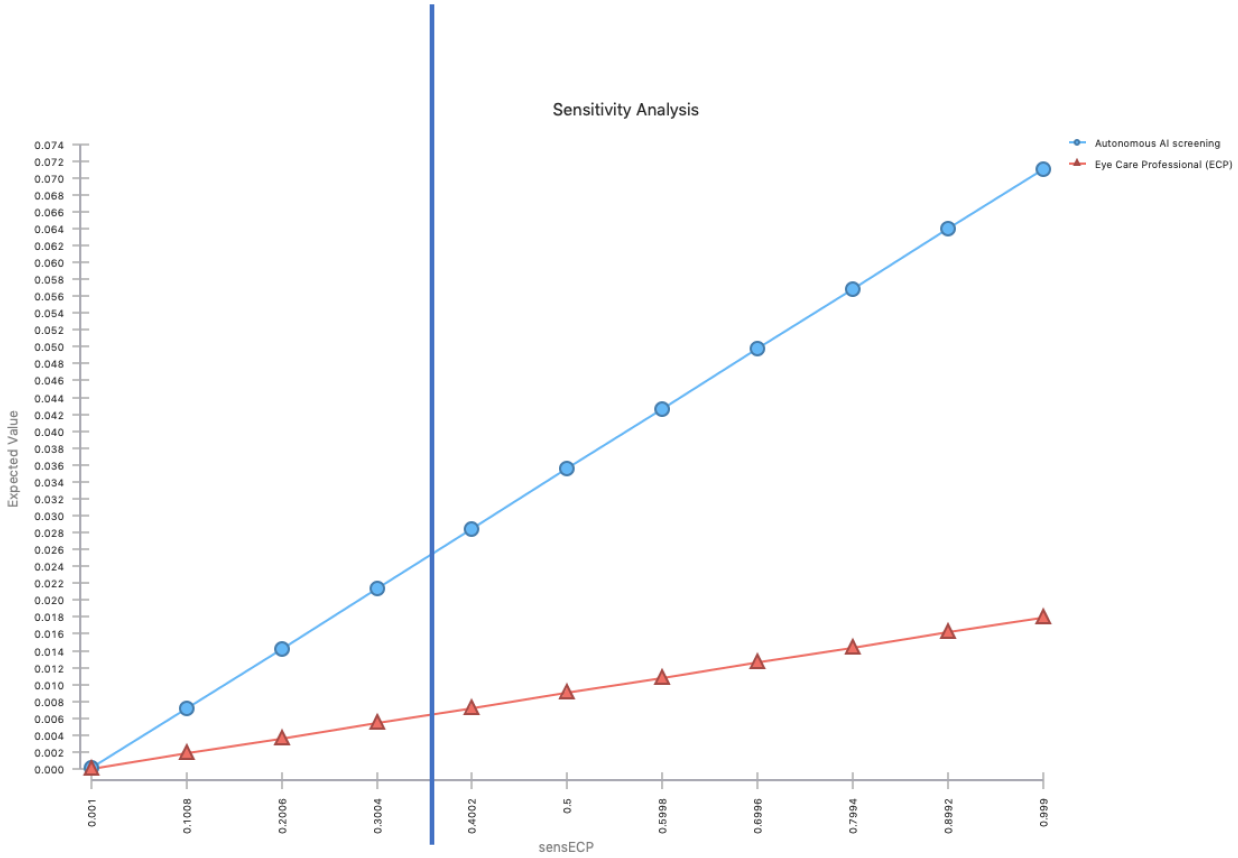


Figure 9

There is no threshold in TP due to sensitivity of the ECP: Because the detection by Autonomous is built on detection by ECP, detection of Autonomous always goes up as the sensitivity of the ECP goes up.

Probability of Going to ECP upon referral

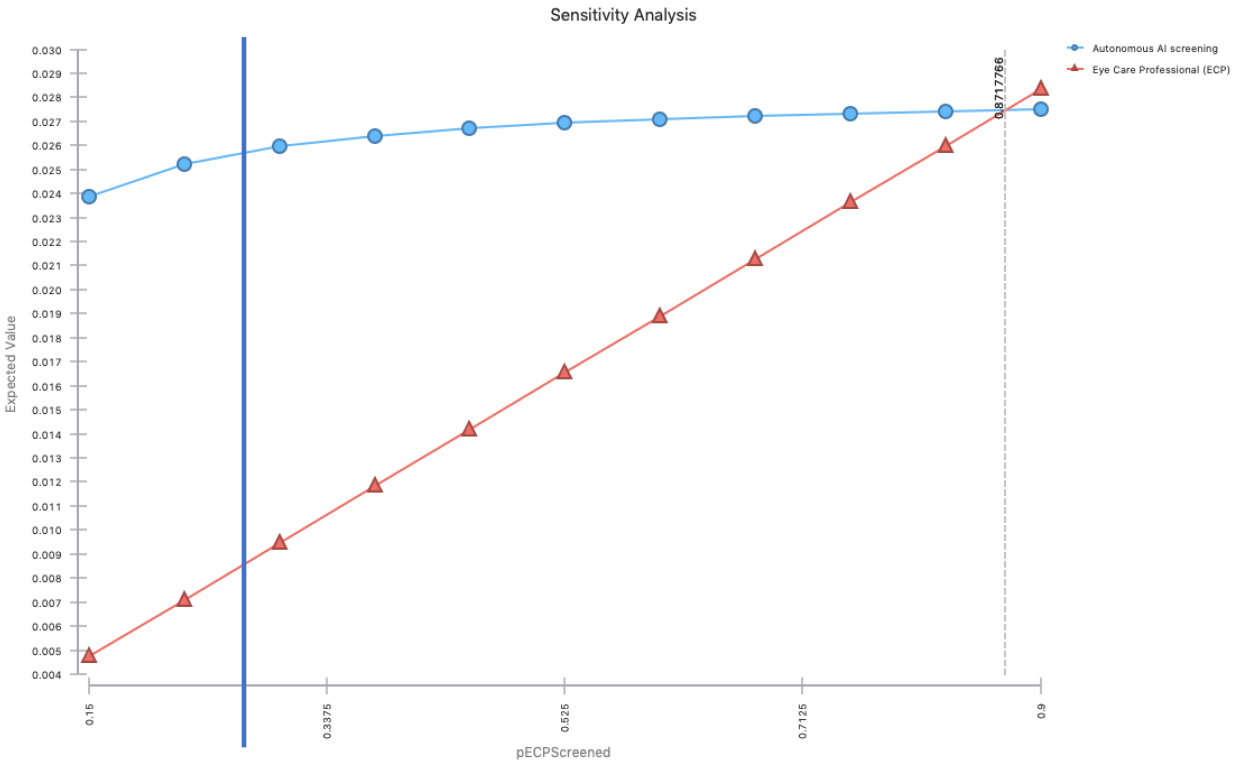


Figure 10

The ECP strategy detects more TPs only if the keeping-appointment probability is above 87%, well above the base rate of 20%. The detection rate by Autonomous does not change much, with an ECP keeping-appointment rate above .2, because the relative odds of Autonomous-positie patients is already so high.

Relative Odds of Keeping ECP Appointment

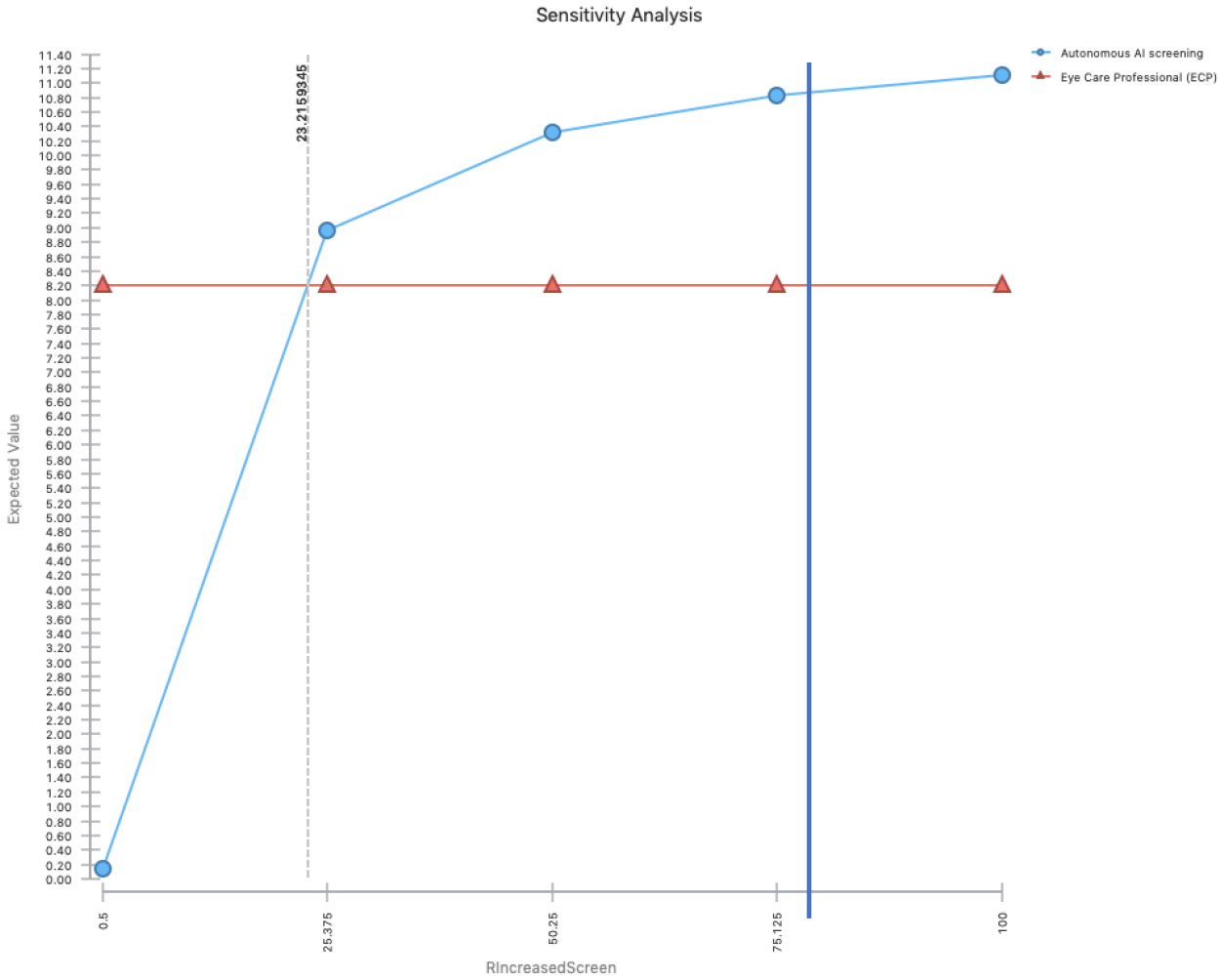


Figure 11

Still the same behavior as before. The threshold here is at a Relative odds of 26 (or probability, based on pECP of .20, of .88), a bit lower than in type 1.

Sensitivity Analysis: Type 1 DM: Out of pocket costs

Here, Expected value is expected (average) cost to the patient family, so *lower* expected vaues are *preferred.*

Tornado Diagram

Tornado Diagram

Variable	Type	Low entry	High entry	Intervals	Low value	High value
pECPScreened	Values	0.15	0.9	10	0.15	0.9
prev	Values	0.056	0.137	14	0.056	0.137
RIncreasedScreen	Values	0.5	100	4	0.5	100
sensECP	Values	0.001	0.999	10	0.001	0.999
specECP	Values	0.001	0.999	9	0.001	0.999
sensAutomated	Values	0.001	0.999	15	0.001	0.999
specAutomated	Values	0.001	0.999	14	0.001	0.999
cECPOutofPocket	Values	0	500	4	0	500
cAutonomousOutOfP...	Values	0	100	10	0	100
pAIDiagnosable	Values	0.8	0.99	4	0.8	0.99
cDRRx	Values	0	10,000	4	0	10,000

Figure 12

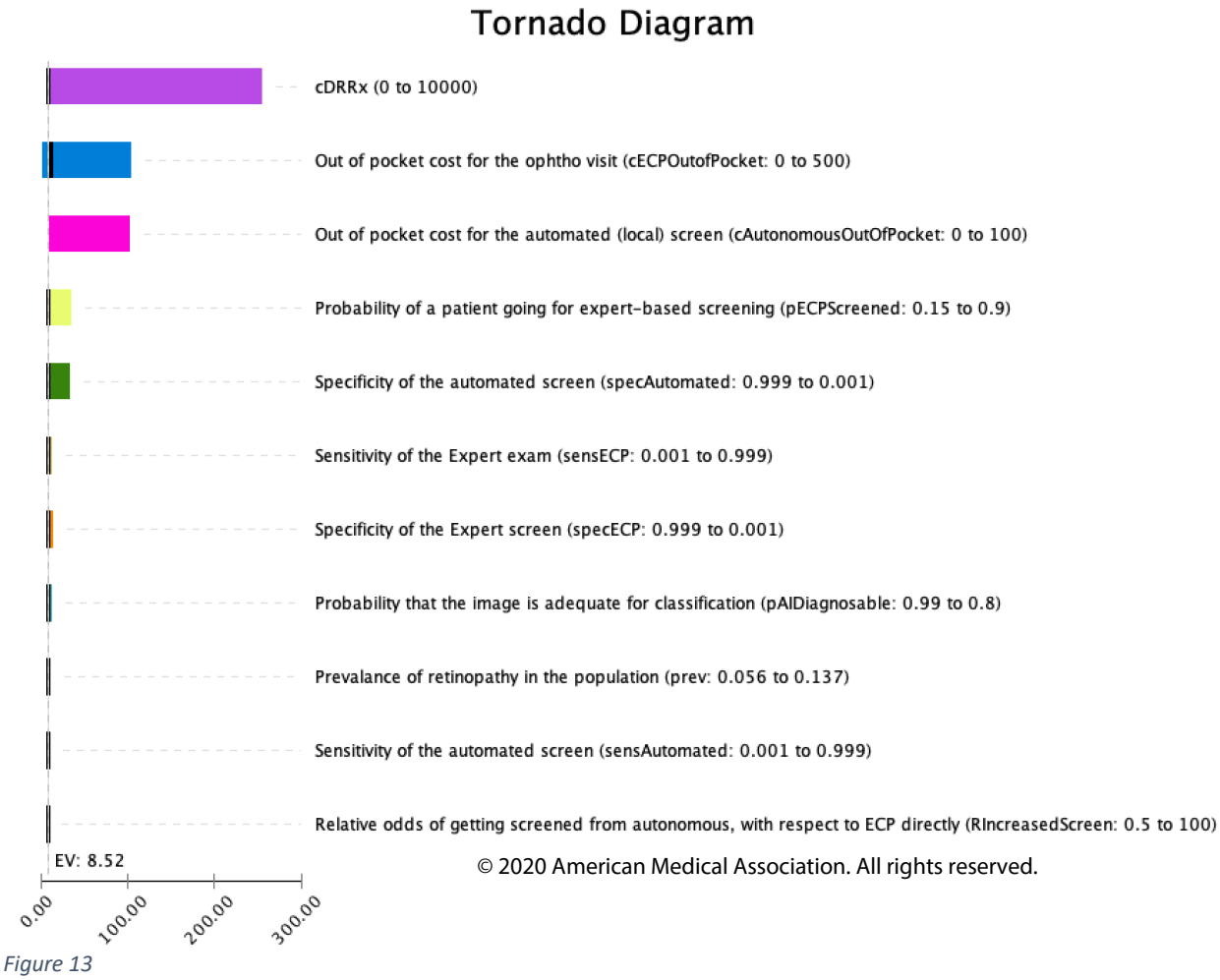


Figure 13

Sensitivity Analyses: Type 1 DM/Out of pocket Costs Autonomous out of pocket cost

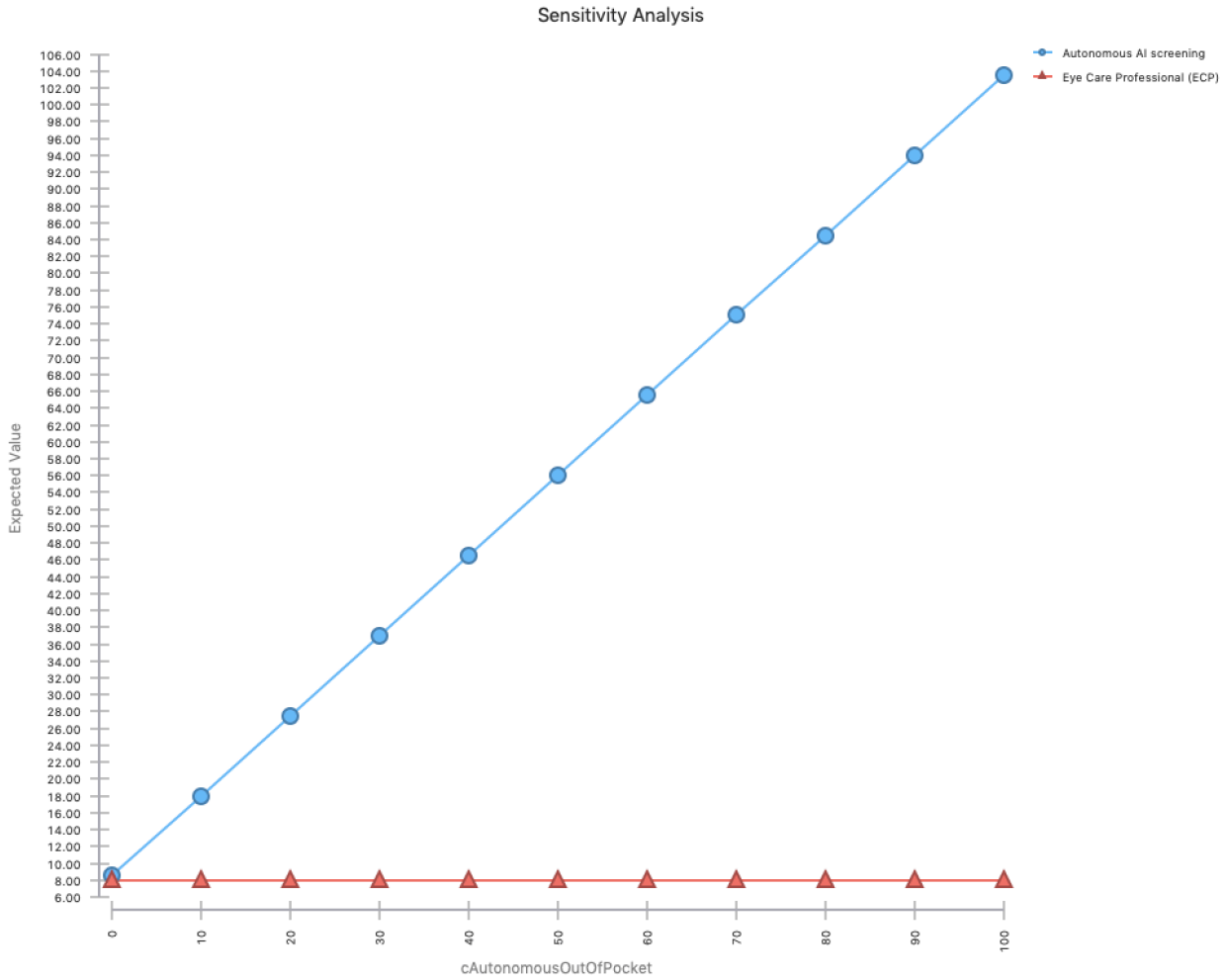
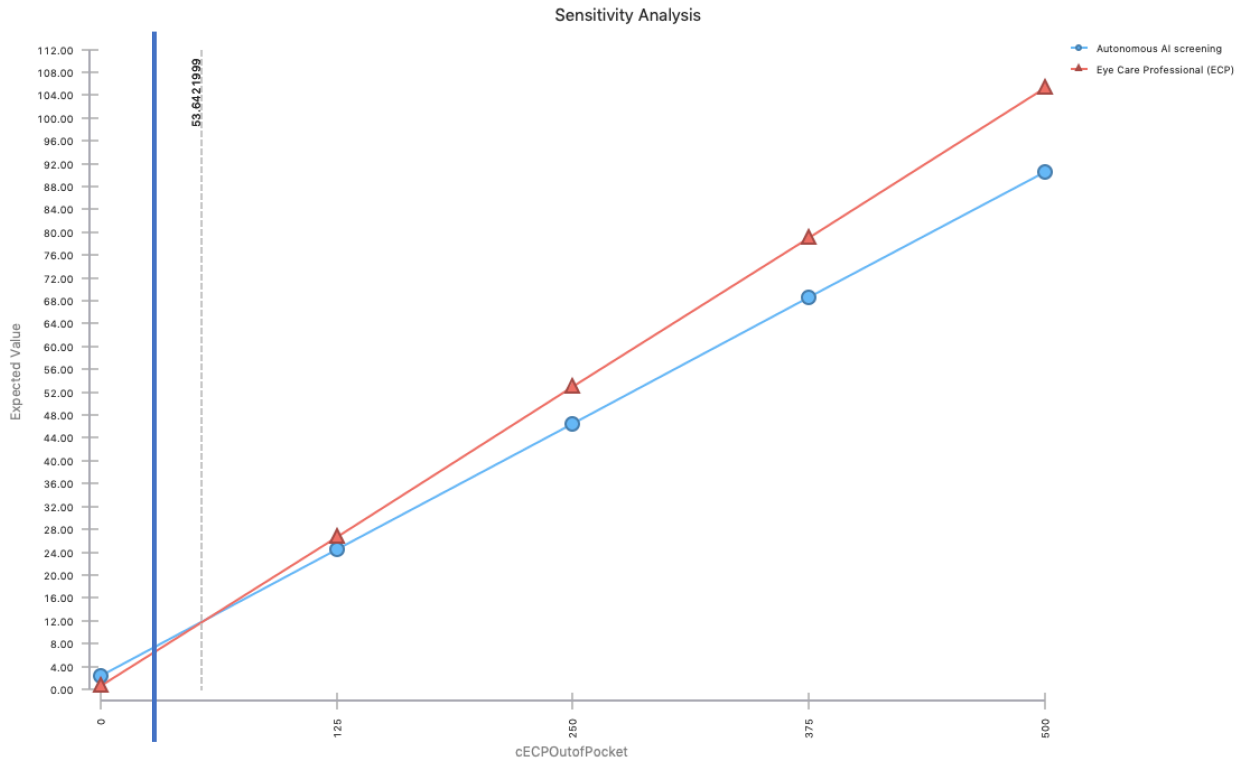


Figure 14

ECP strategy is unaffected by cAutonomous, and remains cheaper.

ECP visit out of pocket cost



Above an ECP-out-of-pocket cost of $53, Autonomous becomes cheaper, probably because of better sensitivity. See the corresponding 2-way sensitivity analysis, below.

DR Treatment out of pocket cost

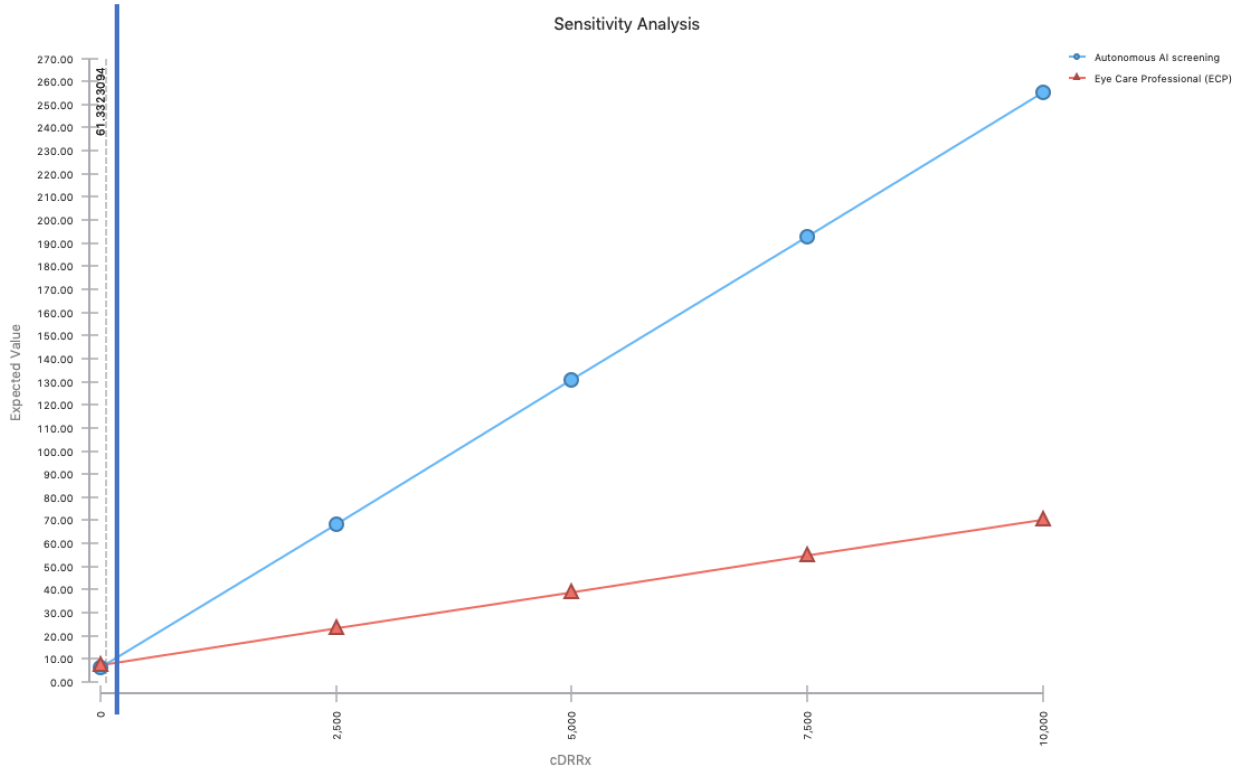


Figure 15

If the out-of-pocket cost to the patient of DR Rx is under $61 (below the base-case rate of $94), then Autonomous ends up being cheaper to the patient, on average. Even at an out-of-pocket cost of $10,000, the *average* cost to the patient is only $260. (However, patients are risk averse to paying $10,000 for treatment.)

DR prevalence in Type 1 DM

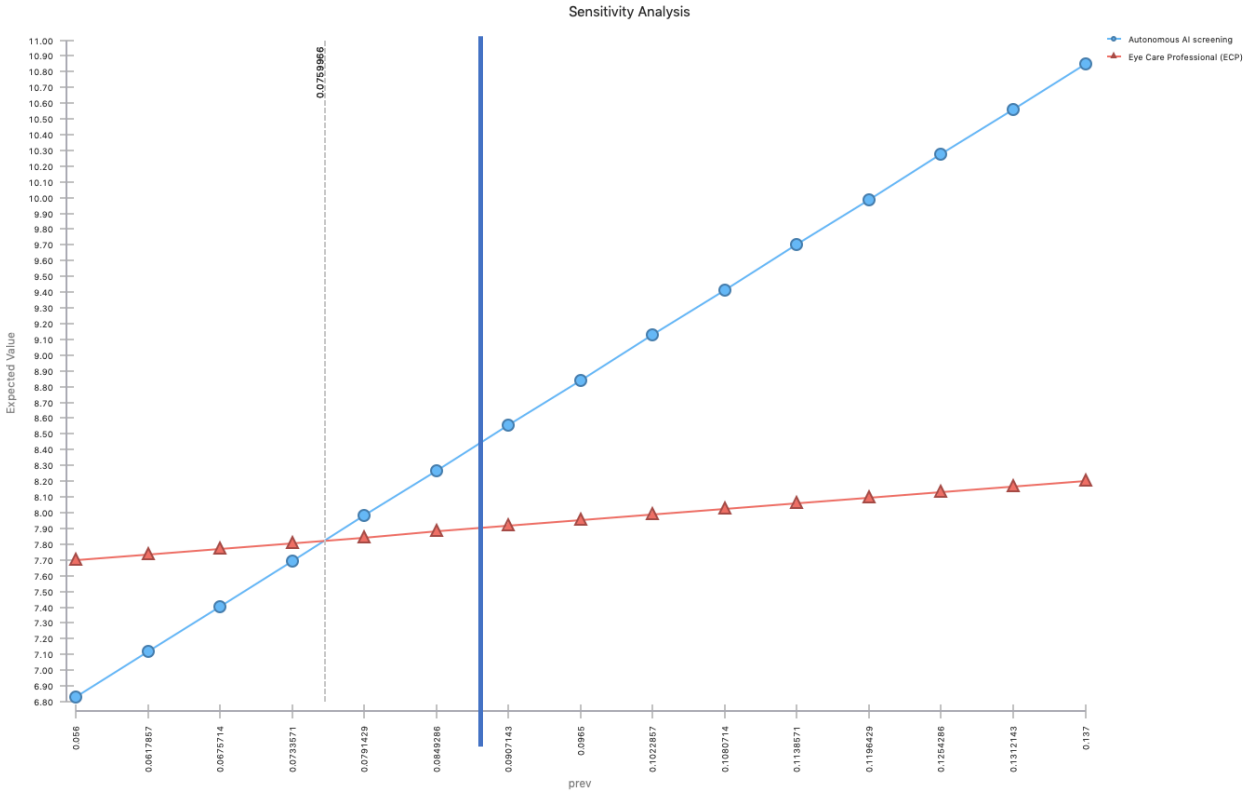


Figure 16

If the prevalence of DR in children with Type 1 DM were below .076, Autonomous is cheaper on average. The base case value is .09, significantly higher. If DR prevalence can be driven lower, Autonomous is preferred.

Sensitivity Autonomous

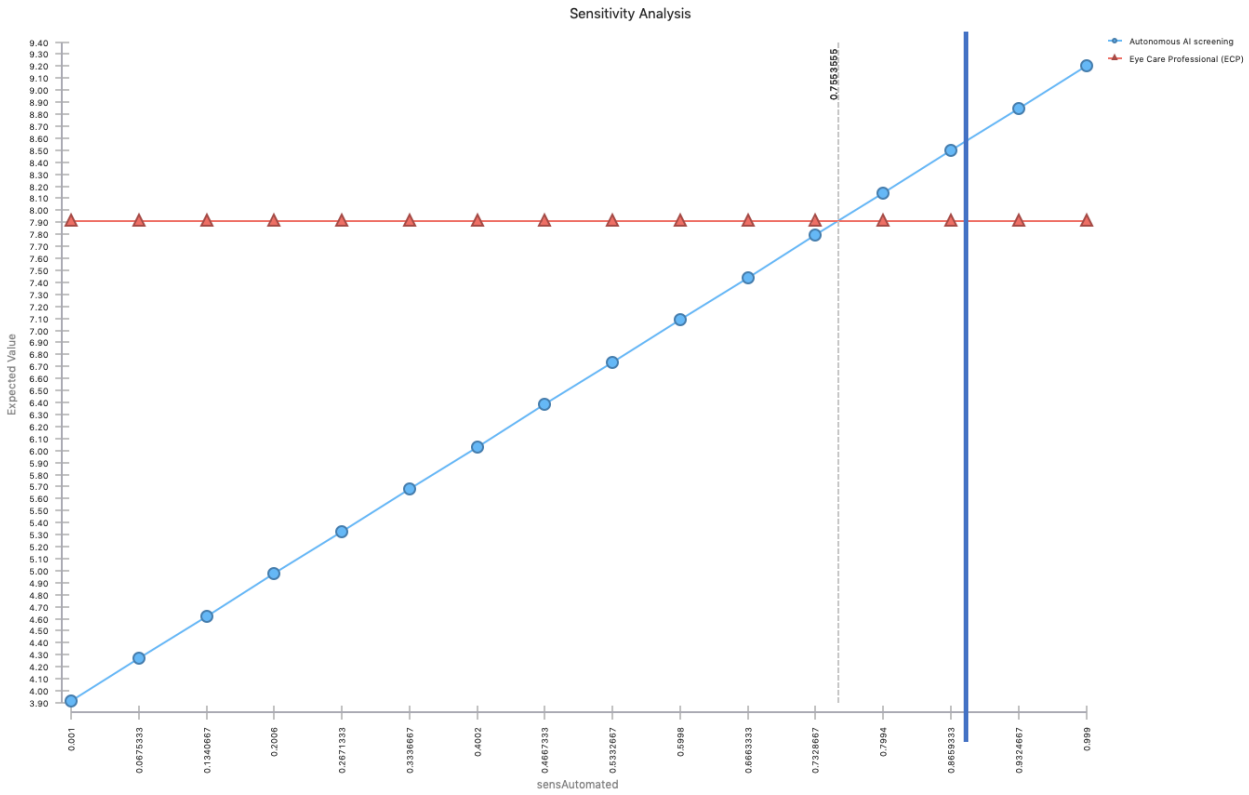


Figure 17

If the sensitivity of Autonomous were below .76 (rather than the base case value of .87), ECP would be cheaper on average, presumably because the low ECP referral rate leads to a comparable detection rate; see 2-way analysis (cECP vs sensAut). The 1-way analysis confirms thae thought behind the conclusion re cECP.

Specificity Autonomous

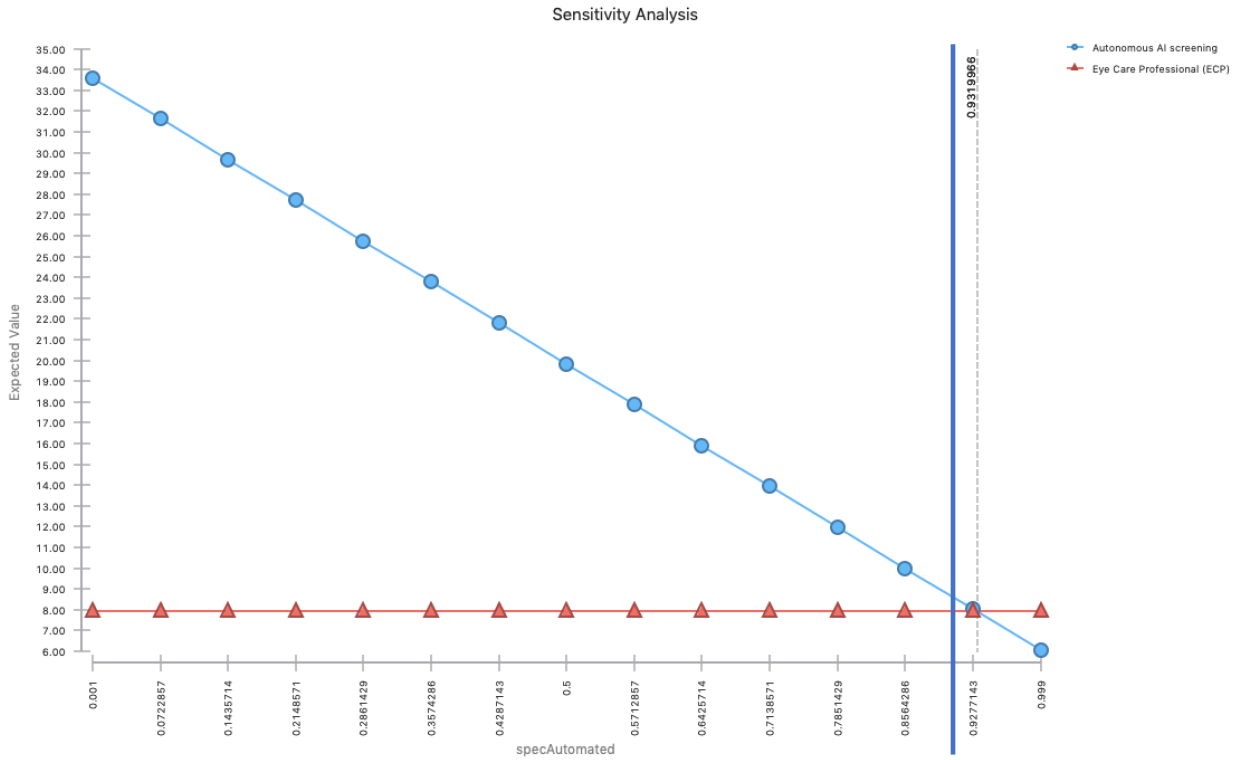


Figure 18

If the specificity of Autonoous were higher than .93 (base case is .91), Autonomous would have a lower average out-of-pocket cost (presumably because of the lower false-positive rate and lower referrals to ECP). If Aut specificity were a little higher, it would be cheaper on average.

Sensitivity of ECP

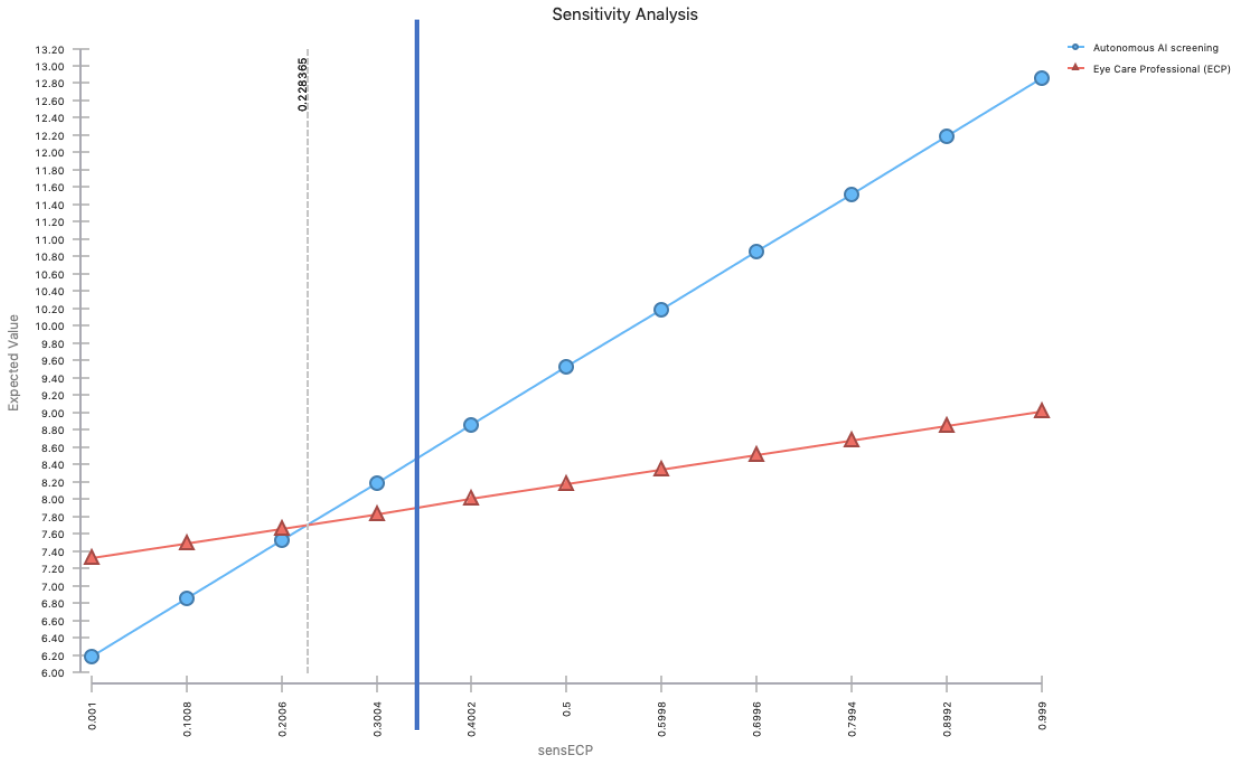


Figure 19

The threshold (going to the left) that would make Autonomous cheaper on average than ECP is an ECP sensitivity of .23, below the current .35. ECP loses its cost advantage if its sensitivity drops below .23

Specificity ECP

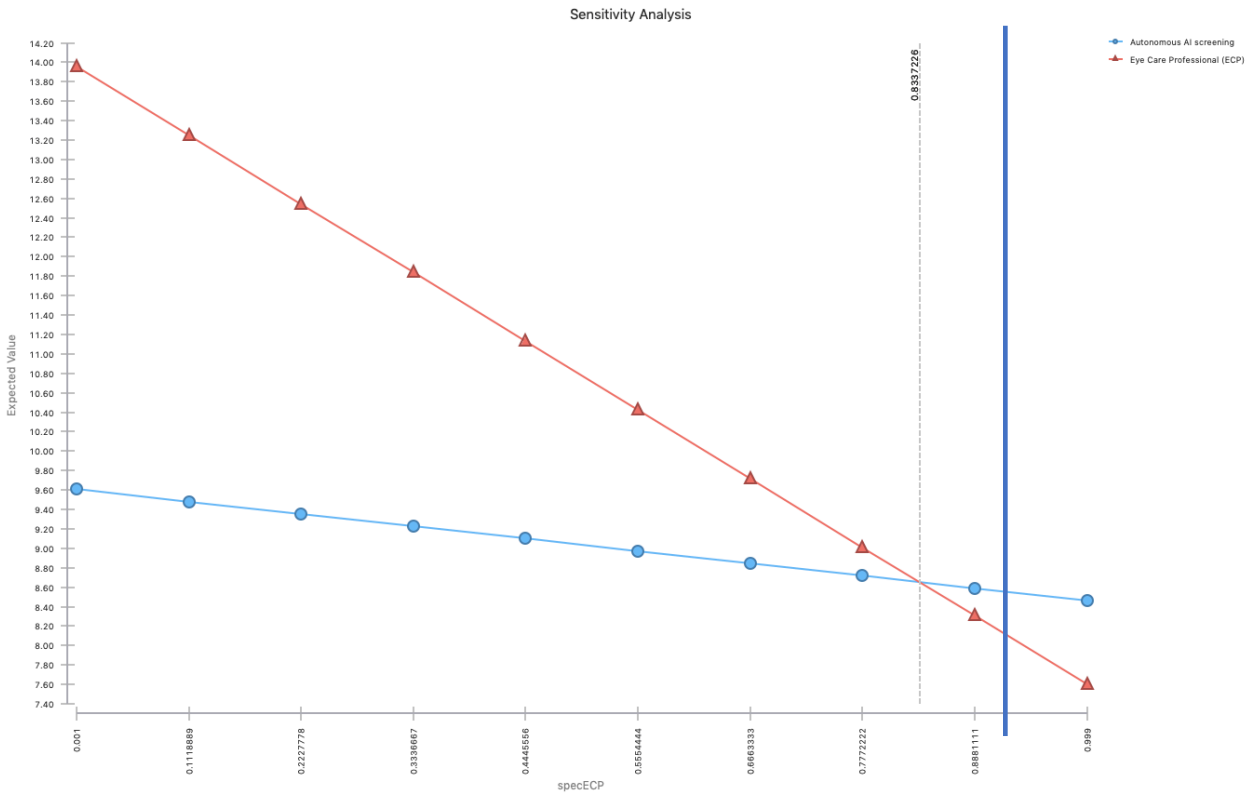


Figure 20

The base-case specificity of .95 is already above the threshold value of .83, where ECP becomes cheaper than Autonomous, on average.

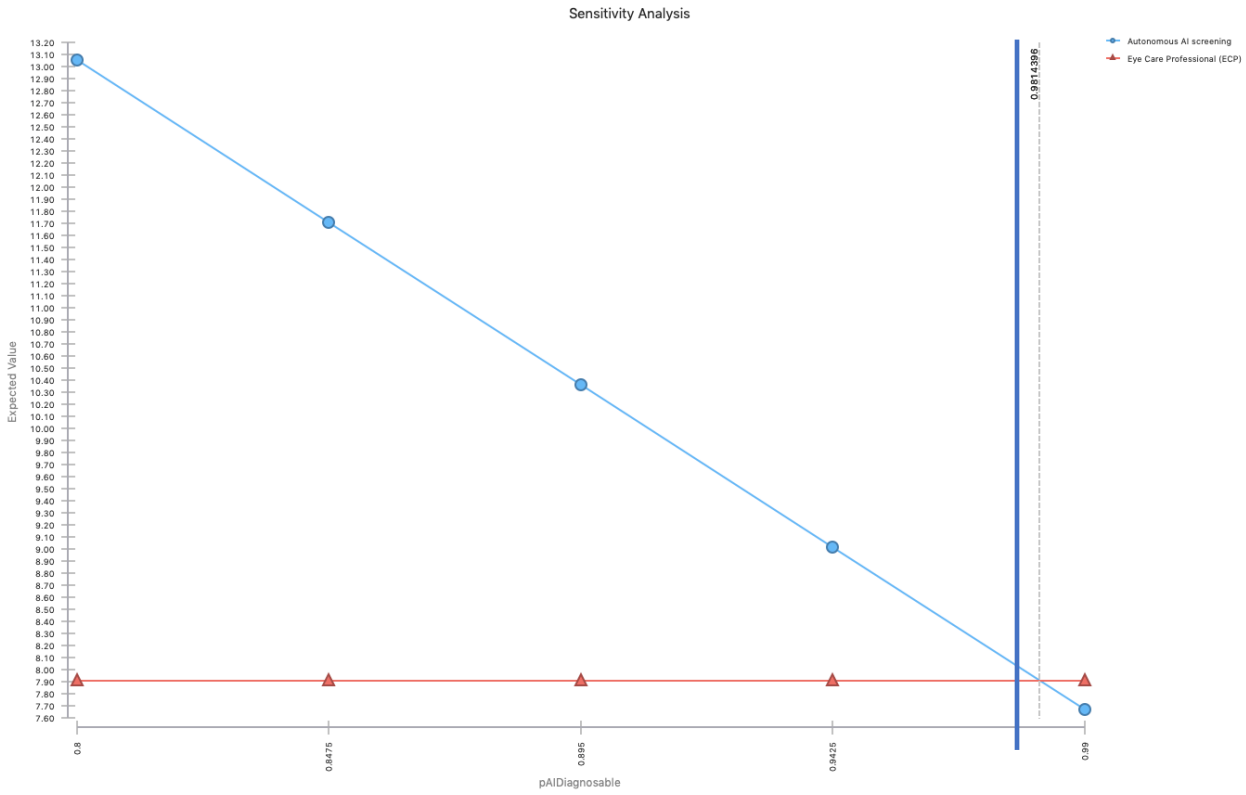


Figure 21

The base case value of .96 is just below the threshold value of .98, where Autonomous becomes cheaper, on average. If diagnosability is improved a bit more, Aut becomes cheaper on average.

Probability of keeping ECP Appoinement

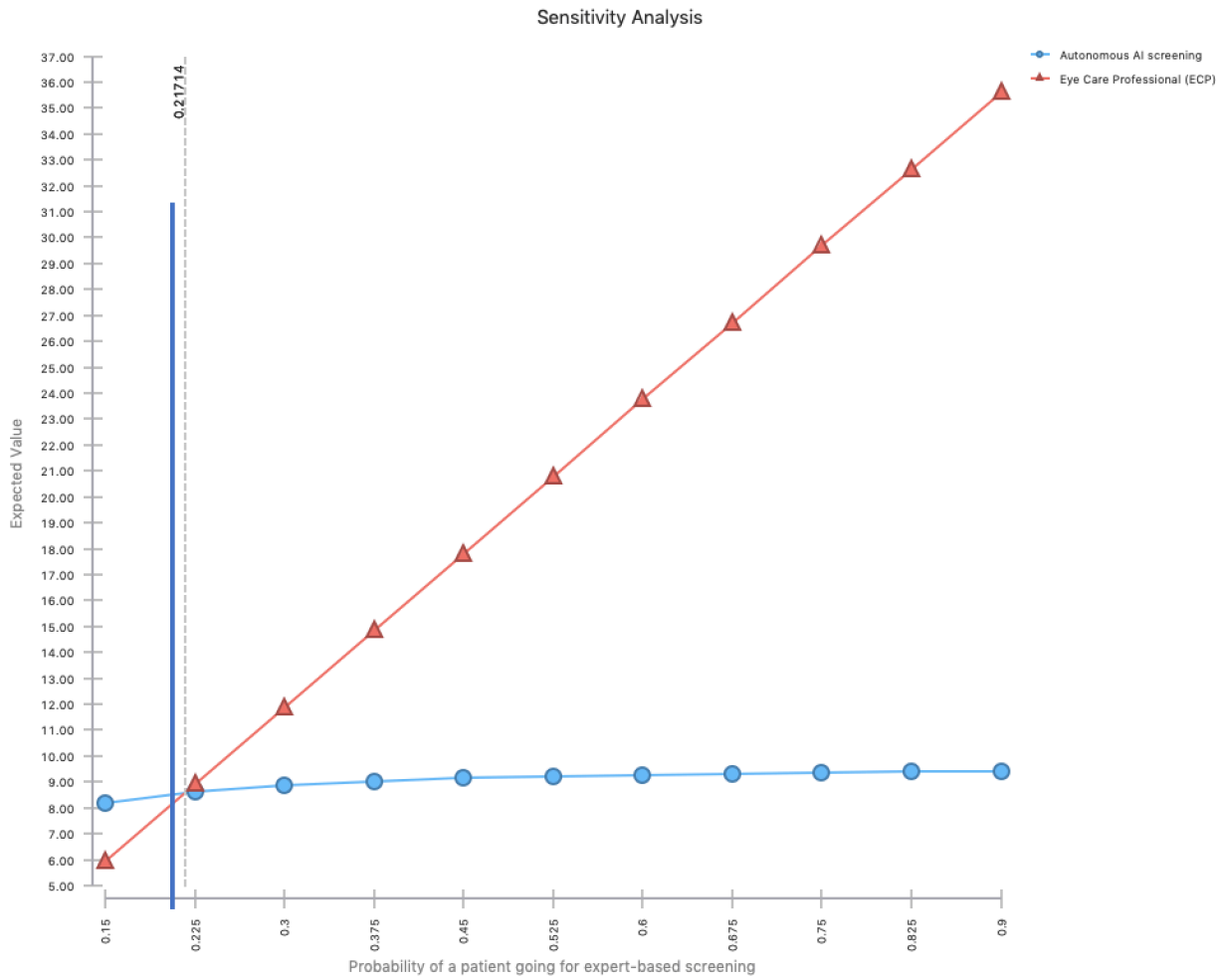


Figure 22

Autonomous becomes cheaper on average if pECPscreened improves from .20 to .22, as more patients go to ECP and incur that cost. Base value is just at threshold, above which Autonomous is preferred.

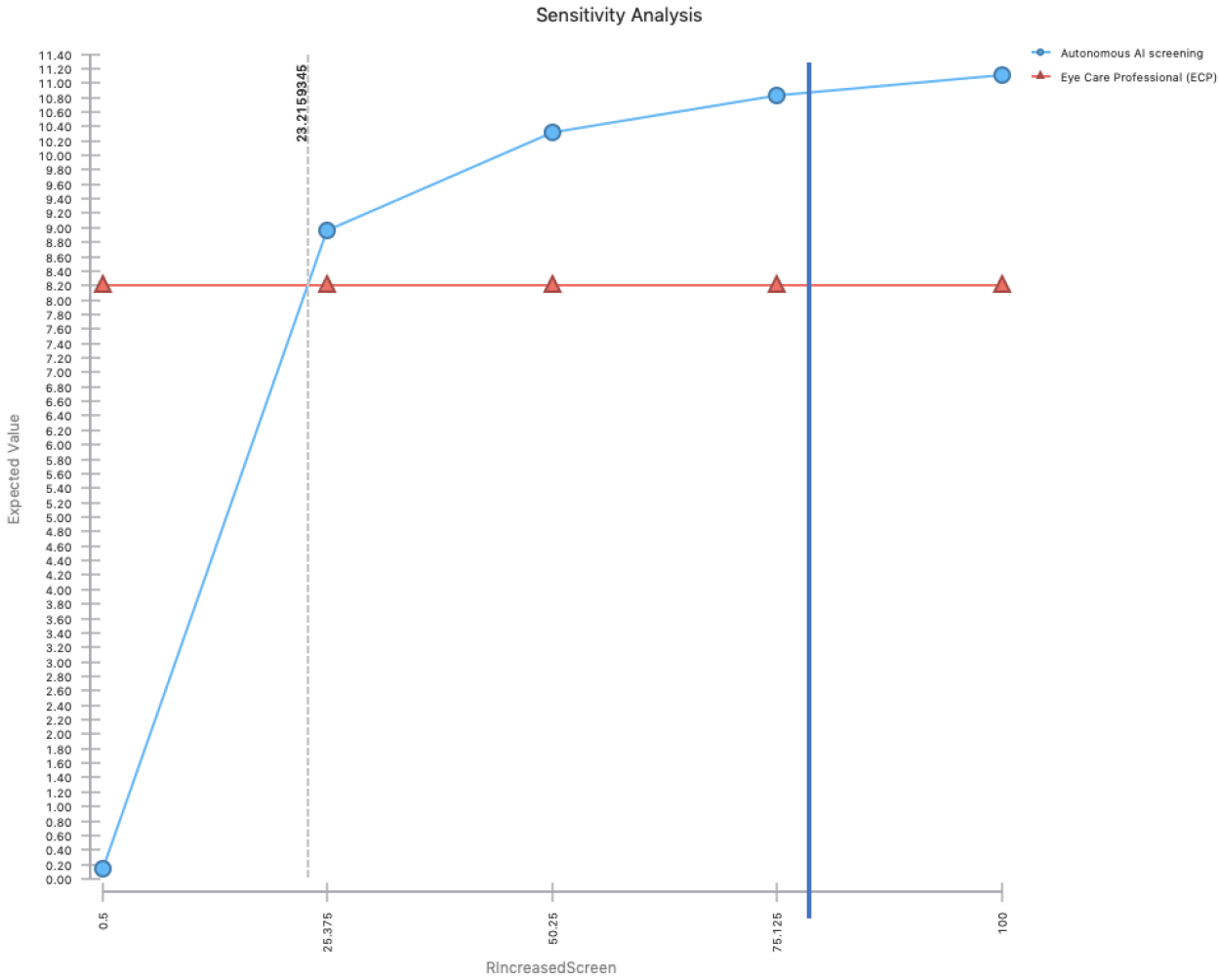


Figure 23

Still the same behavior as before. The threshold here is at a Relative odds of 26 (or probability, based on pECP of .20, of .88), a bit lower than in type 1.

2-way analysis: cECP and sensAutonomous

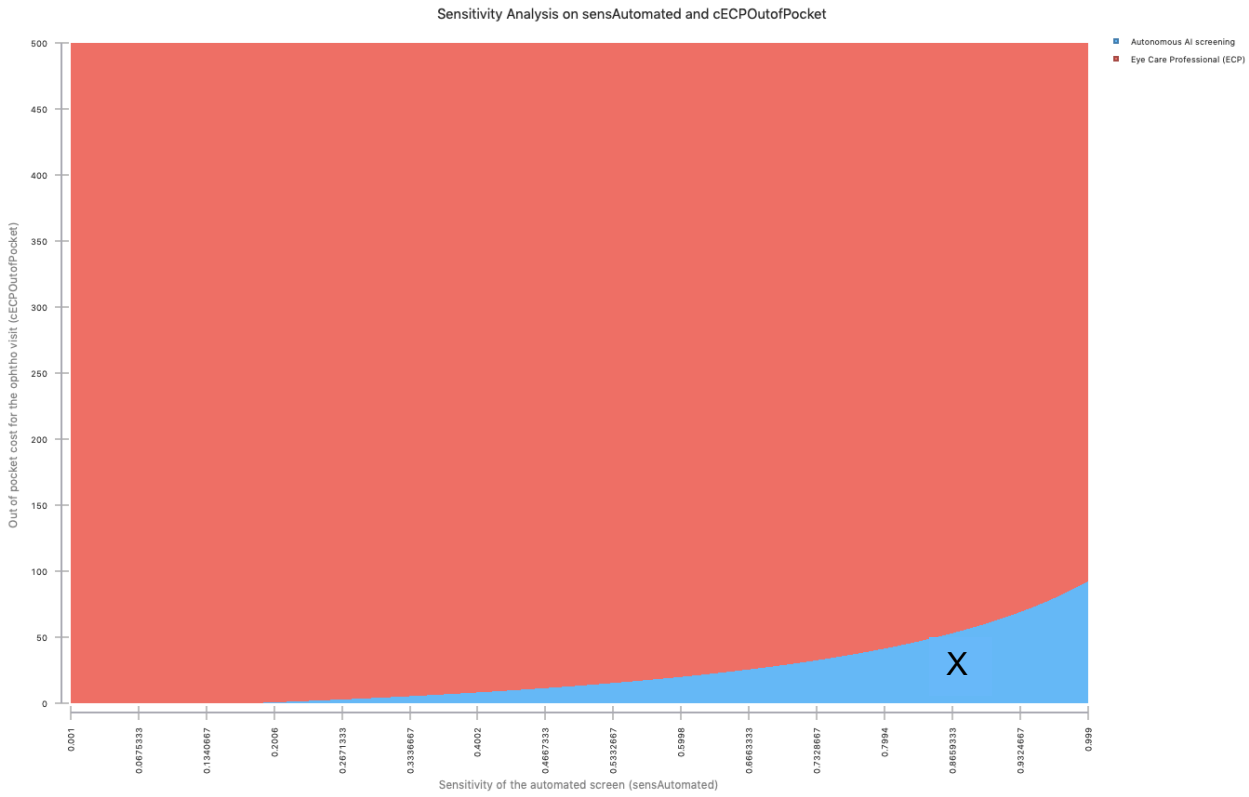


Figure 24

This analysis confirms the thought re cECP, above, that if Autonomous had lower sensitivity, ECP becomes cheaper, on average. "X" represents base case.

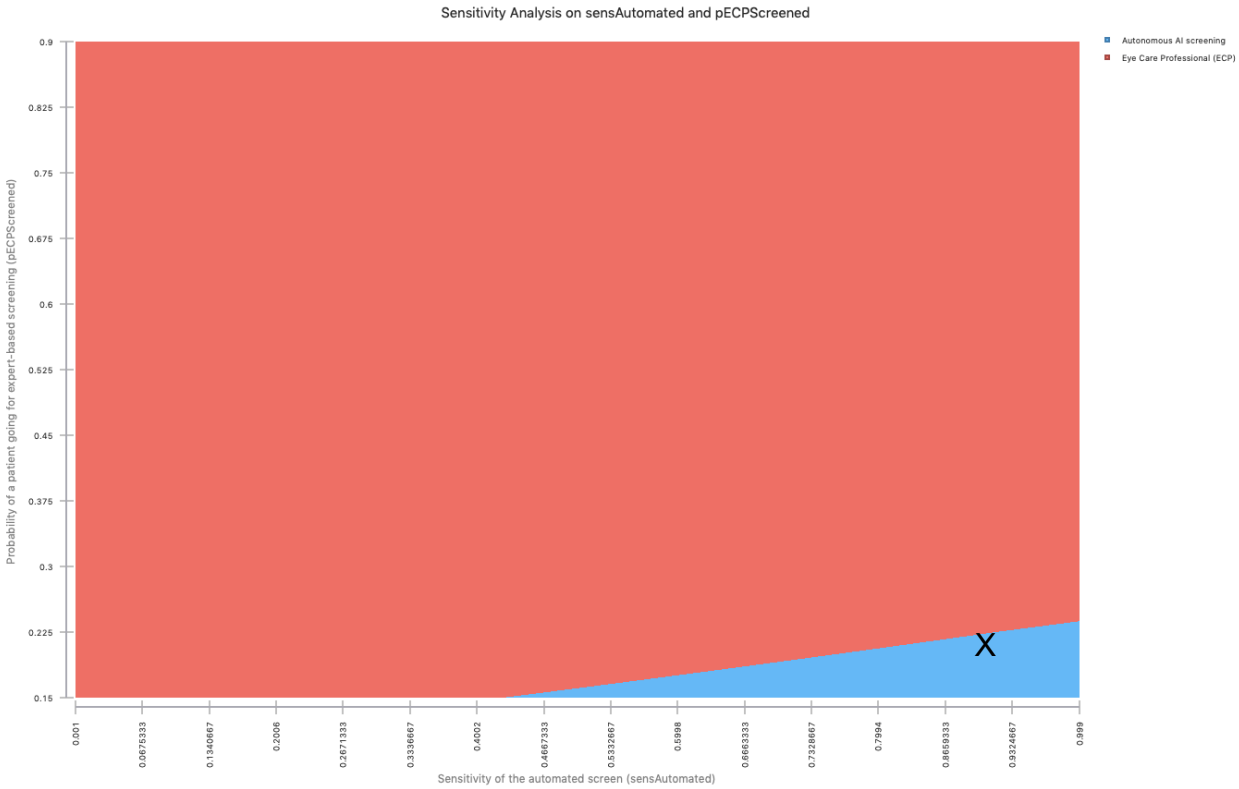


Figure 25

As suggested above, as the sensitivity of Aut goes down, ECP becomes cheaper on average, especially if cECP goes down as well.

2-way analysis: cECP and spec Aut

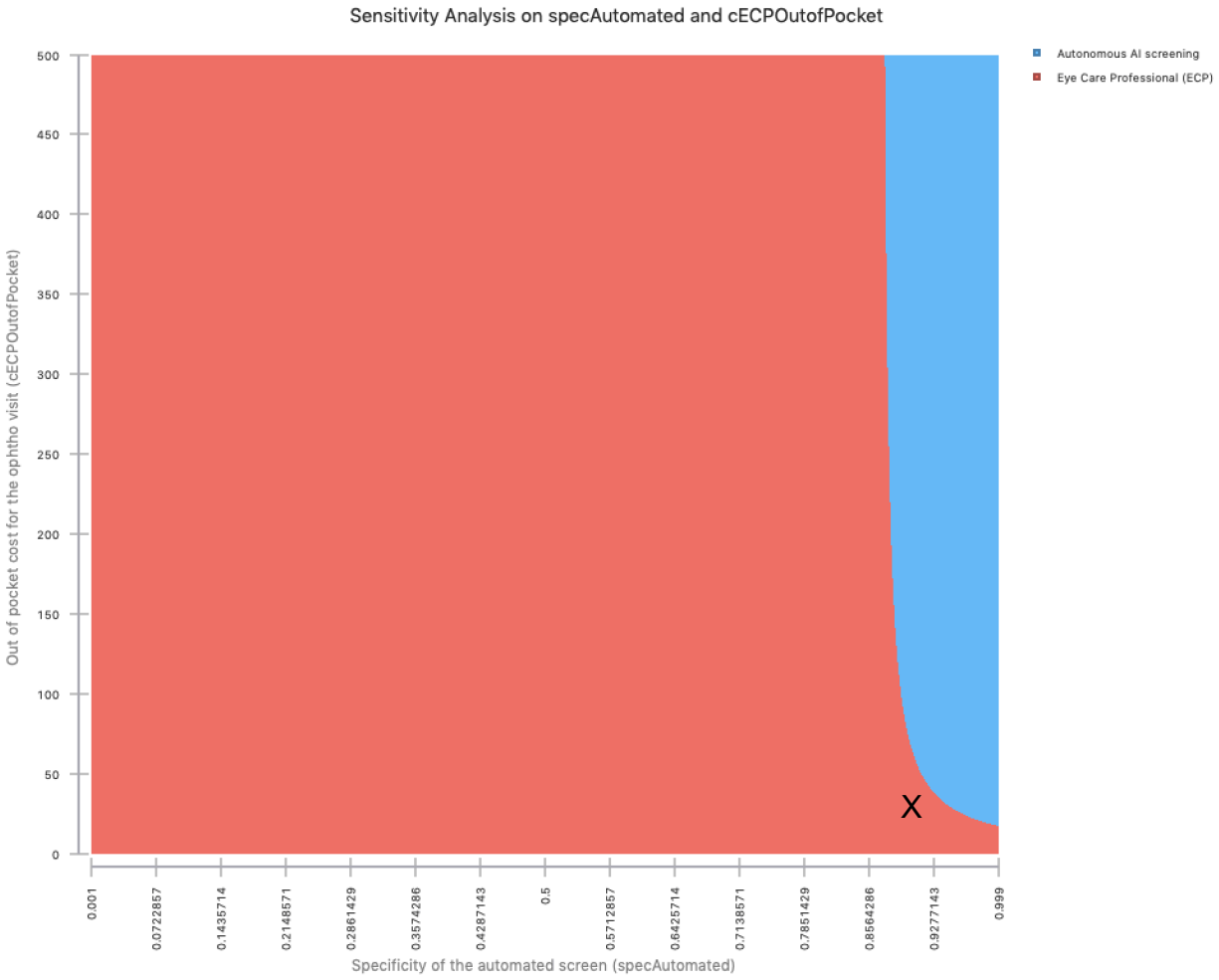


Figure 26

As the specificity of Aut goes up, the threshold on cECP goes down. But if spec Aut is less than .90 or so, ECP remains cheaper on average.

2-way analysis: DR prevalence vs pECPScreened

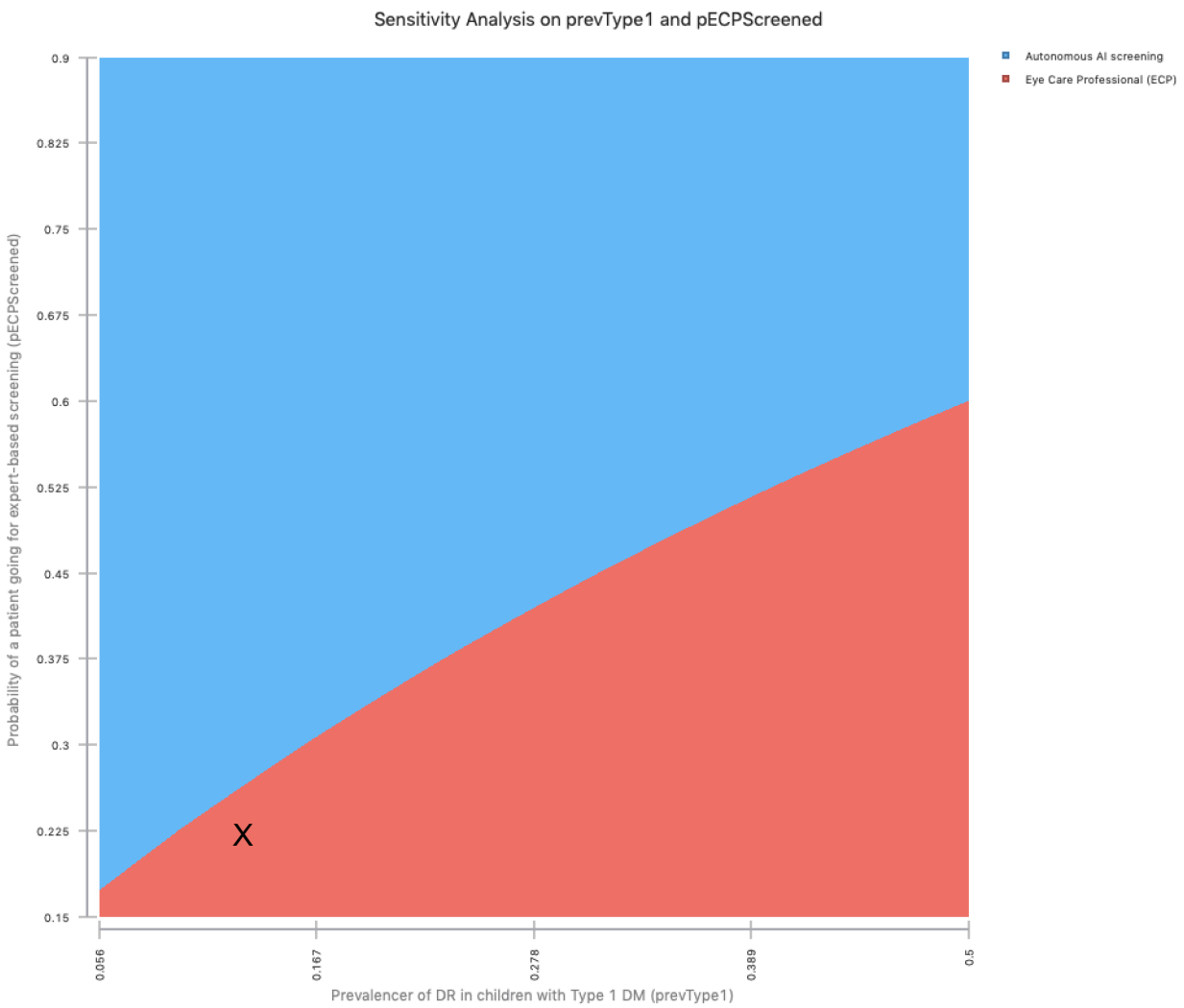


Figure 27

This sensitivity analysis confirms that, as the prevalence of DR goes up, the threshold for families keeping their ECP appointment at which Autonomous becomes cheaper on average also goes up.

2-way analysis: DR Prevalence vs cost of ECP

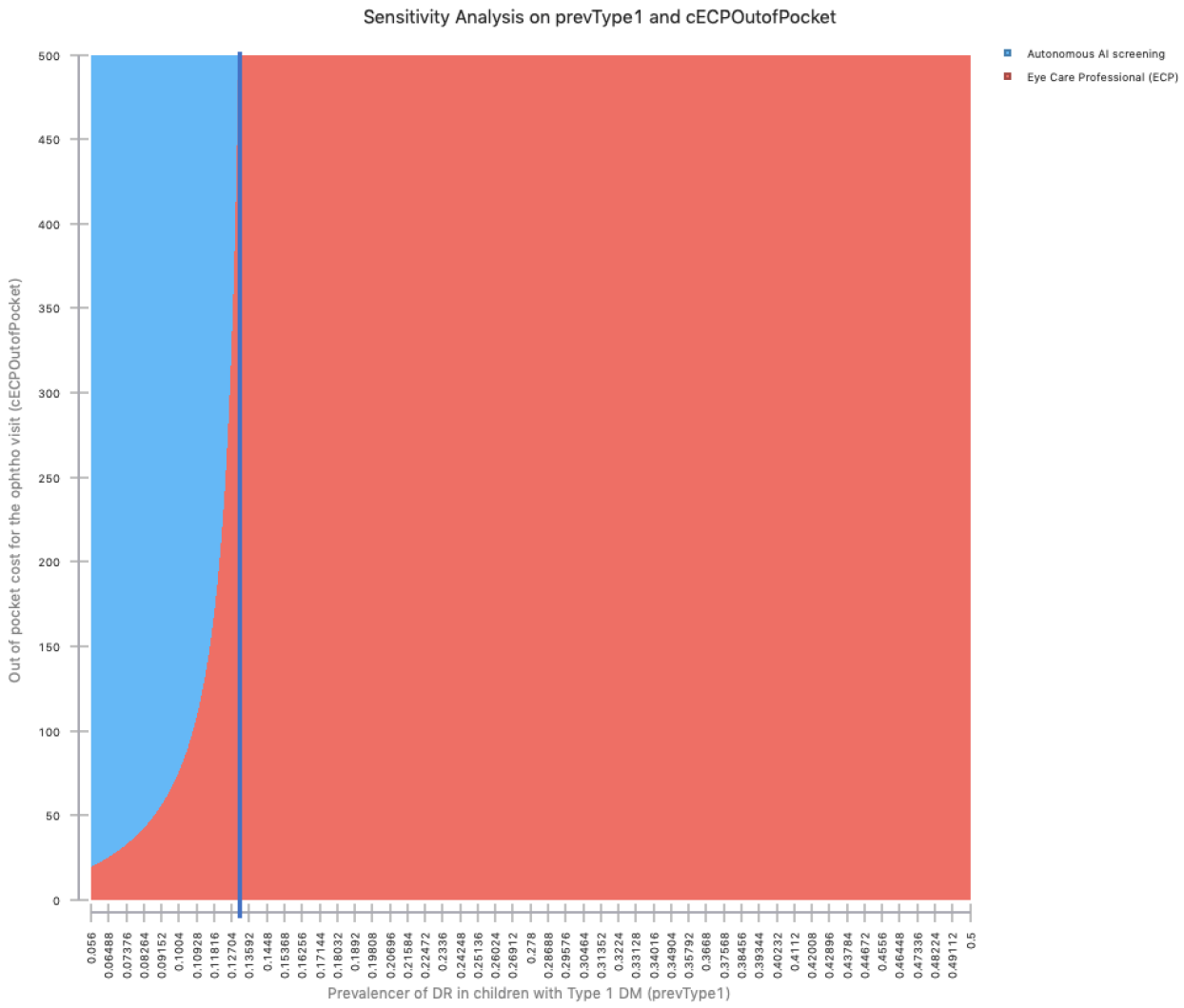


Figure 28

As the prevalence of DR prevalence rises, the threshold for cECP at which Autonomous becomes cheaper on average goes up as well, until a prevalence of about .13, at which point ECP remains cheaper on average for all cECPs.

Cost-Effectiveness

Type 1	Auto	ECP		Difference	Ratio
Cost	$8.52	$7.91	Δ Cost	$0.61	$31
TP	.026	.006	Δ Effectiveness	0.020	

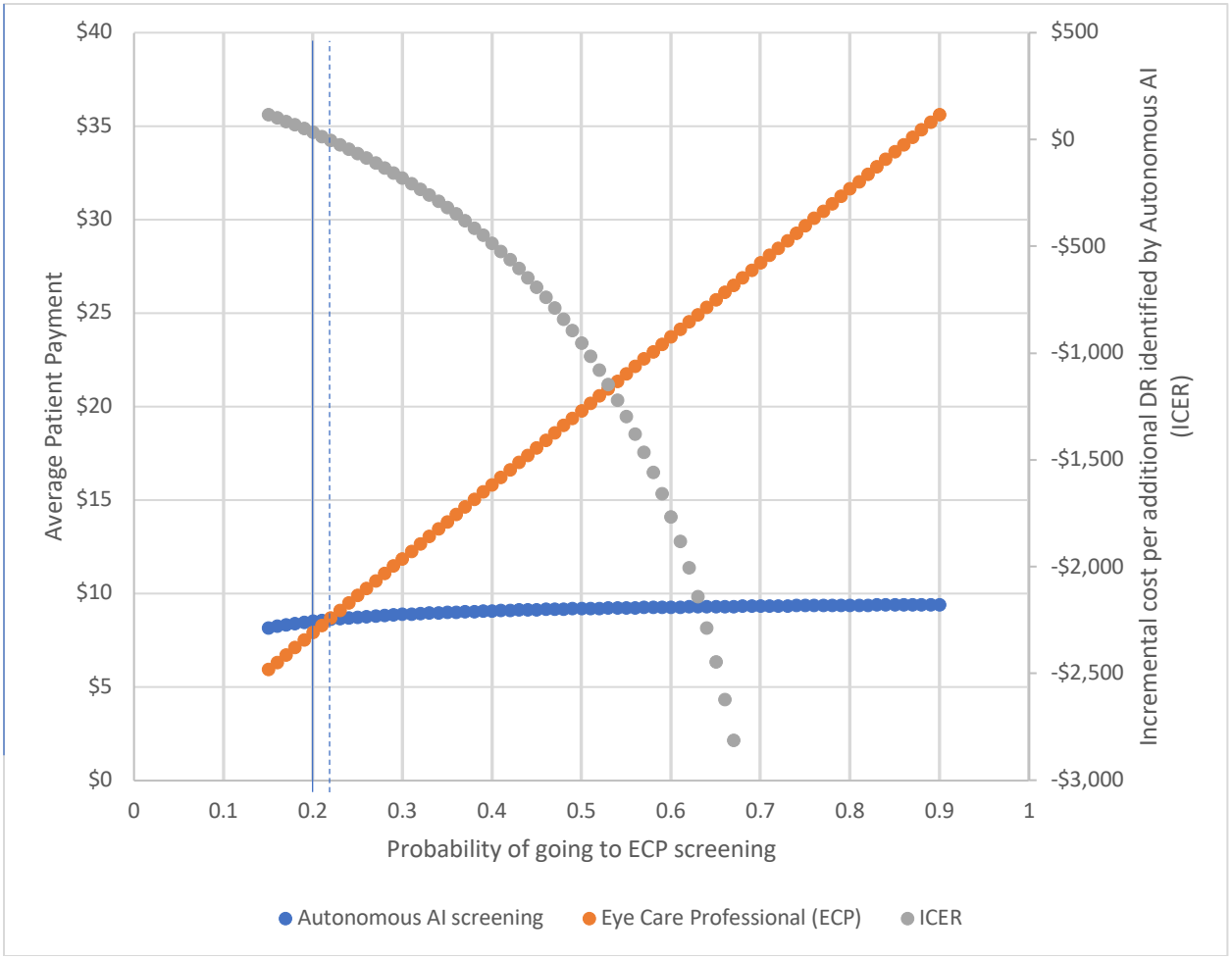


Figure 29

Vertical blue line at Probability of going to ECP screening of .20 represents the base-case value; the dashed vertical line at a probability of .225 represents the threshold.

ICER wrt DR prevalence

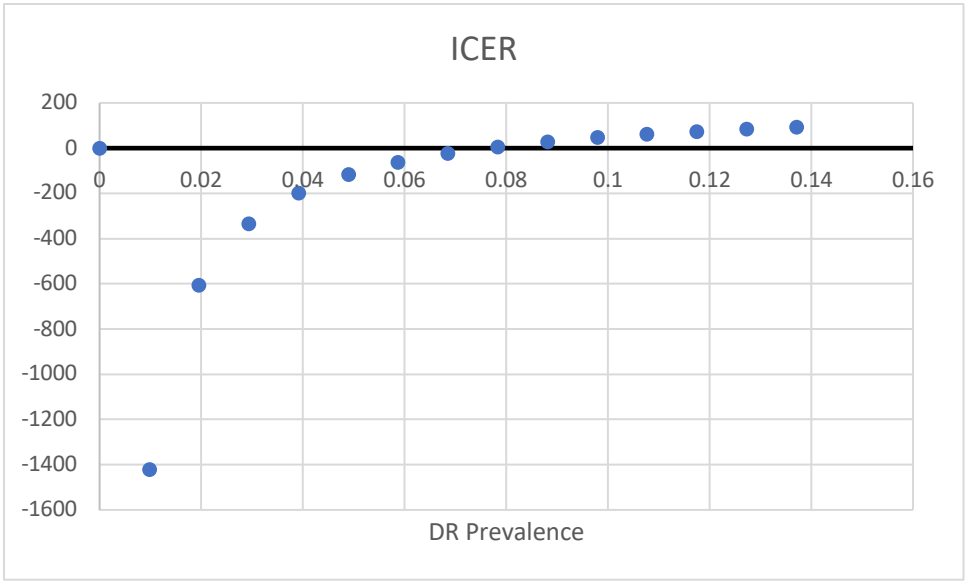


Figure 30

Autonomous becomes more incrementally more expensive on average at a prevalence of about .07, and rises from there.

Type 2 DM

Base Case Type 2 DM

PedsRetinaScreening.JAMAO.15June2020.Type2.png

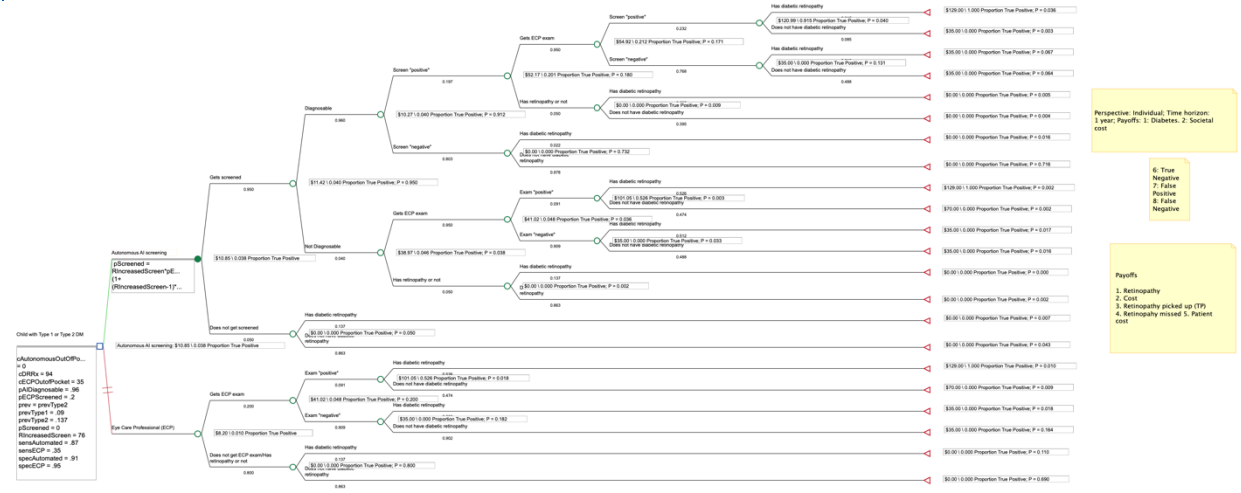
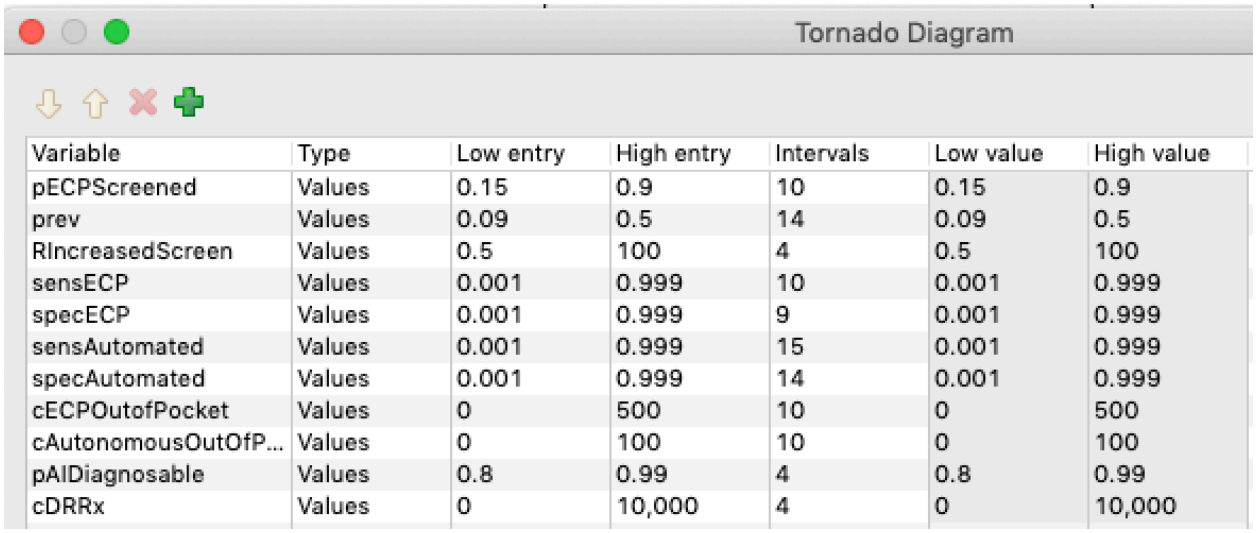


Figure 31

(Results summarized in Table 1)

Tornado Diagram: Type 2 DM: True Positives



Variable	Type	Low entry	High entry	Intervals	Low value	High value
pECPScreened	Values	0.15	0.9	10	0.15	0.9
prev	Values	0.09	0.5	14	0.09	0.5
RIncreasedScreen	Values	0.5	100	4	0.5	100
sensECP	Values	0.001	0.999	10	0.001	0.999
specECP	Values	0.001	0.999	9	0.001	0.999
sensAutomated	Values	0.001	0.999	15	0.001	0.999
specAutomated	Values	0.001	0.999	14	0.001	0.999
cECPOutofPocket	Values	0	500	10	0	500
cAutonomousOutOfP...	Values	0	100	10	0	100
pAIDiagnosable	Values	0.8	0.99	4	0.8	0.99
cDRRx	Values	0	10,000	4	0	10,000

Figure 32

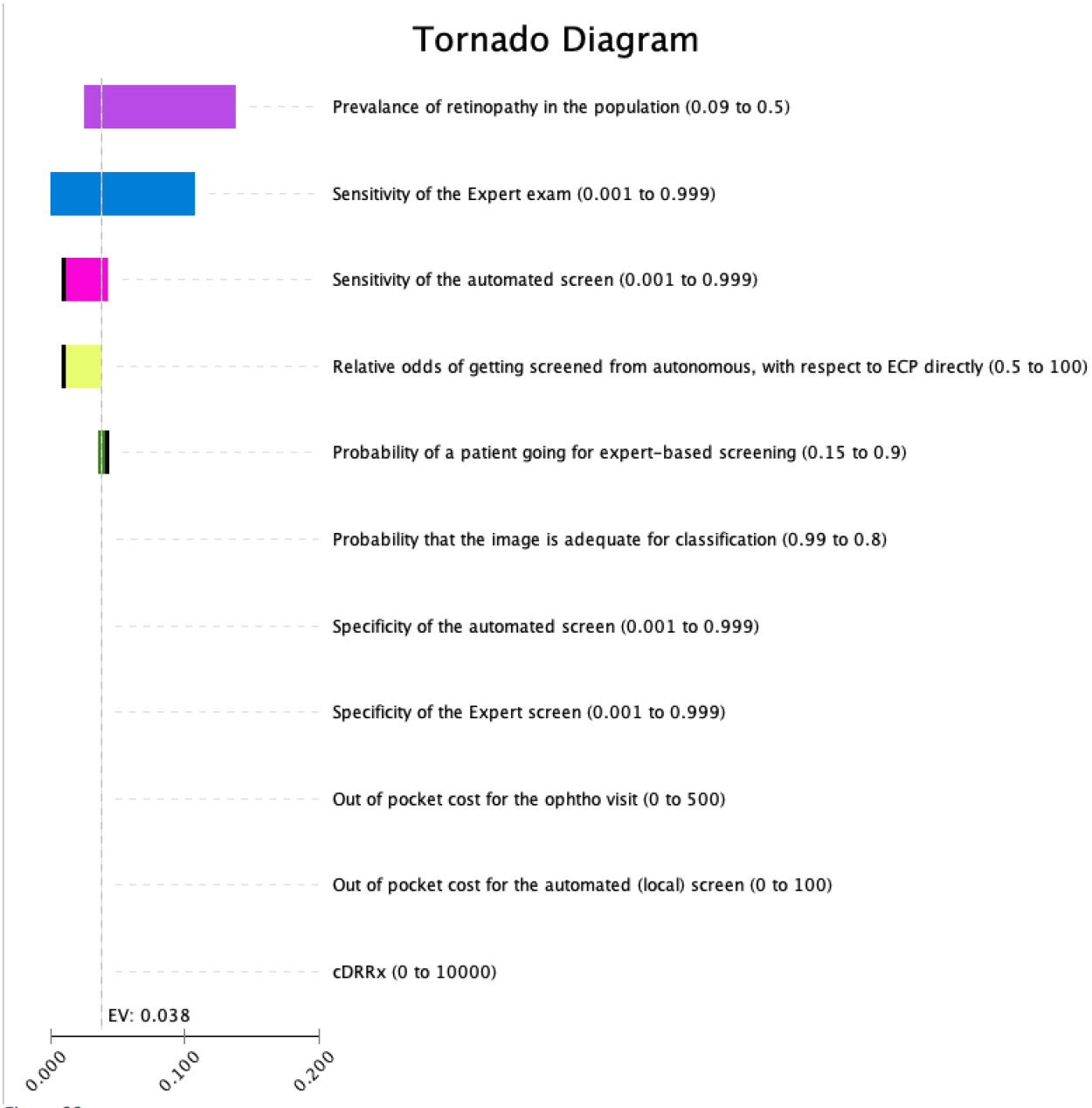


Figure 33

Sensitivity Analyses: Type 2 DM: True Positives DR Prevalence

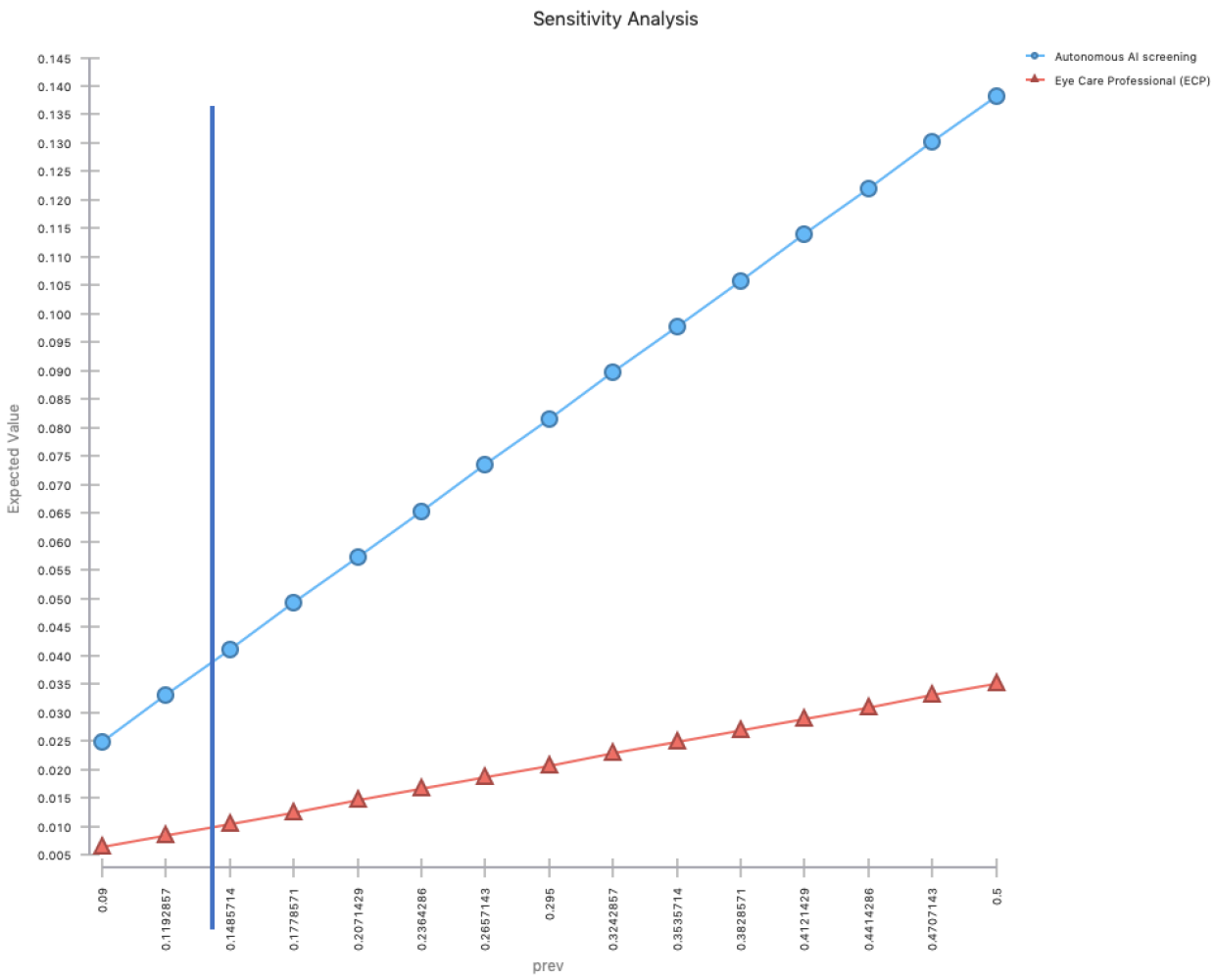


Figure 34

As in type 1, there is no threshold: the high sensitivity of Autonomous yields higher TPs than ECP.

Sens Autonomous

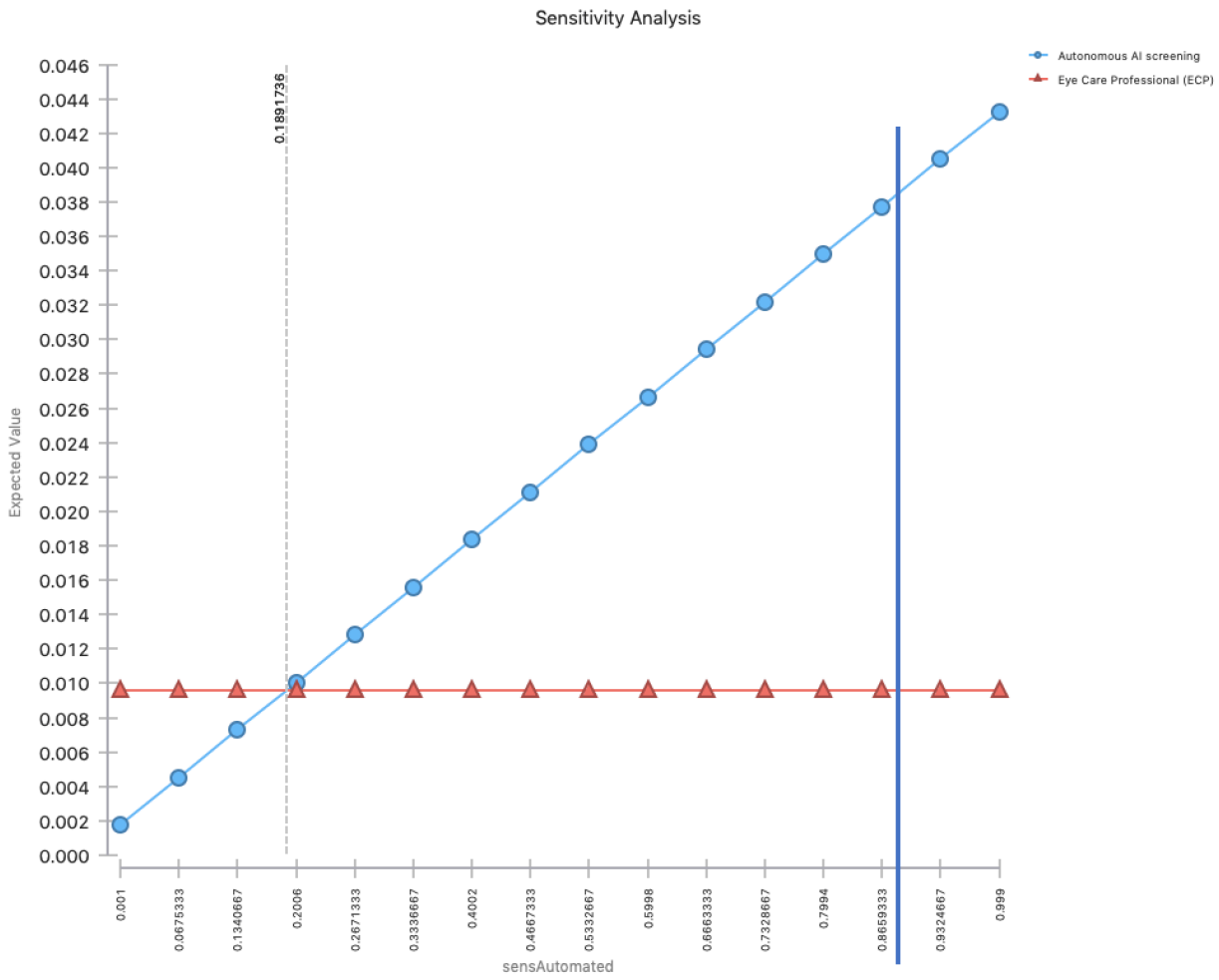


Figure 35

As in Type 1 DM, the threshold sensitivity (here, of .19) is much lower than the base case (.87), so doubt about the Autonomous system's sensitivity does not change the conclusion of Autonomous's higher TP detection.

Probability of going to ECP

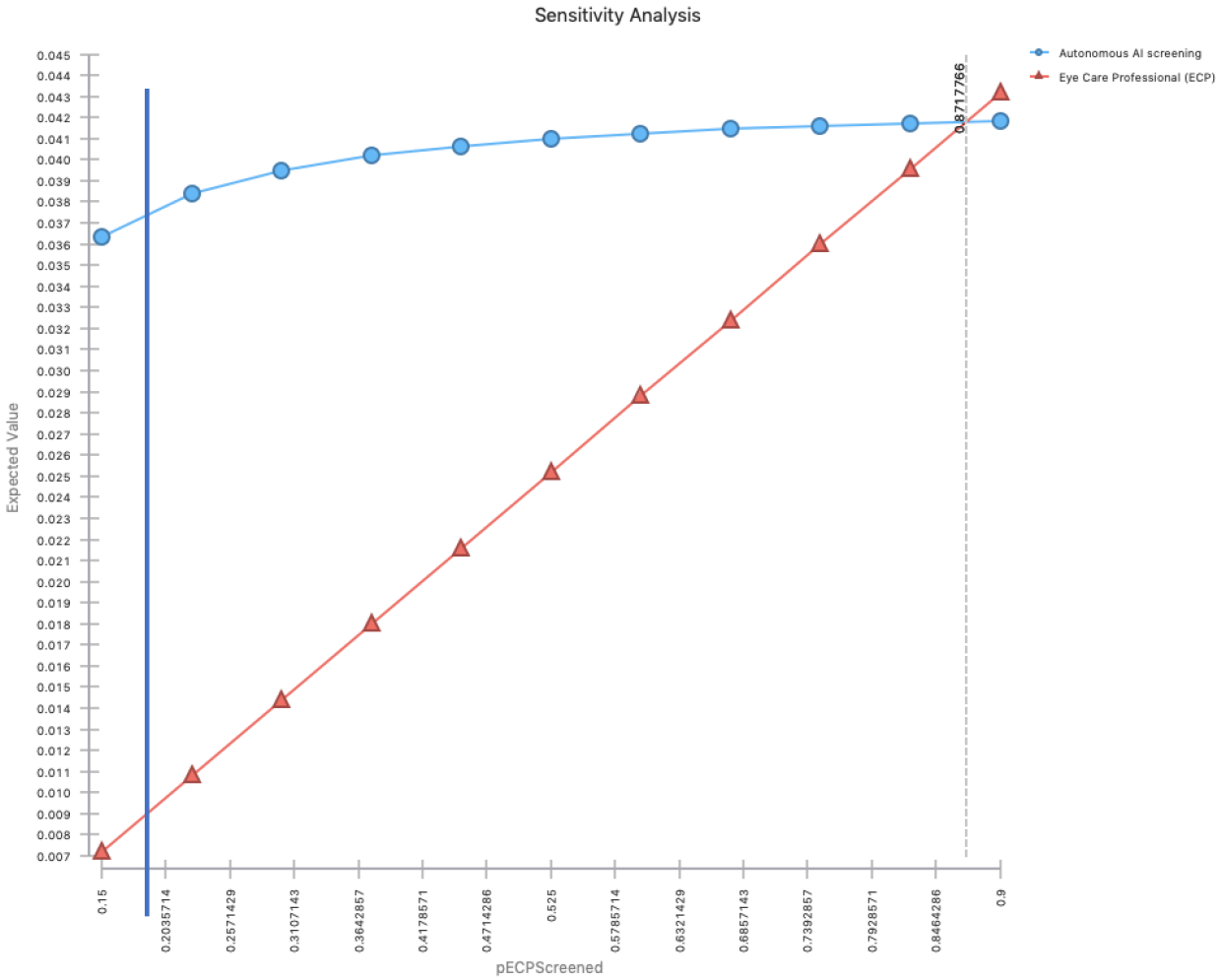


Figure 36

The threshold, where ECP detects more TPs than Autonomous, does not happen until a threshold of .87, much higher than the base rate of .20.

Relative Odds of Keeping ECP Appointment

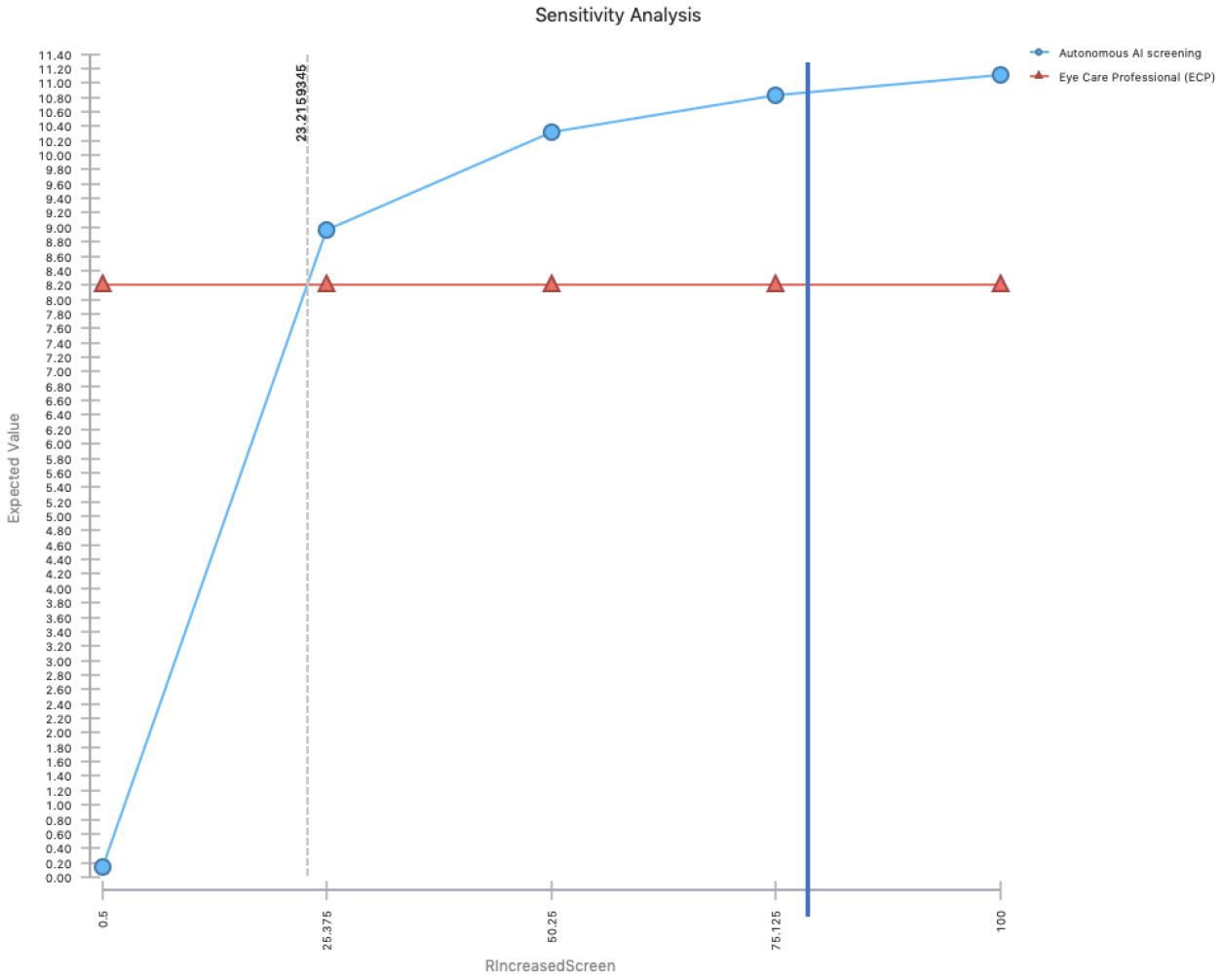


Figure 37

Still the same behavior as before. The threshold here is at a Relative odds of 26 (or probability, based on pECP of .20, of .88), a bit lower than in type 1.

Tornado Diagram: Type 2 DM: Out of Pocket Cost

Tornado Diagram

Variable	Type	Low entry	High entry	Intervals	Low value	High value
pECPScreened	Values	0.15	0.9	10	0.15	0.9
prev	Values	0.09	0.5	14	0.09	0.5
RIncreasedScreen	Values	0.5	100	4	0.5	100
sensECP	Values	0.001	0.999	10	0.001	0.999
specECP	Values	0.001	0.999	9	0.001	0.999
sensAutomated	Values	0.001	0.999	15	0.001	0.999
specAutomated	Values	0.001	0.999	14	0.001	0.999
cECPOutofPocket	Values	0	500	10	0	500
cAutonomousOutOfP...	Values	0	100	10	0	100
pAIDiagnosable	Values	0.8	0.99	4	0.8	0.99
cDRRx	Values	0	10,000	4	0	10,000

Figure 38

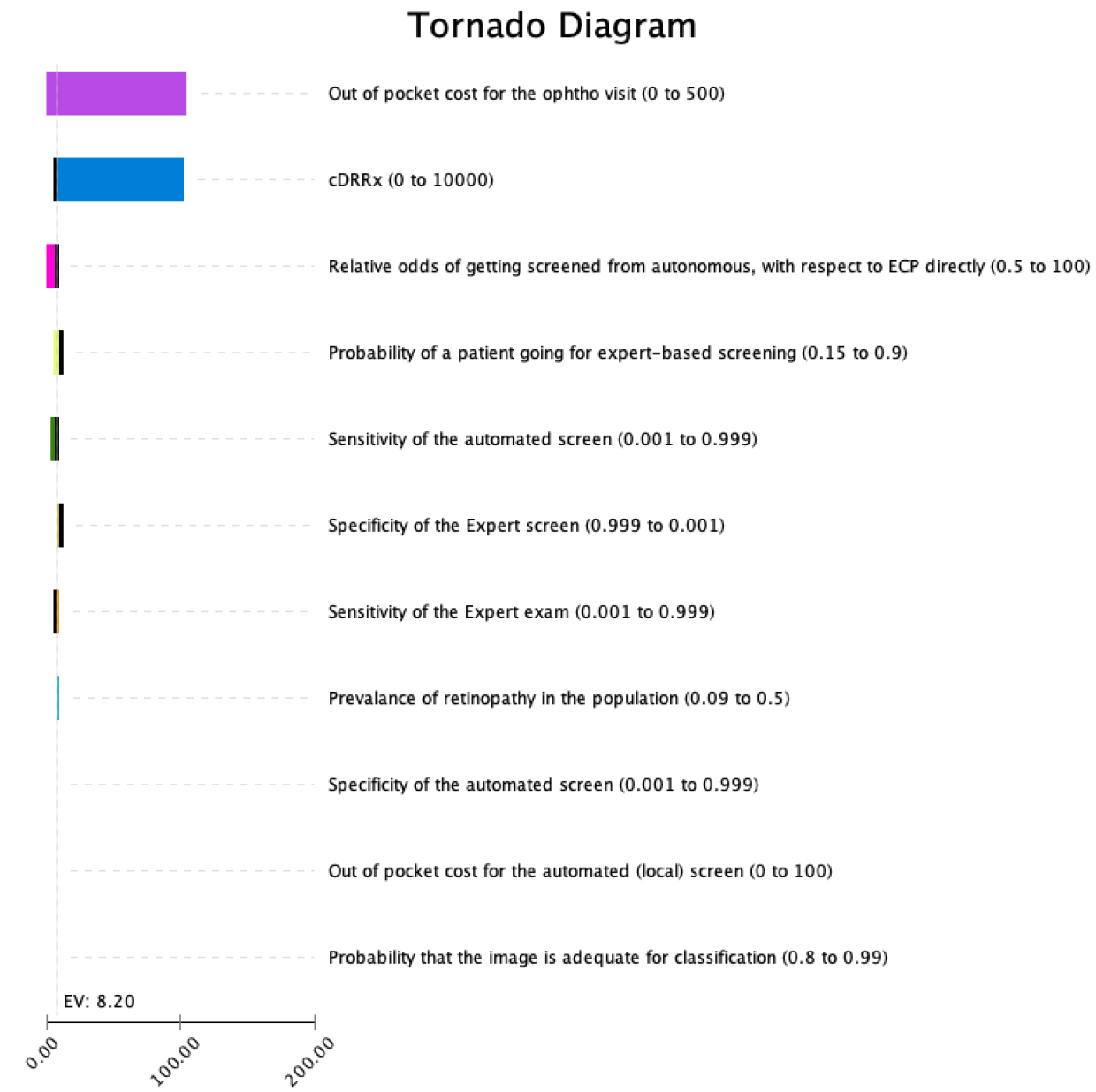


Figure 39

Sensitivity Analysis Type 2 DM: Out of Pocket Costs

Autonomous out of pocket cost

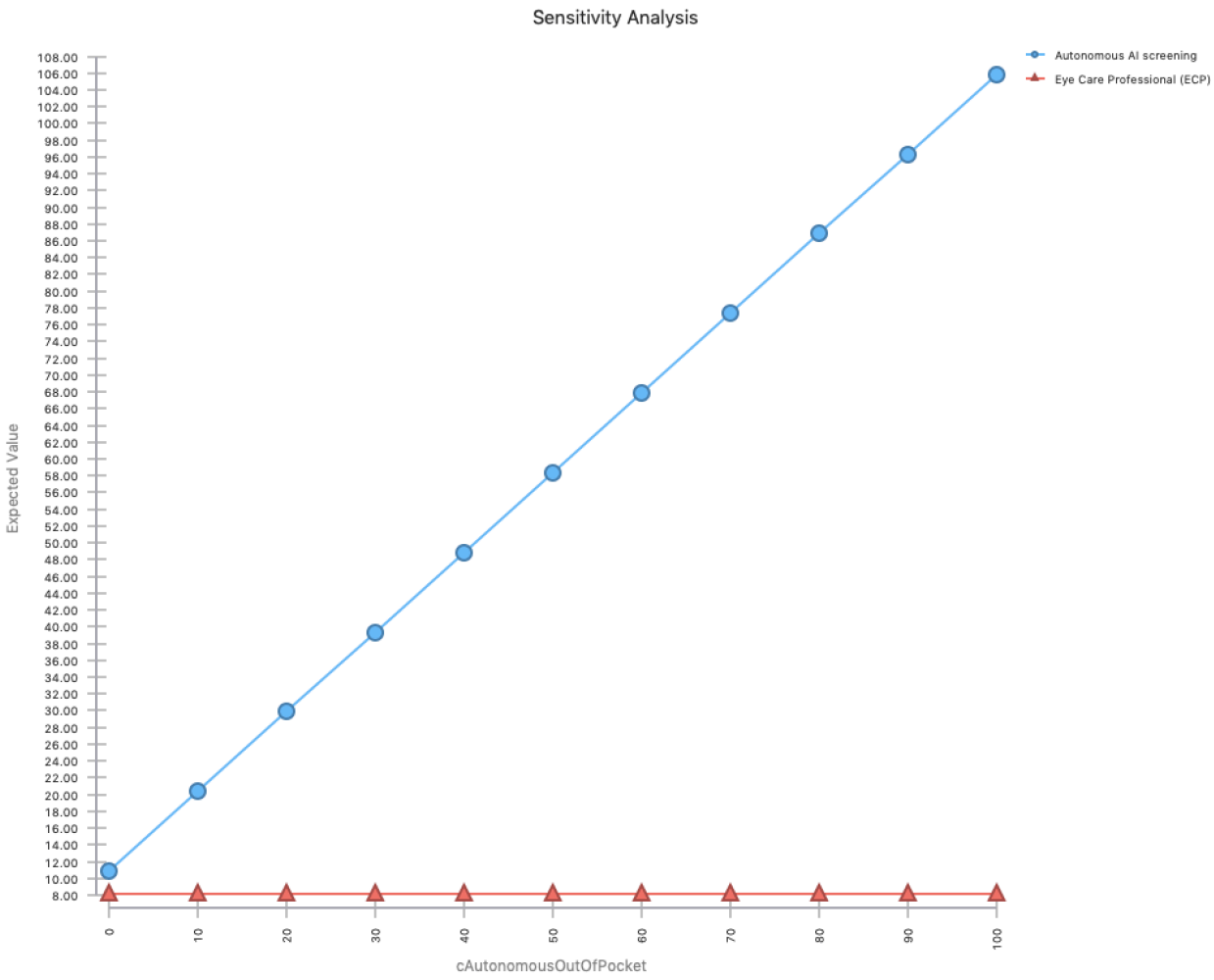


Figure 40

ECP strategy is unaffected by Autonomous out of pocket cost, and remains cheaper.

ECP out of pocket

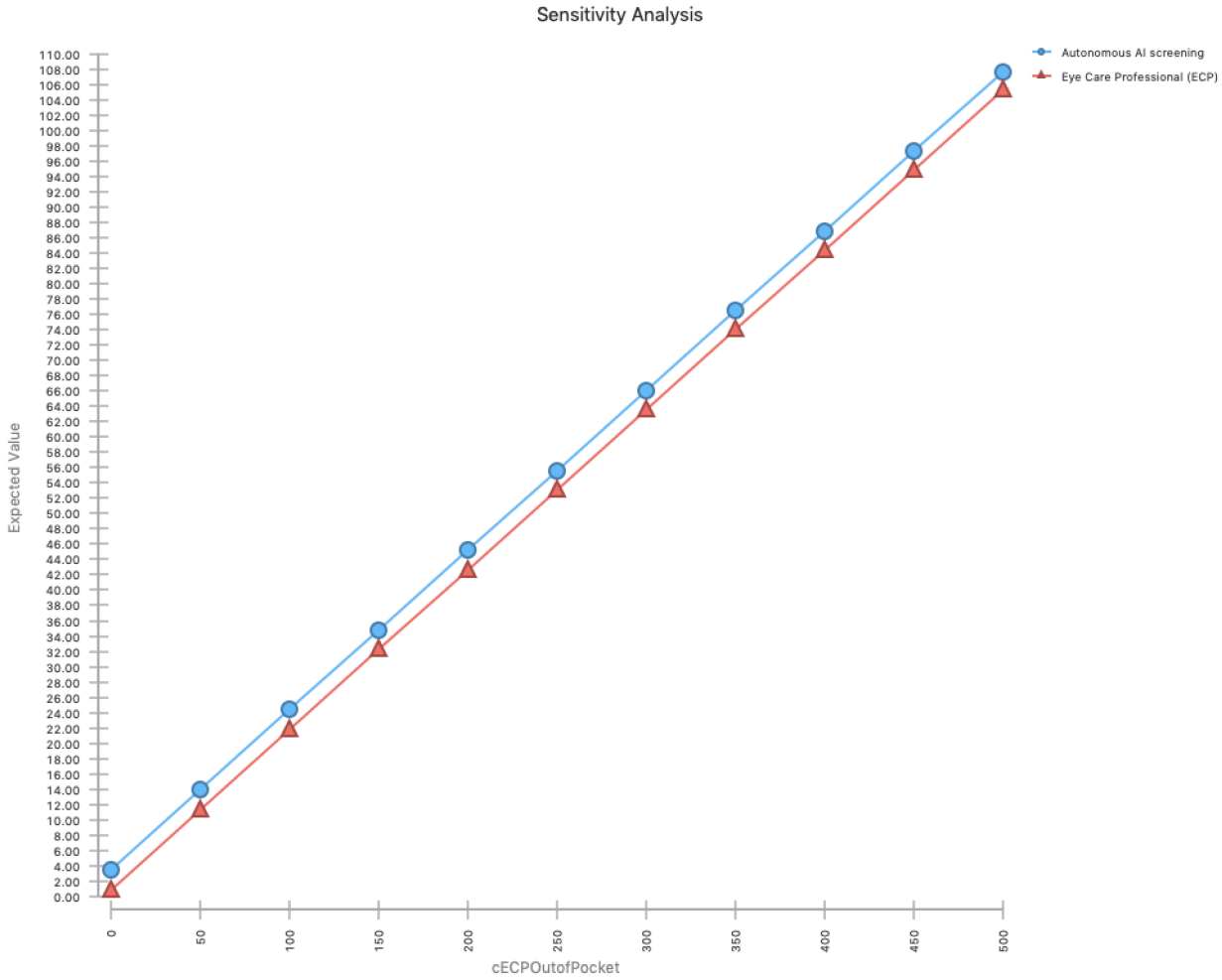


Figure 41

There is no threshold: Whatever the out of pocket cost is to ECP, the ECP strategy is always cheaper, on average, than Autonomous, because Autonomous leads to more ECP visits.

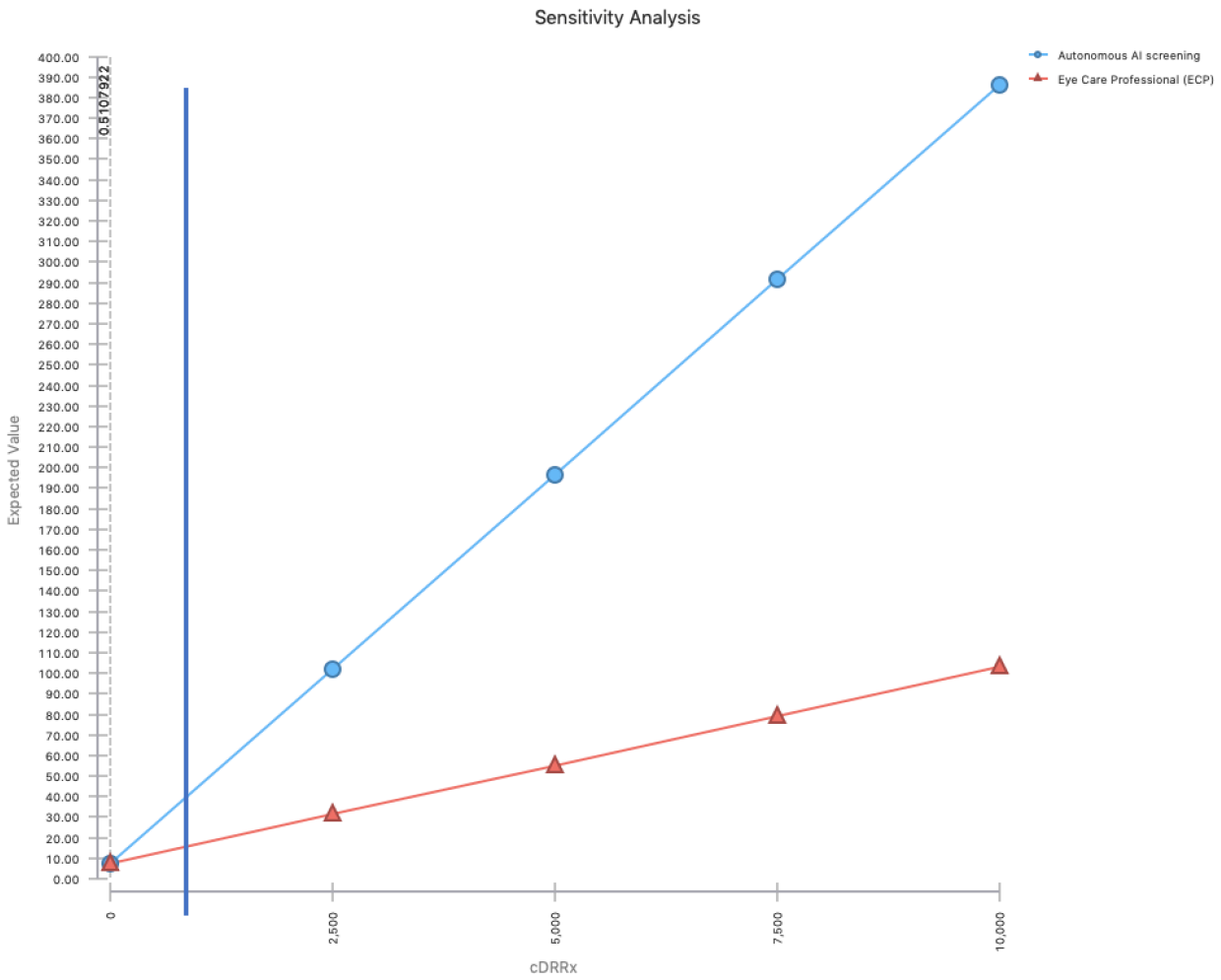


Figure 42

The threshold is at $0, below the current base value of $94. The maximum average out of pocket net cost, at a cDDRx of $10,000, is $390, compared with the $260 for type 1 DM. This increase is because the prevalence in this sensitivity analysis is fixed at .137, higher than the .09 of the type 1 sensitivity analysis for cDDRx.

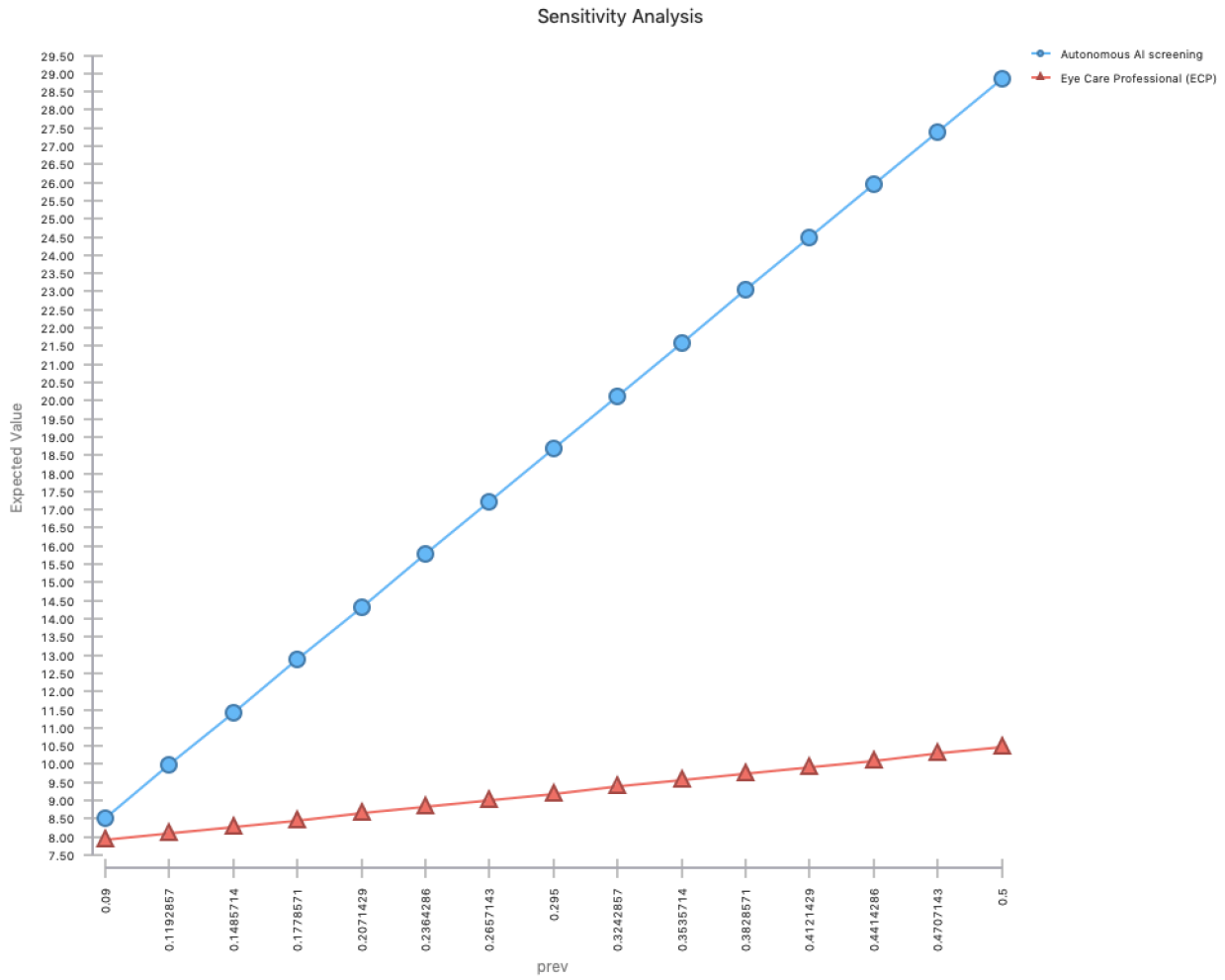


Figure 43

This is really the same curve as in type 1; there, the x-axis ranged from 0 to .137; here, from .09 to .50.

Sens Autonomous

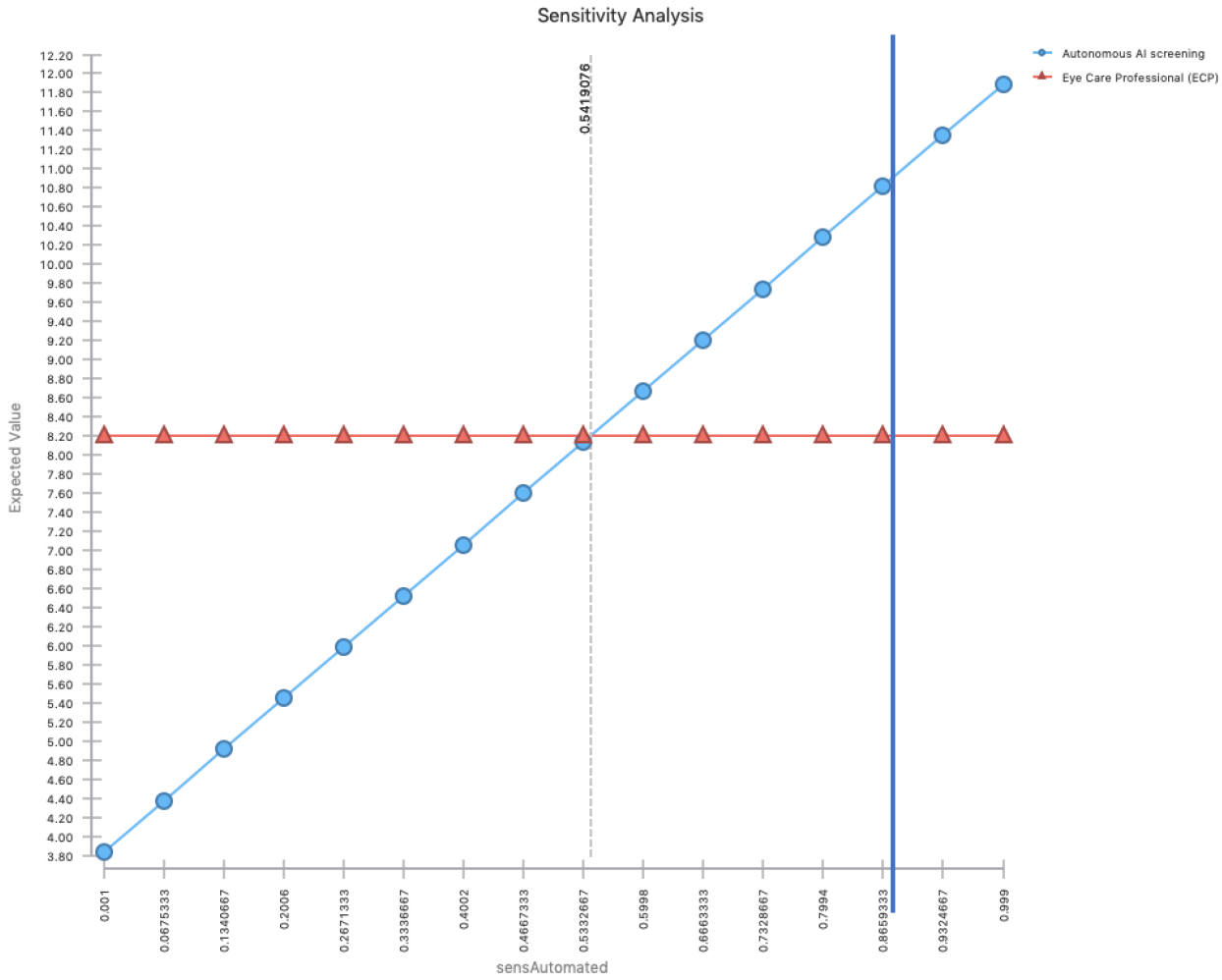


Figure 44

The threshold, of .53 (lower than the base value of .87) is lower here than in type 1 (threshold of .76), because the prevalence of DR is higher, leading to more referrals at lower sensitivities, leading to higher average cost for Autonomous.

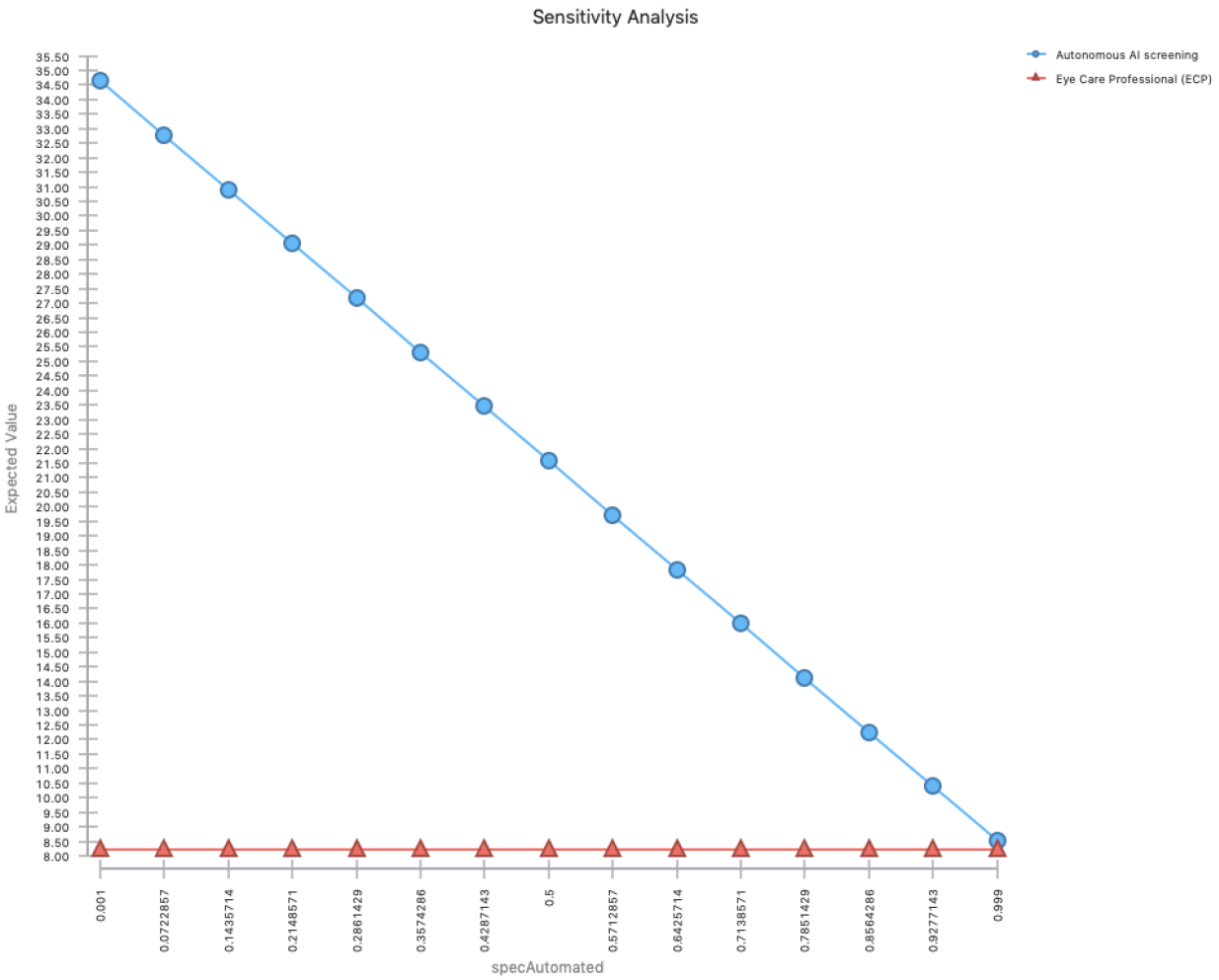


Figure 45

While the curves look similar to those in type 1, there is no threshold here (unlike type 1's threshold of .93). See 2-way sensitivity analysis, below.

Sensitivity ECP

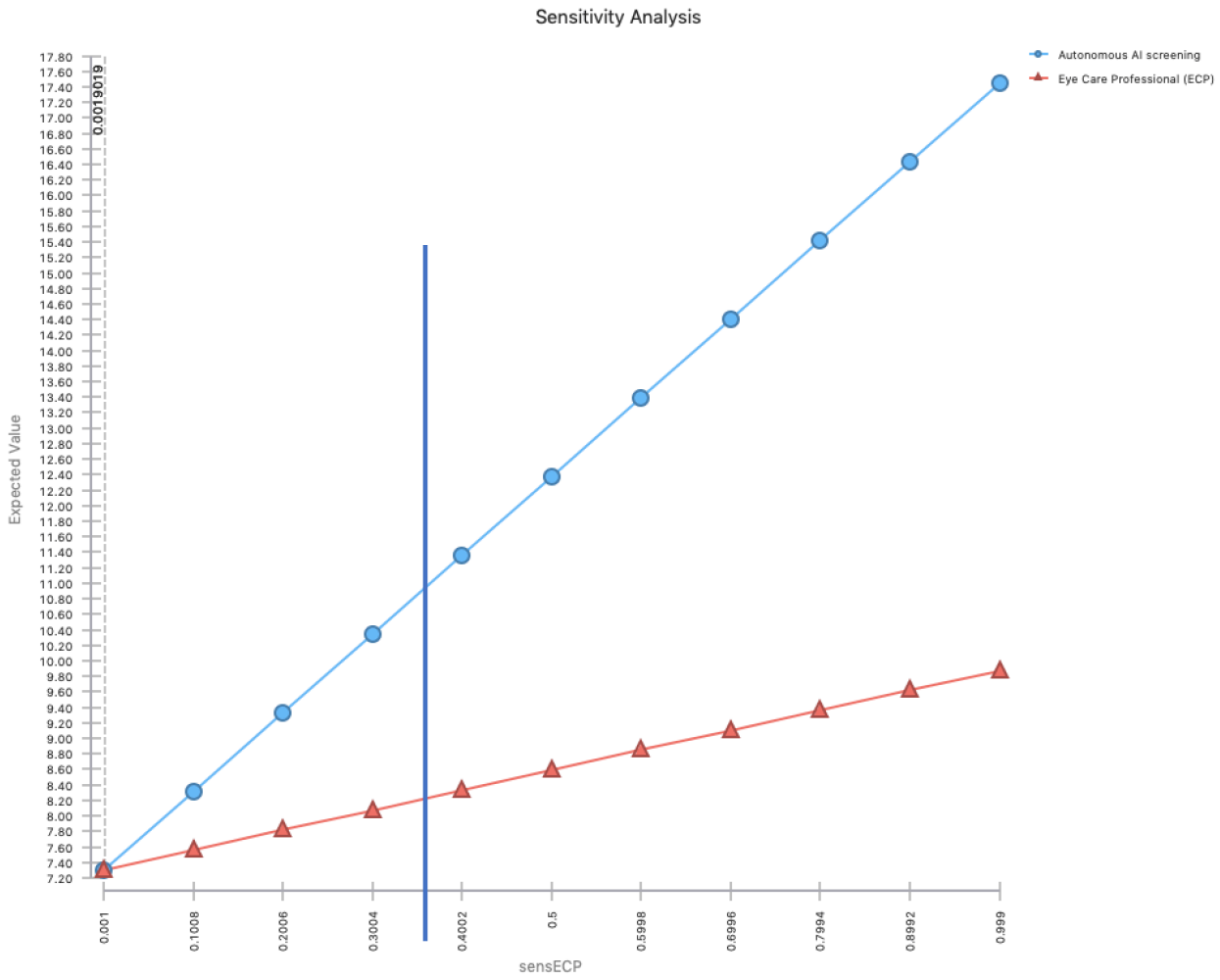


Figure 46

The difference between this graph (threshold of .001) and that in type 1 (threshold of .23) suggest an interaction between sensECP and prevalence of DR; see 2-way sensitivity below)

Specificity ECP

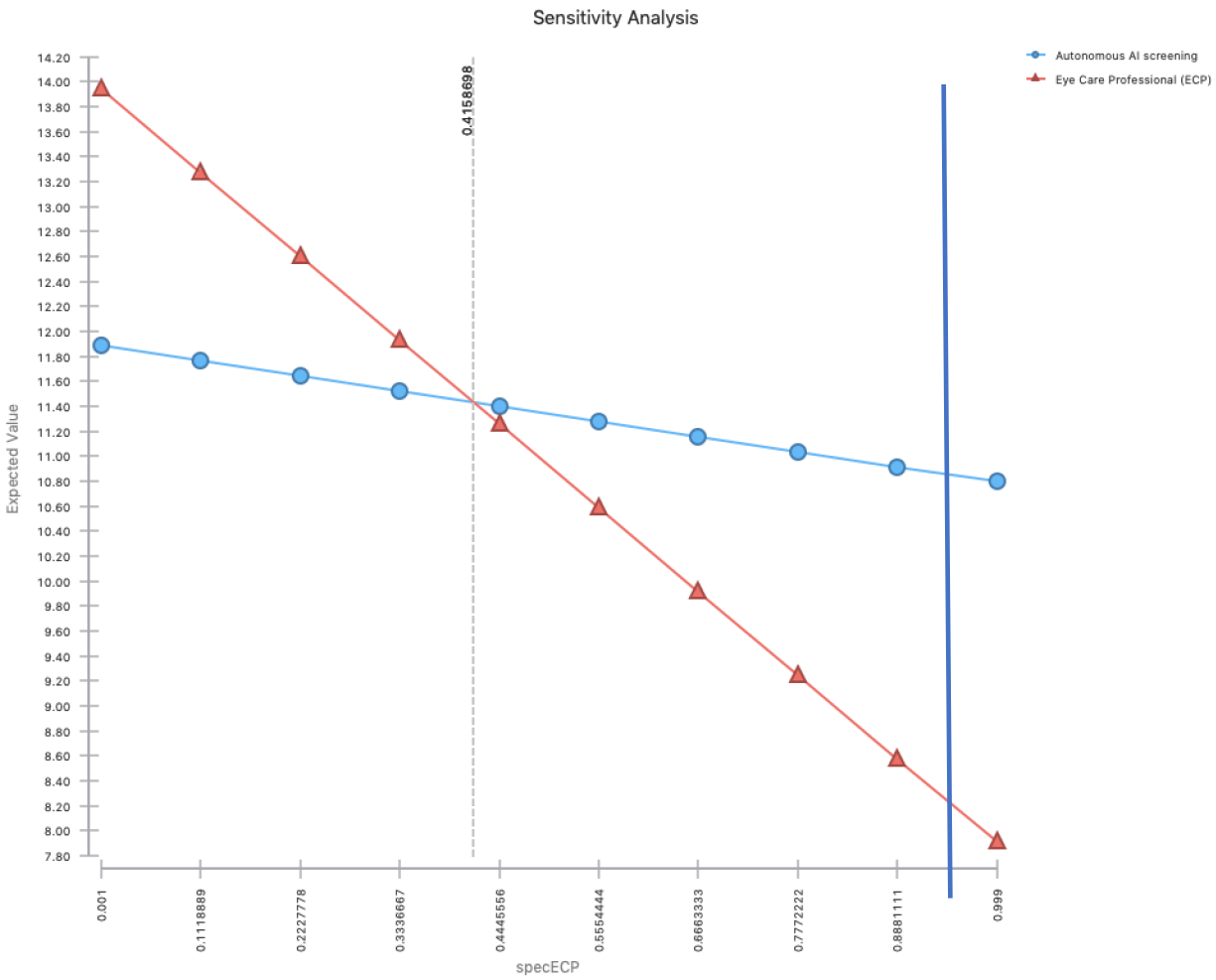


Figure 47

As in type 1 DM, as ECP specificity goes up, the false positive rate goes down, and so the overall average cost goes down. The threshold here is lower (.42, compared with .83) than in type 1, because the prevalence is higher, and the Autonomous line is less steep.

Relative Odds of Keeping ECP Appointment

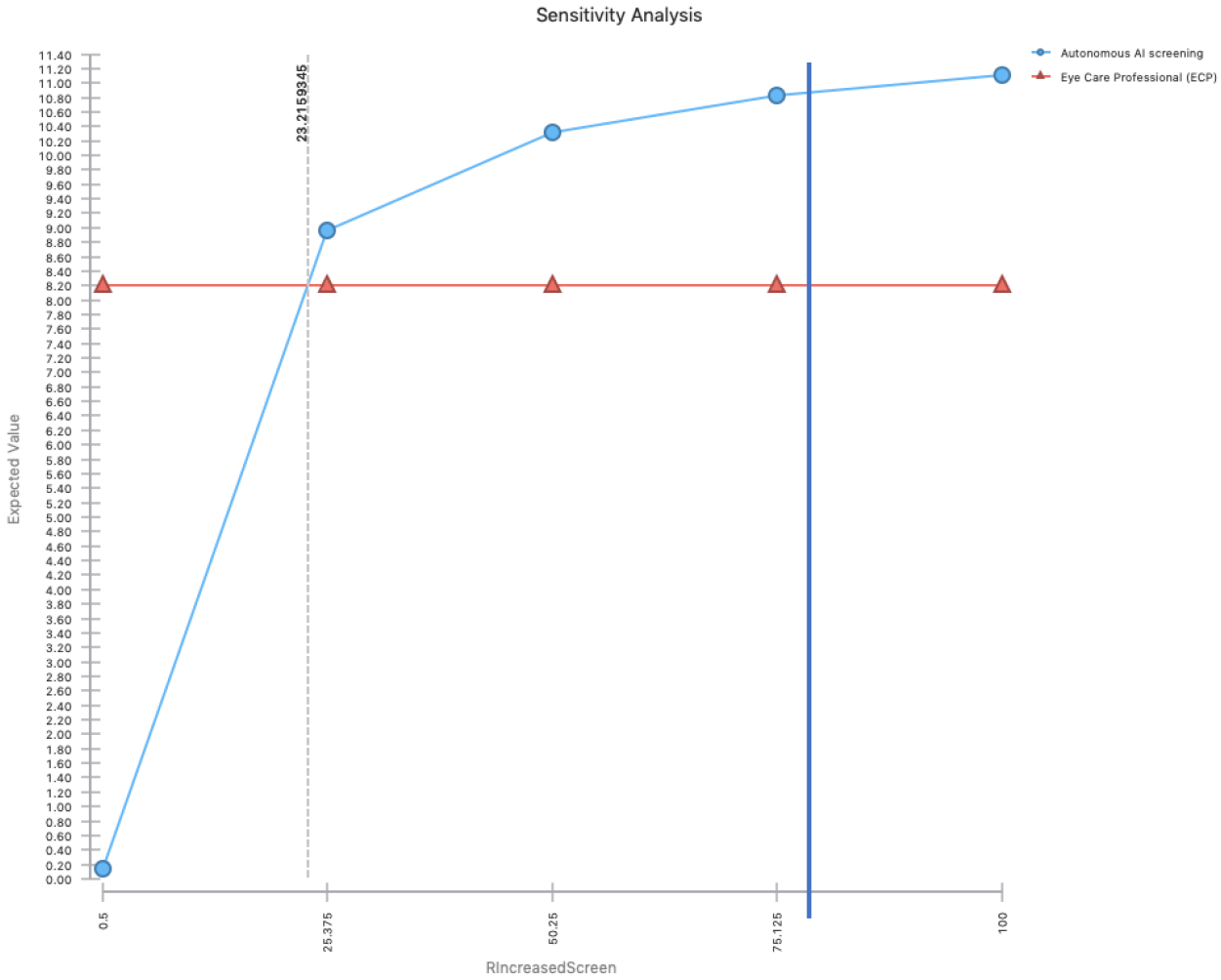


Figure 48

Still the same behavior as before. The threshold here is at a Relative odds of 26 (or probability, based on pECP of .20, of .88), a bit lower than in type 1.

2-way analysis: sensECP and prev

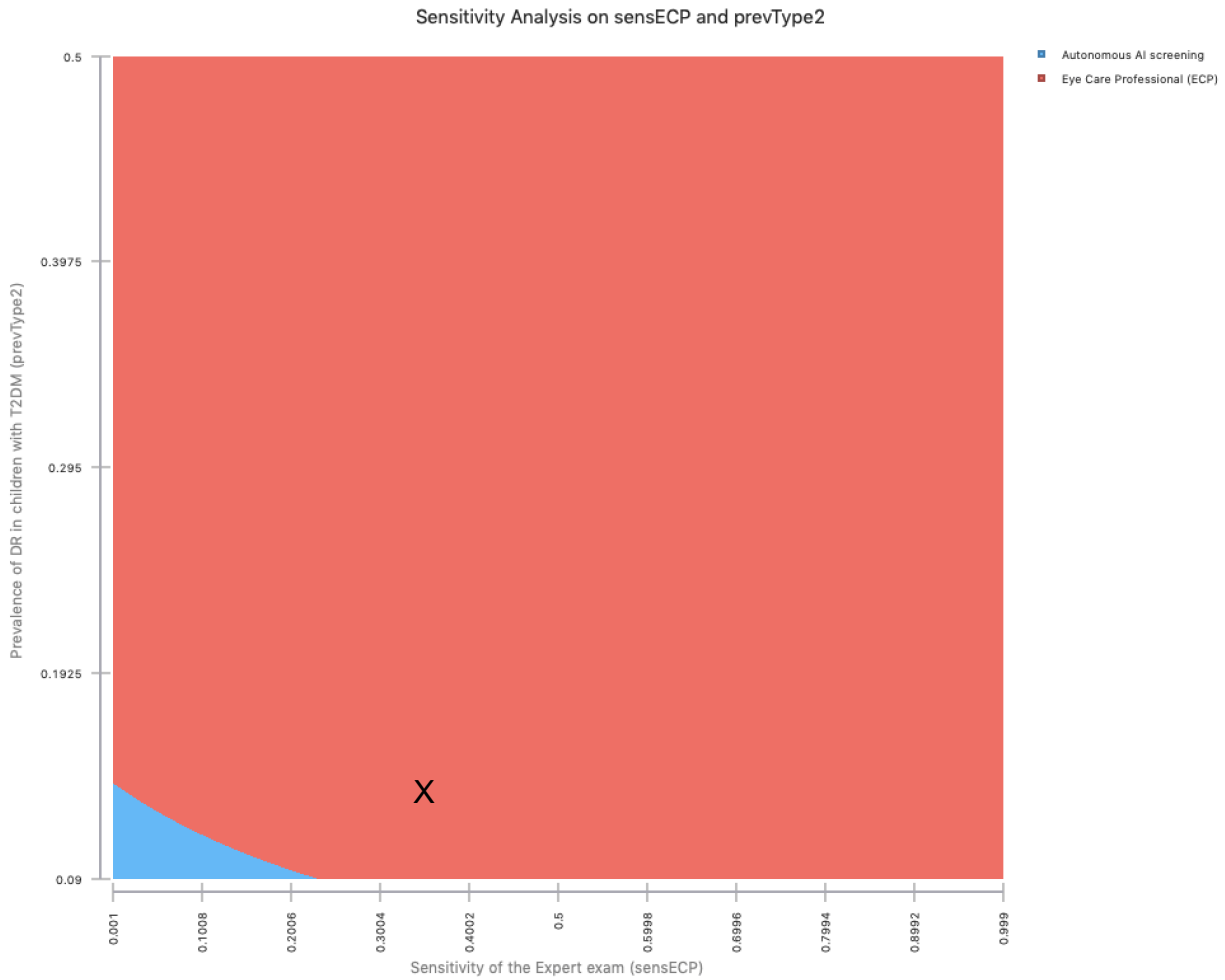


Figure 49

In the discussion above in the 1-way analysis of sens ECP for type 2 DM, it was hypothesized that the lower threshold in the case of a higher prevalence was due to an interaction. This interaction is shown there: the border between blue (Autonomous cheaper) and red (ECP) cheaper is the threshold for prevalence and sens ECP (depending on which you focus). The slope is negative: The higher the prevalence, the lower the threshold, which is what we saw above.

2-way analysis: specAut and prev

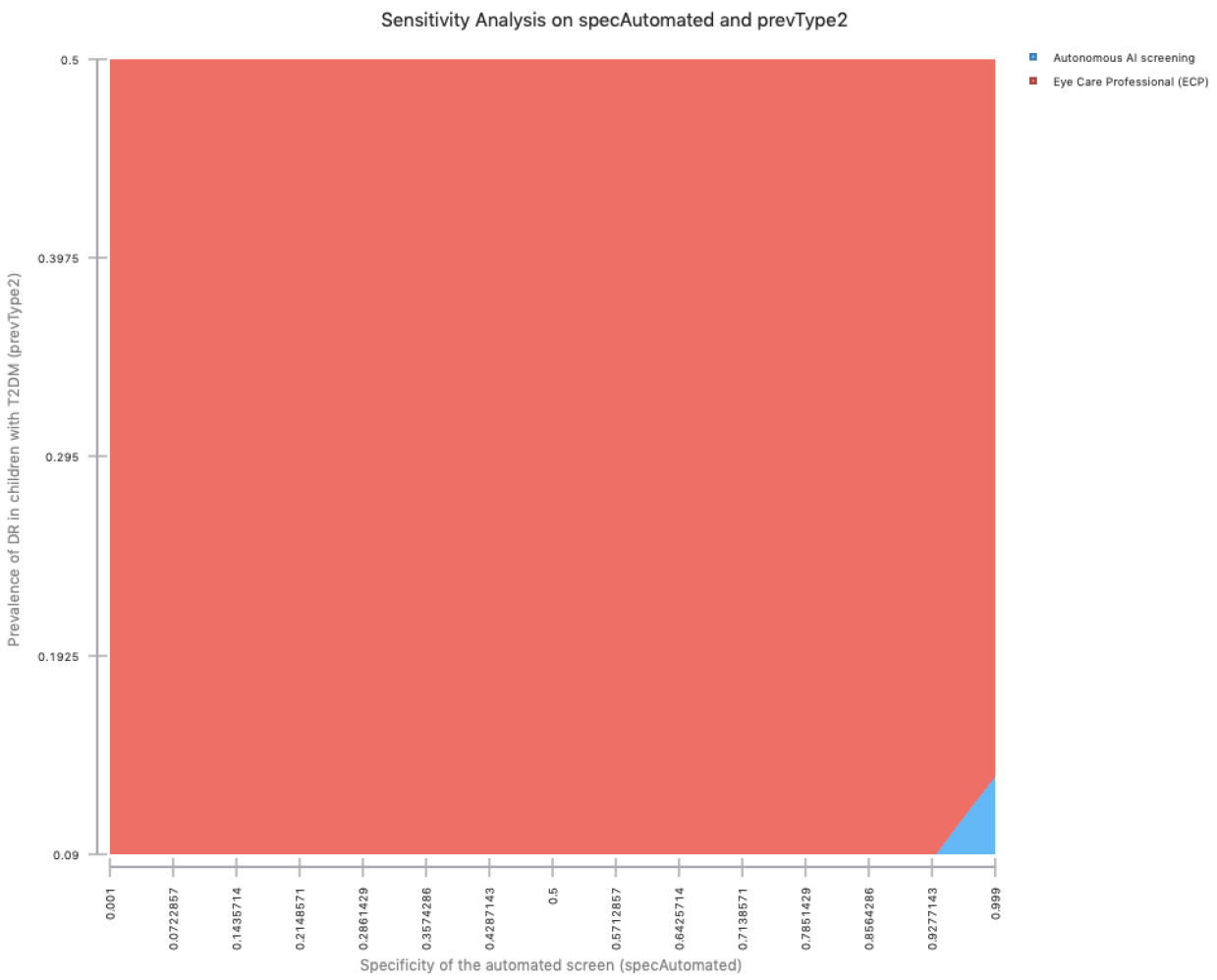


Figure 50

In the discussion of type 2 DM spec Aut 1-way sensitivity analysis above, it was noted that there was no threshold (or, it would be 1.0 or higher), while for type 1, there was a threshold at .93, suggesting that, the higher the prevalence, the higher the threshold. In this 2-way sensitivity analysis, the slope of the threshold border is positive, confirming that hypothesis.

Cost-Effectiveness

Type 2	Auto	ECP		Difference	Ratio
Cost	$10.85	$8.20	Δ Cost	$2.65	$95
TP	.038	.010	Δ Effectiveness	0.028	