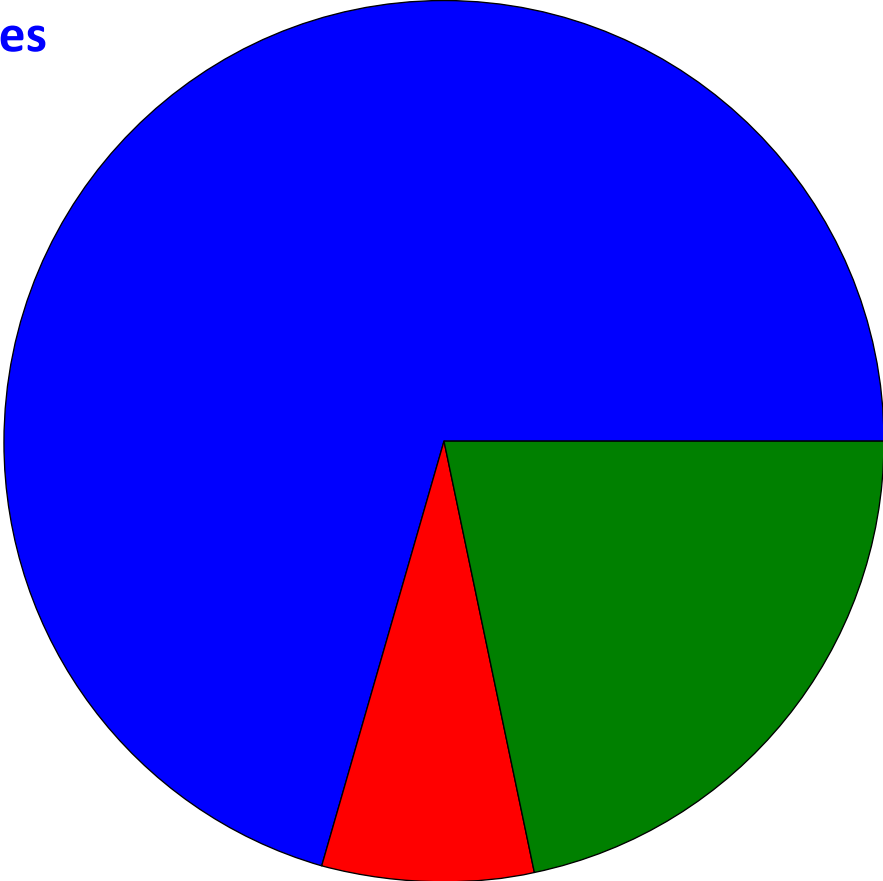


Review: cfDNA and cfRNA screening for preeclampsia and preterm birth



Howard Cuckle

Normal pregnancies

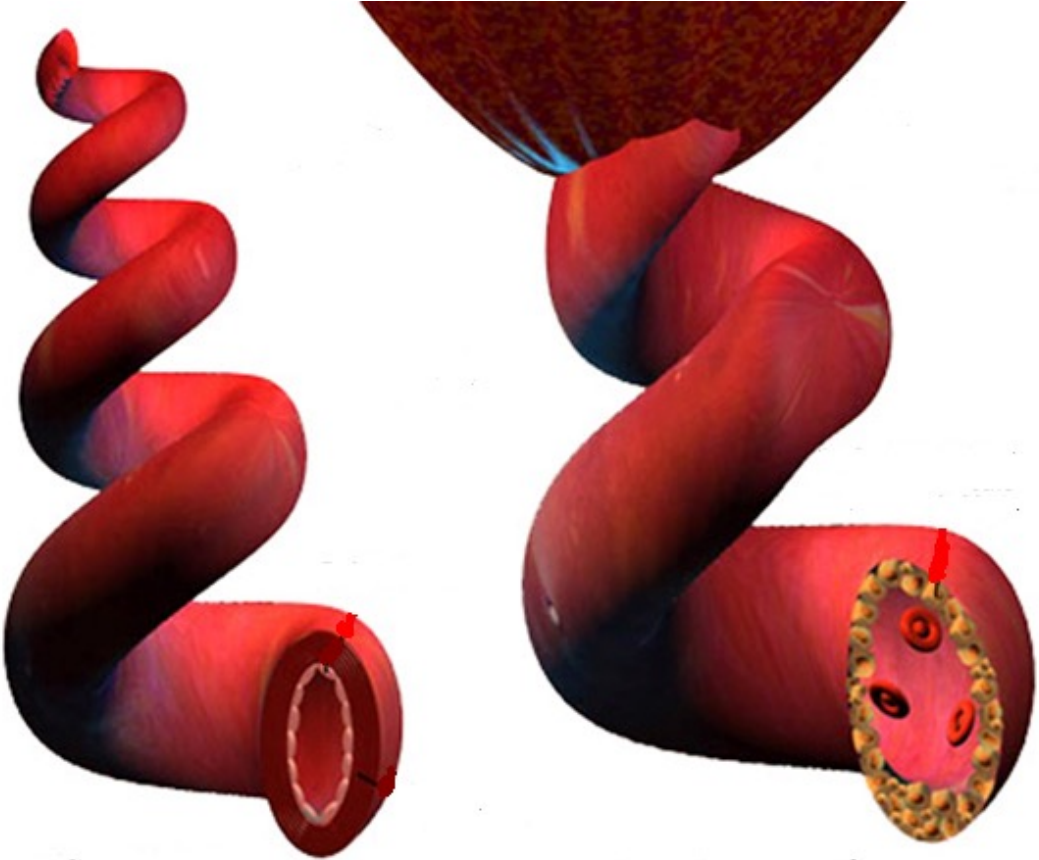


Maternal-fetal complications

Congenital abnormalities

Gestational age

7 8 9 10 11 12 13 14 15 16 17 18 19 20



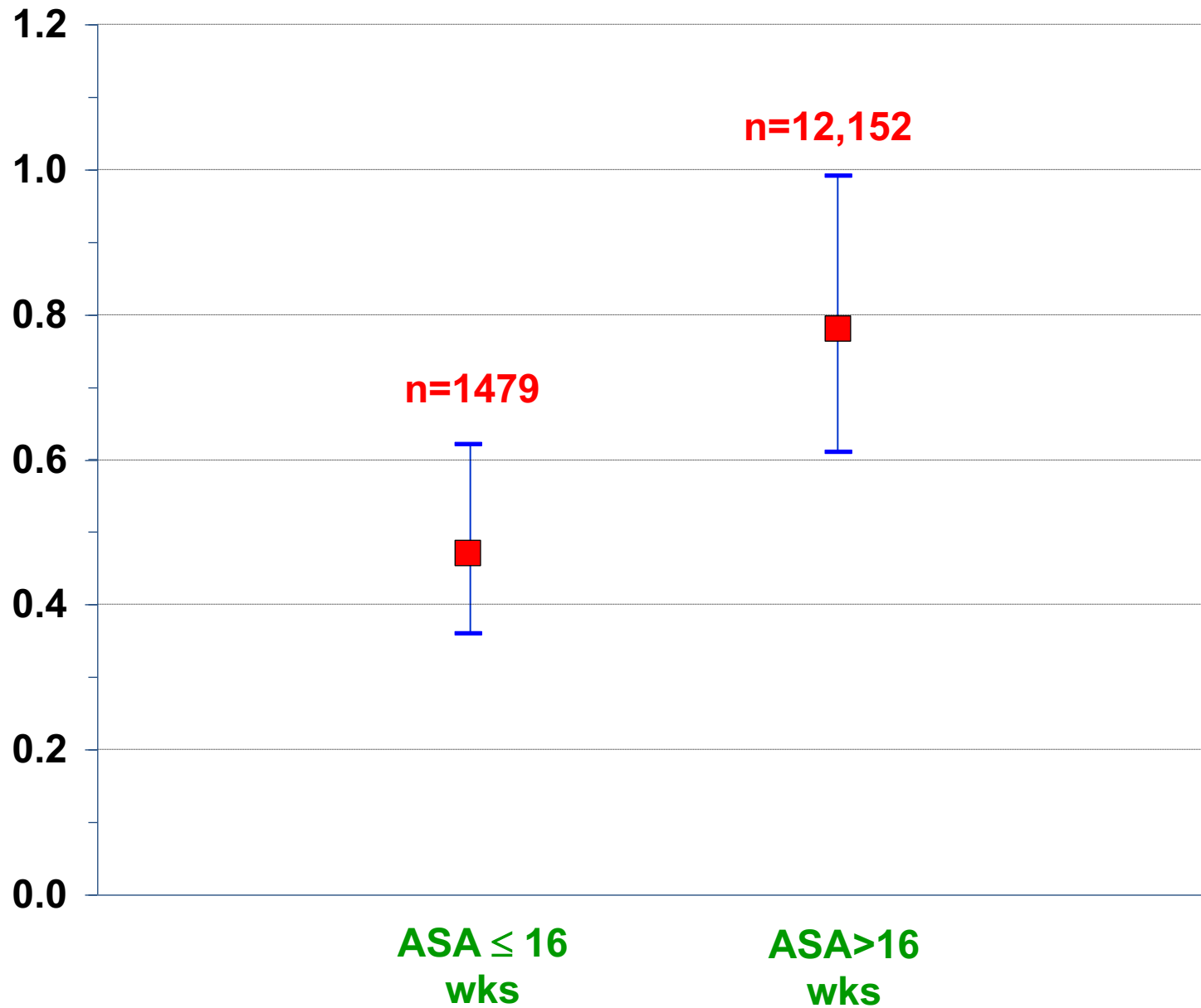
7 8 9 10 11 12 13 14 15 16 17 18 19 20

Gestational age

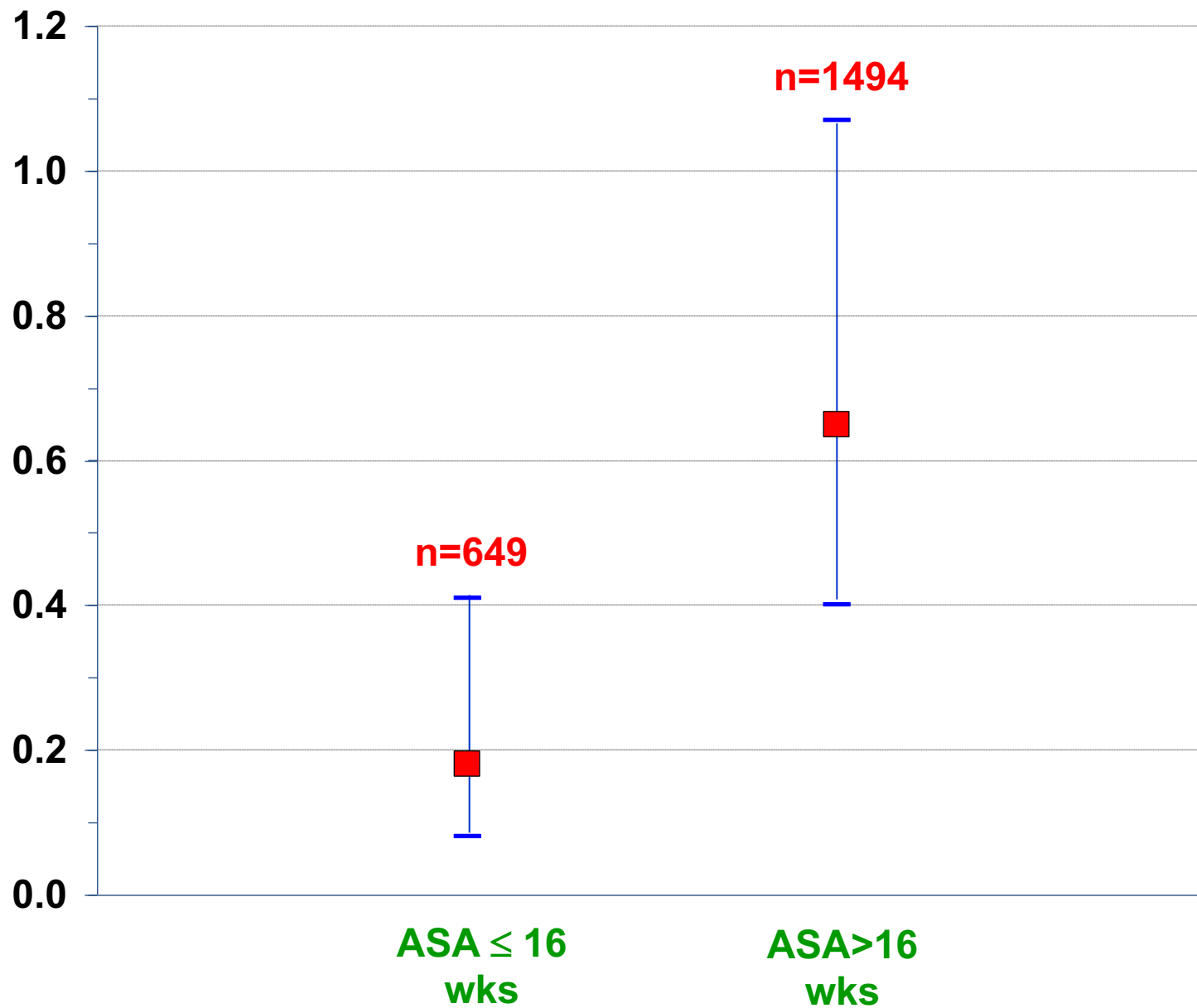


Low dose soluble aspirin

Risk ratio (all PE)



Risk ratio (severe PE)

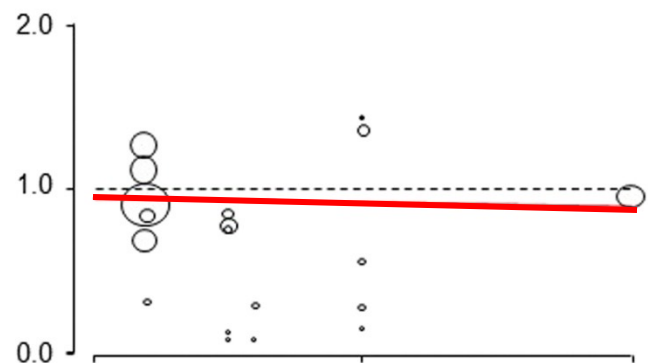
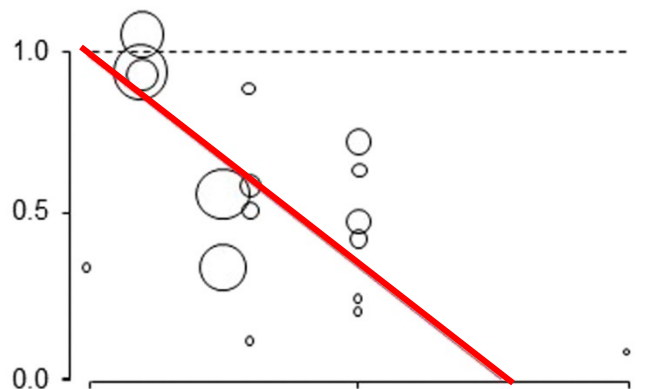


Relative risk

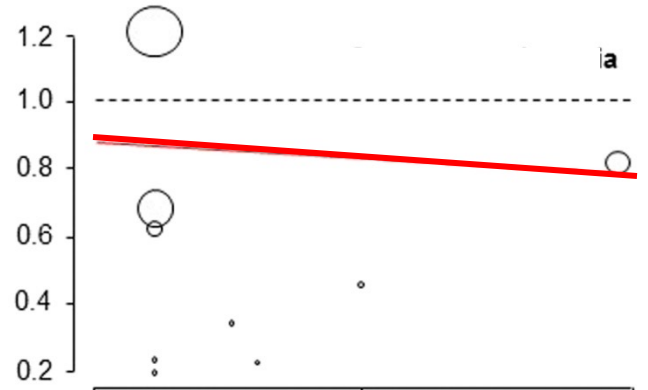
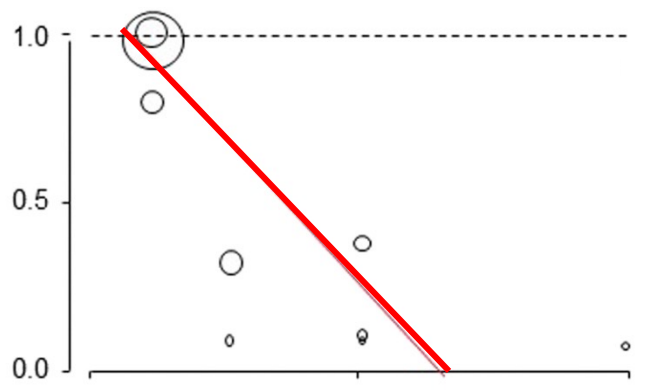
<16 wks

16+ wks

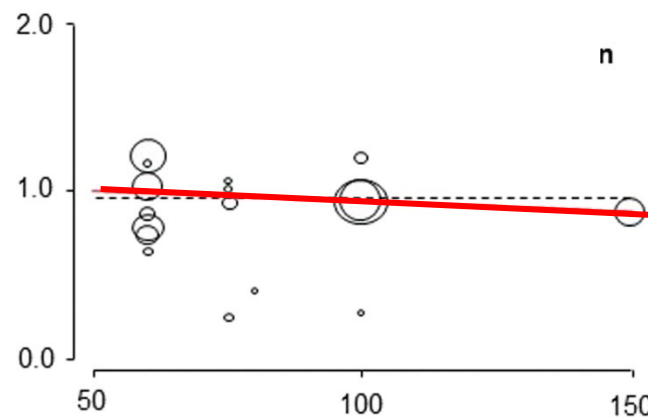
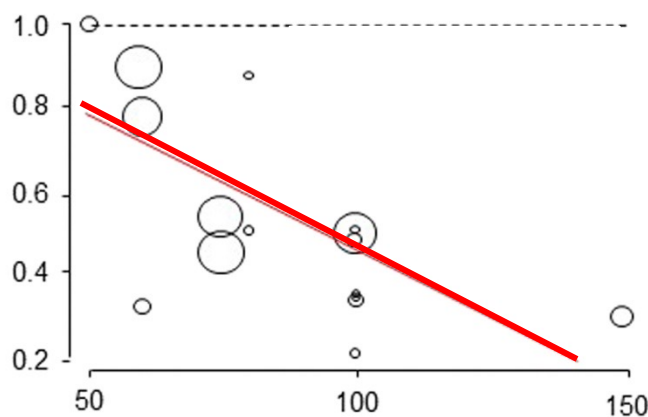
PE



Severe PE



Growth restricted



Aspirin (mg/day)



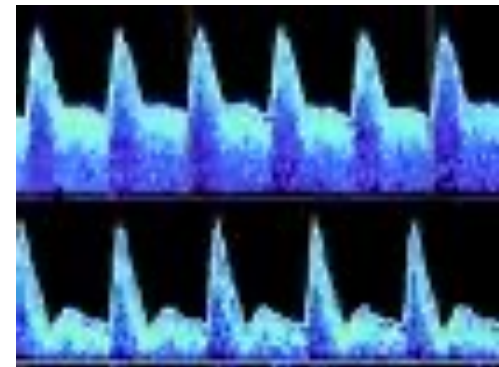
Family Tree





Uterine artery Doppler

Pulsatility index



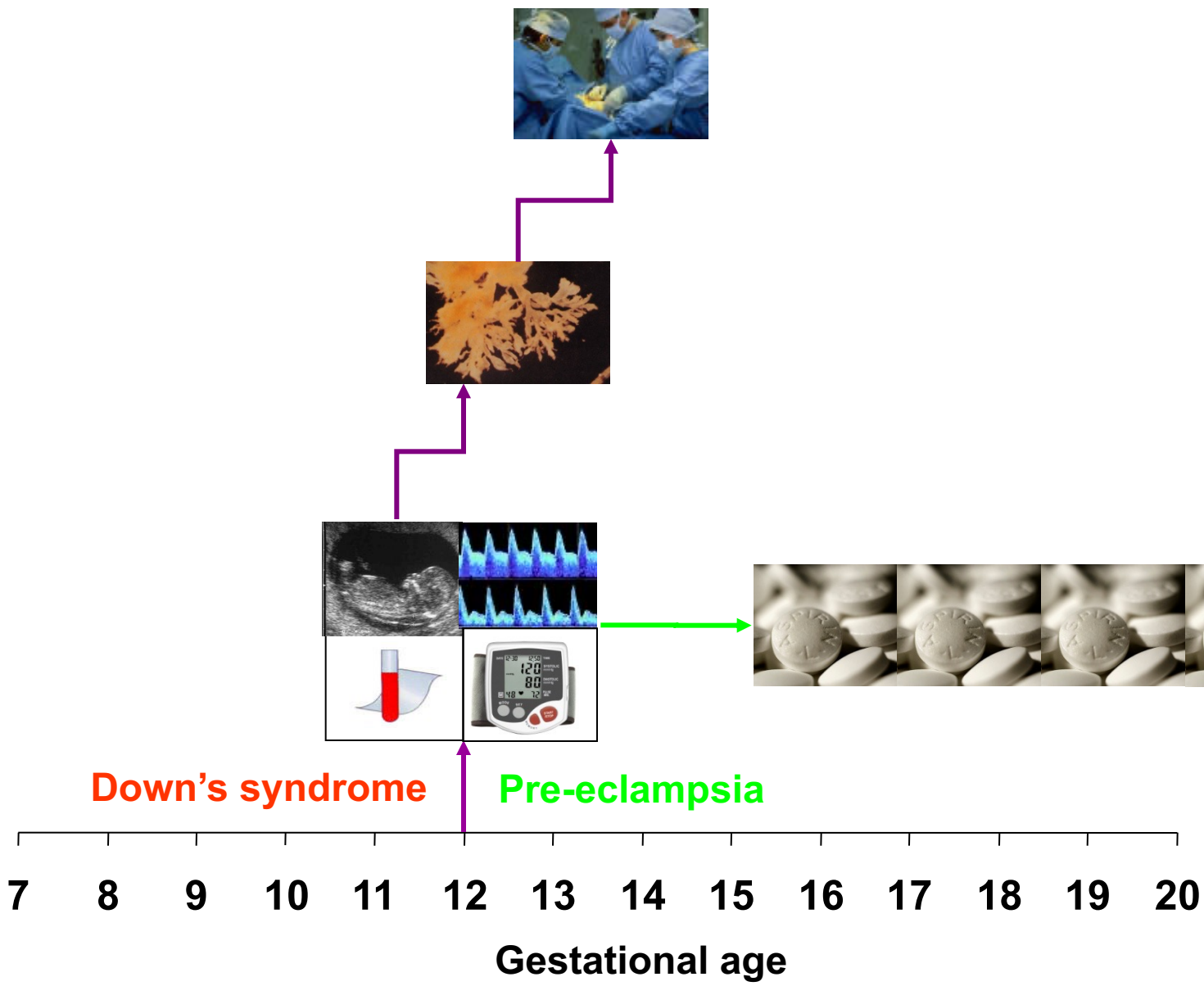
Mean arterial pressure

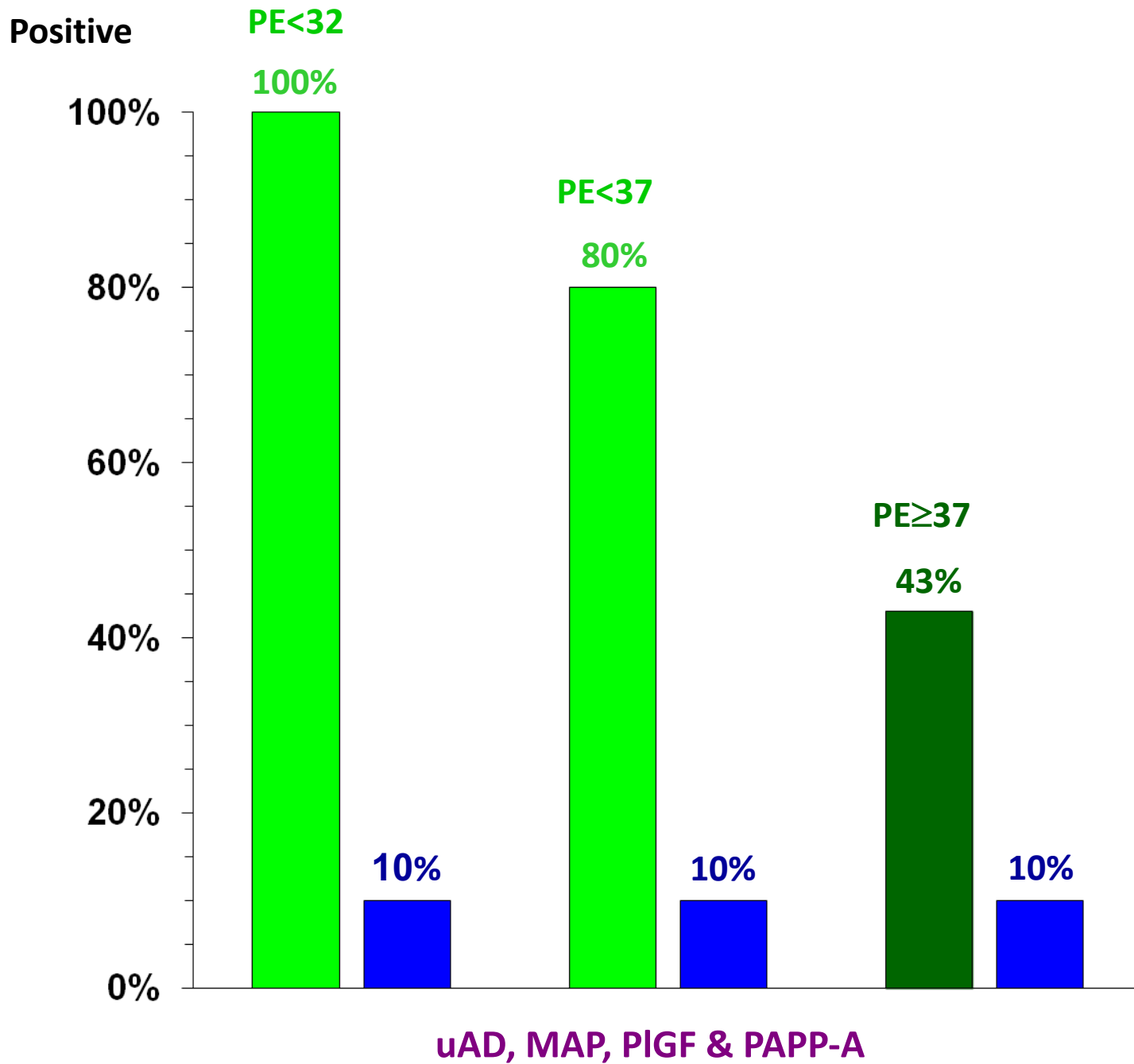
$(\text{Systolic} + 2 * \text{Diastolic}) / 3$





PIGF & PAPP-A



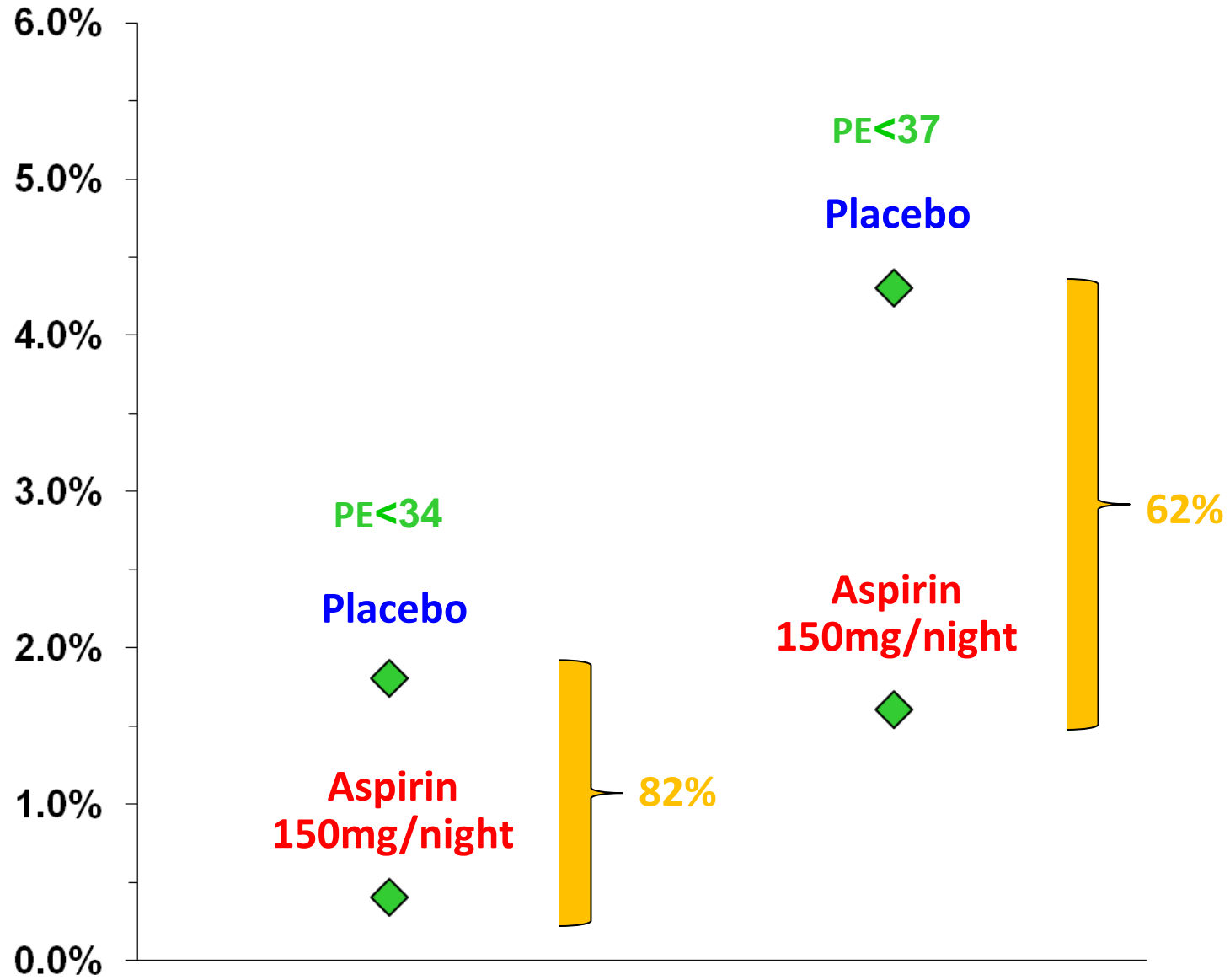


f u n d e d b y E U F P 7

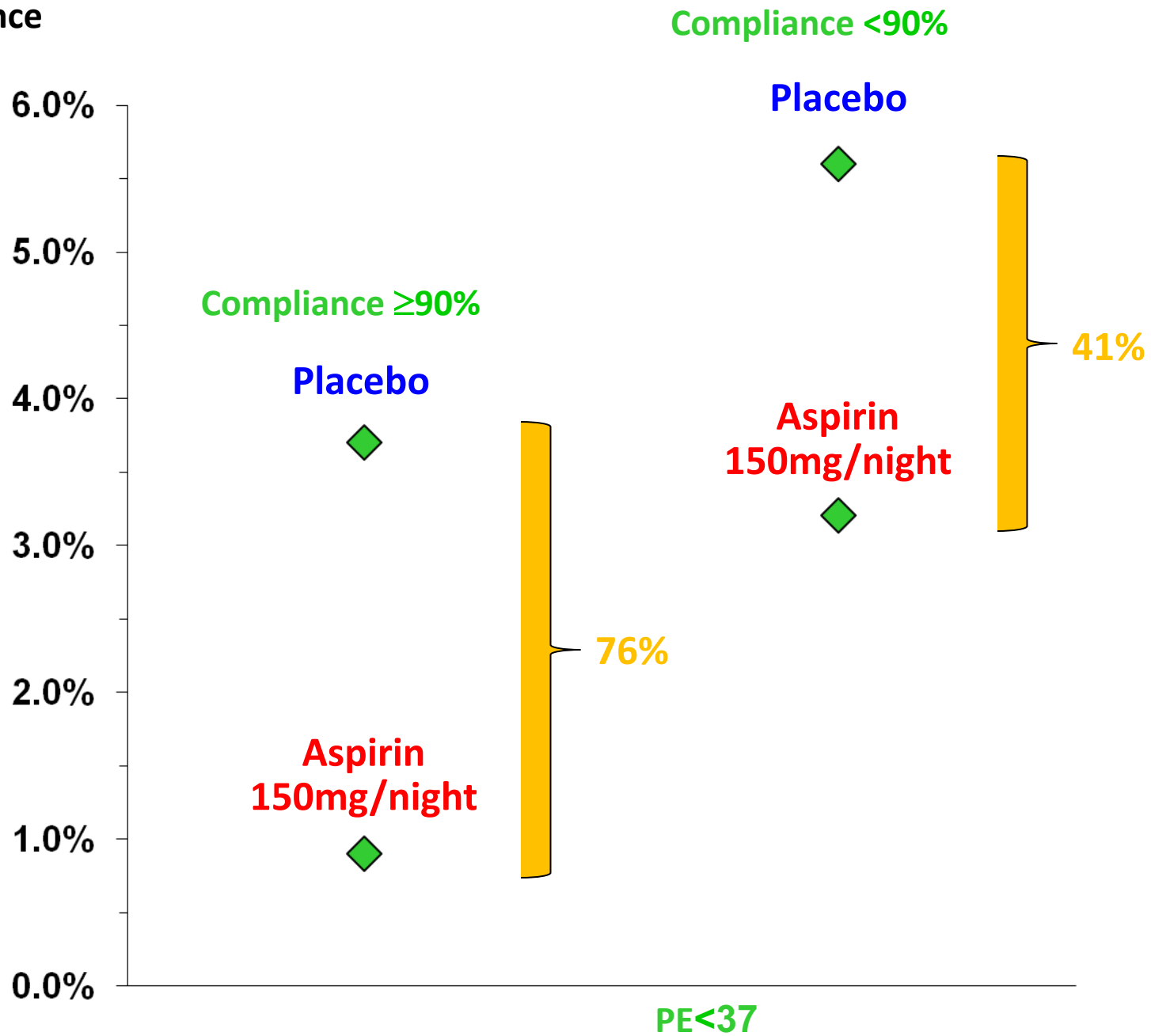
ASPRE

— project

Incidence



Incidence





Total cfDNA

cffDNA

Fetal fraction

cfDNAme

cfmRNA

cfmiRNA

etc

Total cfDNA: Average

	PE onset (wks)	Blood (wks)	Method	Average (n)		P
				PE	OK	
1. Farina, 2004	All	2T	β-globin	439 GE/mL (8)	284 GE/mL (40)	<0.05
2. Crowley, 2007	All	7-20	β-actin	2020 GE/mL (16)	1840 GE/mL (72)	≥0.05
3. Papantonio, 2013	All	11-13	RASSF1A	9400 GE/mL (24)	2700 GE/mL (48)	<0.0001
4. Kim, 2013	All	1T	RASSF1A	26300 C/mL (4)	4010 C/mL (36)	<0.002
5. Poon, 2013	All	11-13	DANSR	151 GE/mL (460)	127 GE/mL (1085)	<0.0125
6. Salvianti, 2015	All	6-23	RASSF1A	610 GE/mL (9)	297 GE/mL (27)	<0.05
7. Rolnik, 2015	<34	11-13	s-MPS	2100 GE/mL (20)	1590 GE/mL (200)	<0.025
	≥34	11-13	s-MPS	2180 GE/mL (20)	1590 GE/mL (200)	≥0.05
8. Kim, 2016	All	1T	HYP2	7170 C/mL (14)	5190 C/mL (53)	<0.05
9. Silver, 2017	All	9-12	β-actin	3.52 NR (175)	3.74 NR (175)	0.96
10. Yuan, 2019	All	12-22	MPSS	6.42 ng/mL (52)	5.99 ng/mL (630)	<0.01
11. Kwak, 2020	Early	2T	HYP2	23400 C/mL (6)	9440 C/mL (78)	<0.05
	Late	2T	HYP2	10000 C/mL (23)	9440 C/mL (78)	0.63
12. Gekas, 2023	<34	11-14	s-MPS	↑ pg/uL (4)	NK pg/uL (71)	<0.05
	≥34	11-14	s-MPS	↔ pg/uL (8)	NK pg/uL (71)	≥0.05

Total cfDNA: Average

	PE onset (wks)	Blood (wks)	Method	Average (n)		P
				PE	OK	
1. Farina, 2004	All	2T	β-globin	439 GE/mL (8)	284 GE/mL (40)	<0.05
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cffDNA: Average

	PE onset (wks)	Blood (wks)	Method	Average (n)		P
				PE	OK	
1. Leung, 2001	All	11-22	SRY	41.9 GE/ml (18)	22.0 GE/ml (33)	<0.001
2. Zhong, 2002	All	19-25	SRY	423 C/ml (10)	128 C/ml (40)	<0.005
3. Levine, 2004	<37	2T	DYS1	74 GE/mL (36)	16 GE/mL (137)	<0.01
	≥37	2T	DYS1	22 GE/mL (102)	16 GE/mL (137)	≥0.05
4. Crowley, 2007	All	7-20	SRY	30.5 GE/ml (16)	27.5 GE/ml (72)	≥0.05
5. Sifakis, 2009	<34	11-13	DSY14	95.5 GE/ml (11)	51.5 GE/ml (176)	<0.05
	≥34	11-13	DSY14	50.8 GE/ml (33)	51.5 GE/ml (176)	≥0.05
6. Papantonio, 2013	All	11-13	RASSF1A	934 GE/ml (24)	62 GE/ml (48)	<0.0001
7. Kim, 2013	All	1T	RASSF1A	120 C/ml (4)	60.2 C/ml (36)	0.14
8. Poon, 2013	All	11-13	DANSR	12.9 GE/ml (460)	13.3 GE/ml (1085)	≥0.05
9. Salvianti, 2015	All	6-23	RASSF1A	1.79 GE/ml (9)	2.85 GE/ml (27)	≥0.05
10. Kim, 2016	All	1T	DSCR3	939 C/mL (14)	891 C/mL (53)	≥0.05
	All	1T	RASSF1A	669 C/mL (14)	446 C/mL (53)	≥0.05
11. Thurik, 2016	All	8-13	DSY14	54.6 GE/ml (37)	49.4 GE/ml (96)	≥0.05

cffDNA: Average

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9. Salvianti, 2015	All	6-23	RASSF1A	1.79 GE/ml (9)	2.85 GE/ml (27)	≥0.05
10. Kim, 2016	All	1T	DSCR3	939 C/mL (14)	891 C/mL (53)	≥0.05
	All	1T	RASSF1A	669 C/mL (14)	446 C/mL (53)	≥0.05
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	≥37	2T	DYS1	22 GE/mL (102)	16 GE/mL (137)	≥0.05
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11. Thurik, 2016	All	8-13	DSY14	54.6 GE/ml (37)	49.4 GE/ml (96)	≥0.05

Fetal fraction: Average

	PE (wks), severity	Blood (wks)	Method	Average (n)		P
				PE	OK	
1. Rolnik, 2015	<34	11-13	s-MPS	6.85% (20)	8.74% (200)	<0.025
	≥34	11-13	s-MPS	7.69% (20)	8.74% (200)	≥0.05
2. Bender, 2019	≤34, severe	10-14	s-MPS	10.4% (61)	12.4% (1833)	<0.05
	>34, severe	10-14	s-MPS	10.8% (61)	12.4% (1833)	<0.05
	≤34, severe	14-20	s-MPS	14.6% (19)	12.1% (481)	0.32
	>34, severe	14-20	s-MPS	12.3% (25)	12.1% (481)	0.56
3. Gerson, 2019	Not severe	mn=13	SNPs or DANSR	44%<Q1 (25)	23% <Q1 (594)	<0.02
	Severe	mn=13	SNPs or DANSR	45%<Q1 (20)	23% <Q1 (594)	<0.05
4. De Borre, 2023	<34	10-15	s-MPS	6.2% (61)	9.6% (136)	<0.001
5. Gekas, 2023	<34	11-14	s-MPS	↓ (4)	NR (71)	≥0.05
	≥34	11-14	s-MPS	↓ (8)	NR (71)	<0.05

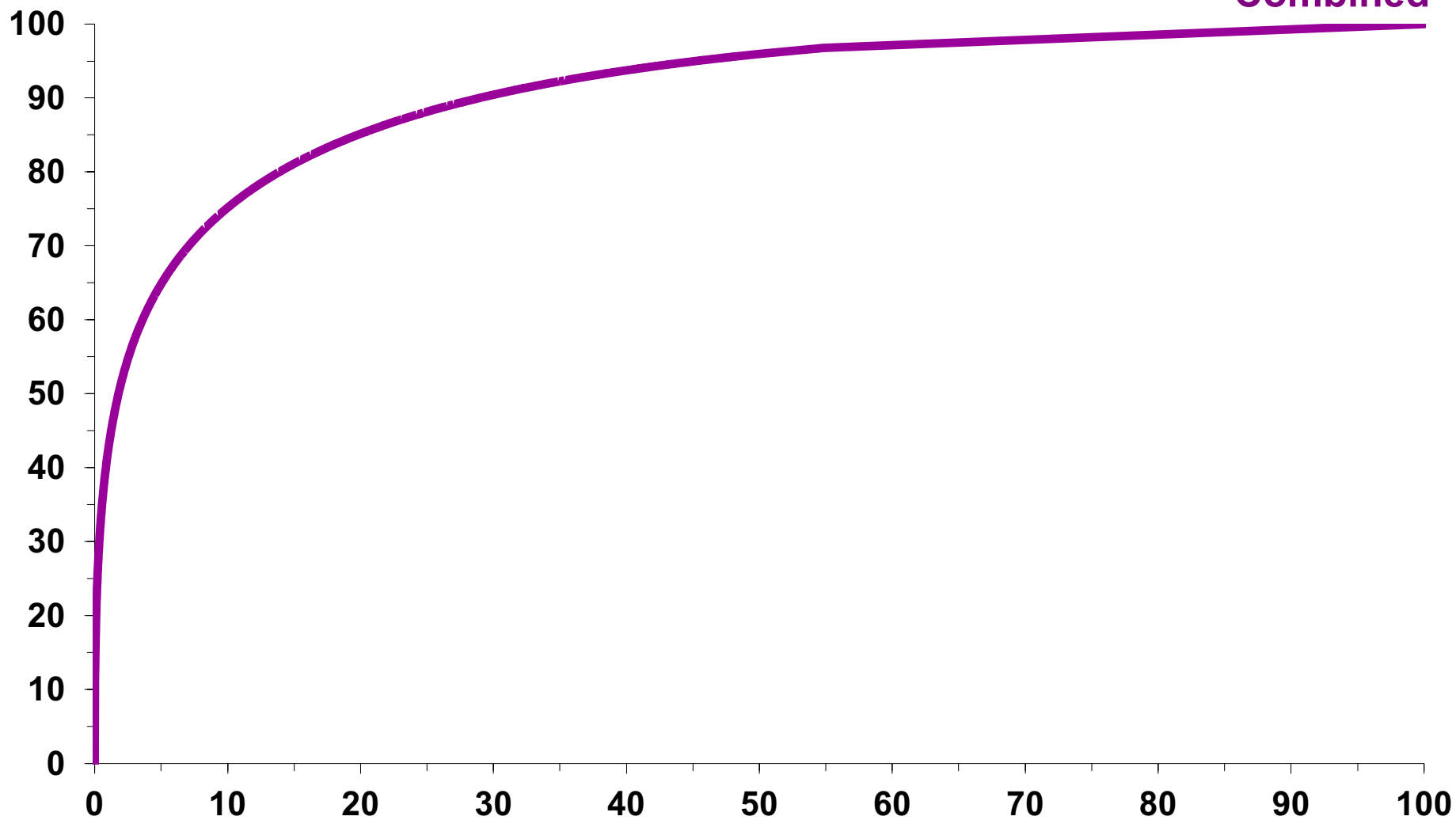
Fetal fraction: Average

	PE (wks), severity	Blood (wks)	Method	Average (n)		P
				PE	OK	
1. Rolnik, 2015	<34	11-13	s-MPS	6.85% (20)	8.74% (200)	<0.025
	≥34	11-13	s-MPS	7.69% (20)	8.74% (200)	≥0.05
2. Bender, 2019	≤34, severe	10-14	s-MPS	10.4% (61)	12.4% (1833)	<0.05
	>34, severe	10-14	s-MPS	10.8% (61)	12.4% (1833)	<0.05
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	≥34	11-14	s-MPS	↓ (8)	NR (71)	<0.05

Fetal fraction: Average

	PE (wks), severity	Blood (wks)	Method	Average (n)		P
				PE	OK	
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	≥34	11-13	s-MPS	7.69% (20)	8.74% (200)	≥0.05
2. Bender, 2019	≤34, severe	10-14	s-MPS	10.4% (61)	12.4% (1833)	<0.05
	>34, severe	10-14	s-MPS	10.8% (61)	12.4% (1833)	<0.05
	≤34, severe	14-20	s-MPS	14.6% (19)	12.1% (481)	0.32
	>34, severe	14-20	s-MPS	12.3% (25)	12.1% (481)	0.56
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	Severe	mn=13	SNPs or DANSR	45%<Q1 (20)	23% <Q1 (594)	<0.05
4. De Borre, 2023	<34	10-15	s-MPS	6.2% (61)	9.6% (136)	<0.001
5. Gekas, 2023	<34	11-14	s-MPS	↓ (4)	NR (71)	≥0.05
	≥34	11-14	s-MPS	↓ (8)	NR (71)	<0.05

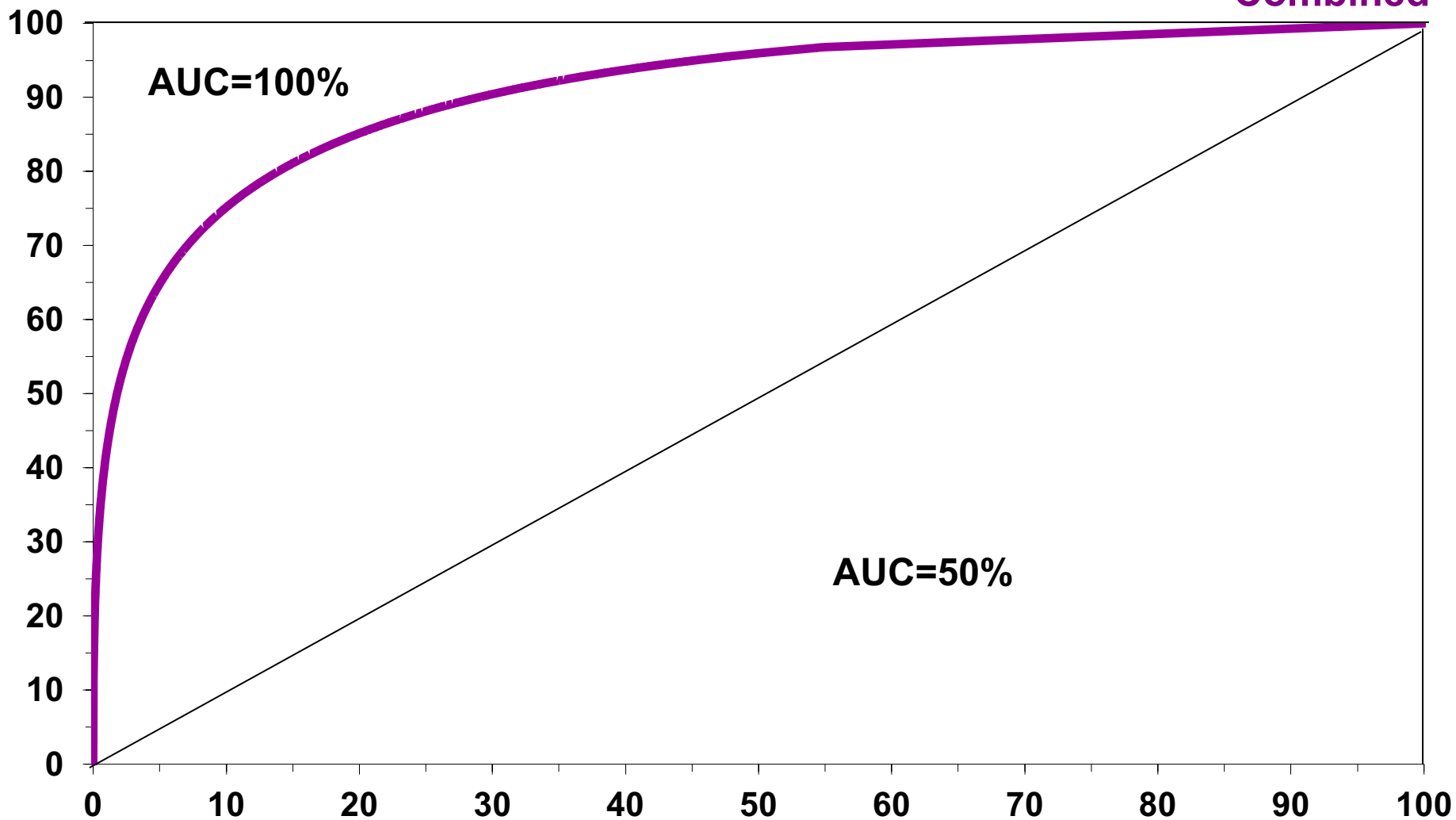
Detection rate (%)



Combined

False-positive rate (%)

Detection rate (%)



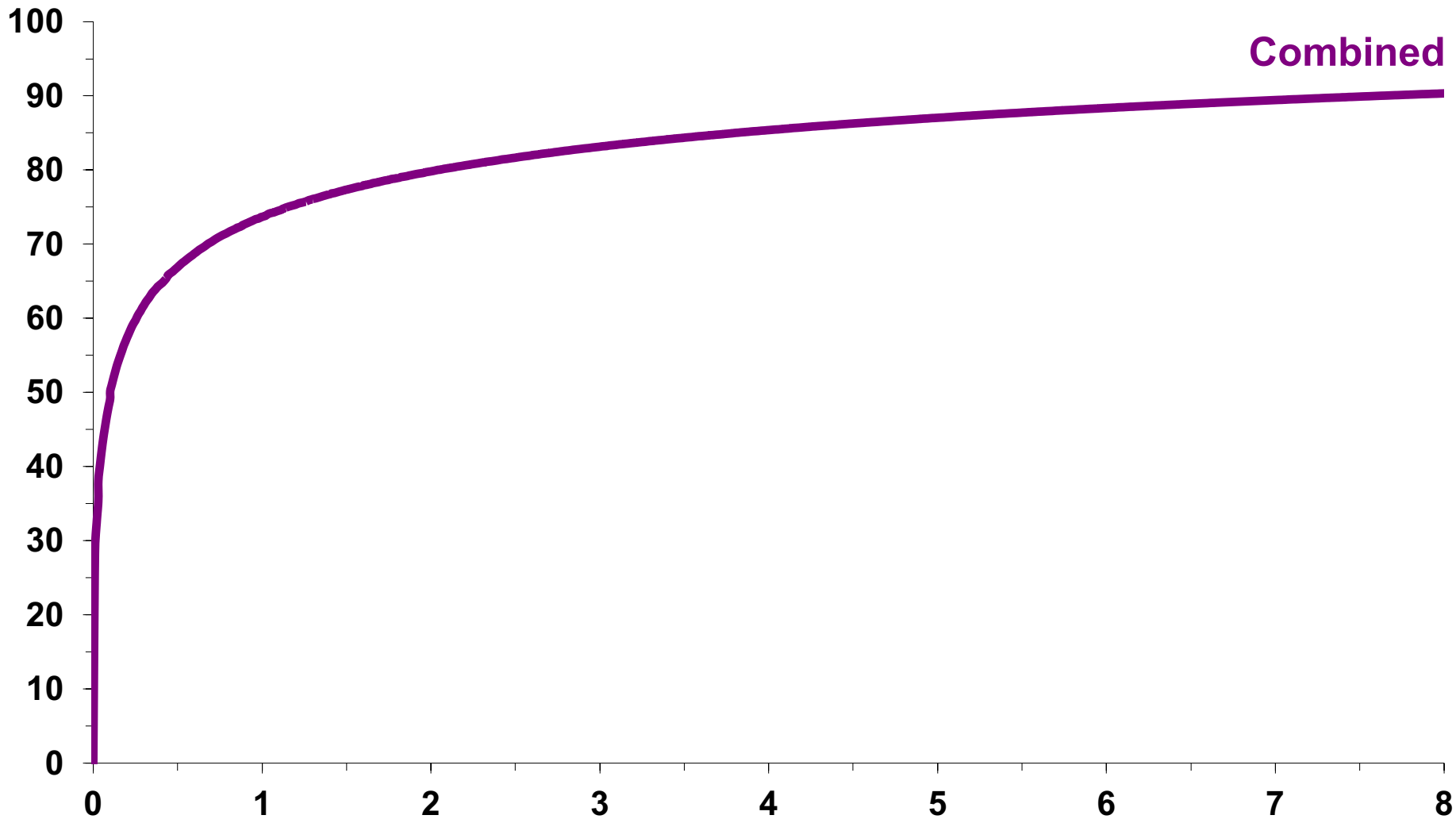
Combined

AUC=100%

AUC=50%

False-positive rate (%)

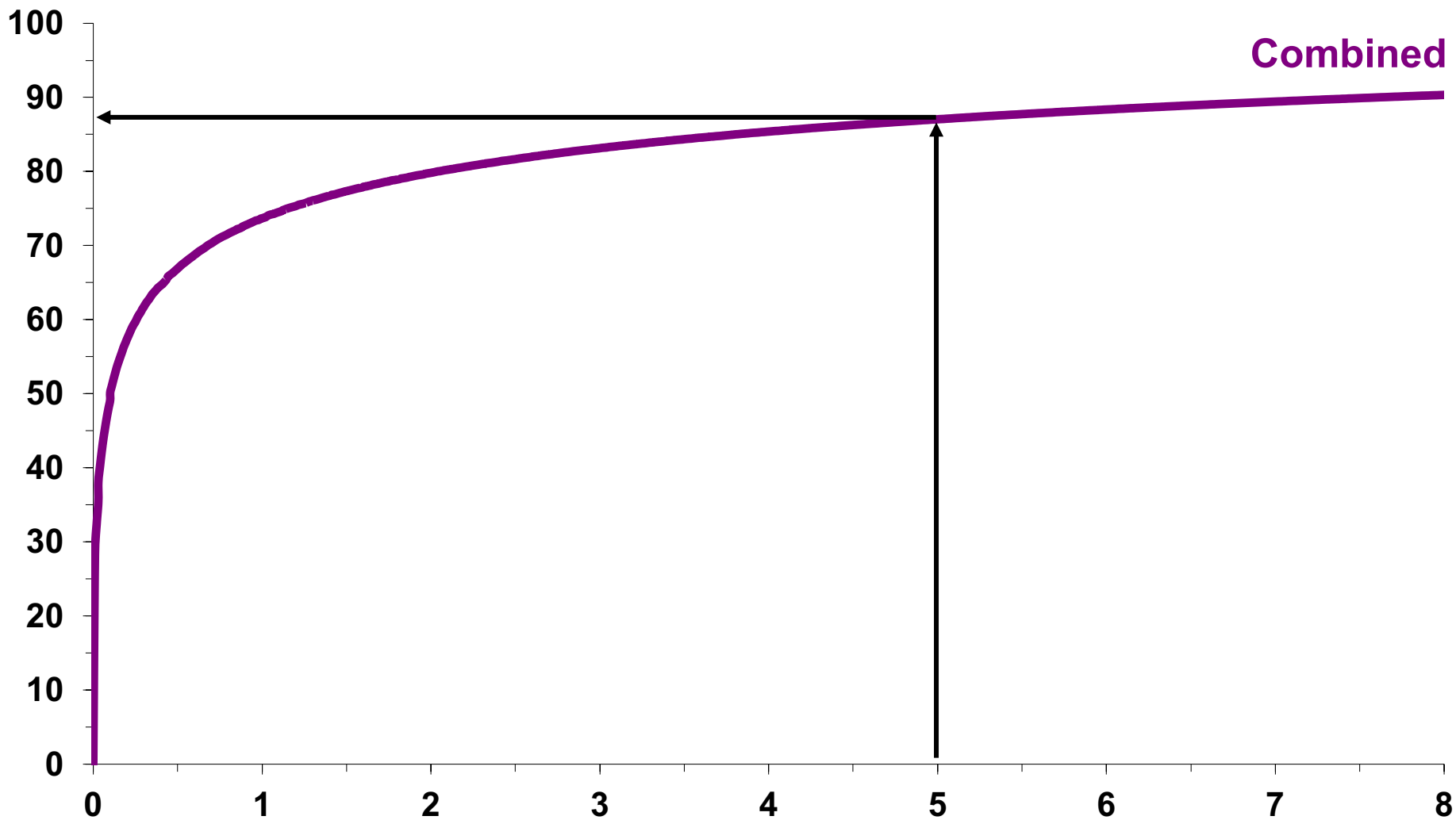
Detection rate (%)



Combined

False-positive rate (%)

Detection rate (%)



Combined

False-positive rate (%)

AUC, DR & FPR

	PE (wks)	Blood (wks)	Markers	AUC	P	DR (n)	FPR (n)	P
Total cfDNA								
1. Papantonio, 2013	All	11-13	RASSF1A	0.93	NR	75% (24)	2% (48)	<0.0001
2. Kim, 2016	All	1T	HYP2	0.68	<0.05	45% (14)	10% (53)	<0.005
						33% (14)	5% (53)	<0.005
cffDNA								
3. Leung, 2001	All	11-22	SRY	0.78	<0.0001	67% (18)	8% (33)	<0.0001
4. Papantonio, 2013	All	11-13	RASSF1A	1.00	NR	100% (24)	0% (48)	<0.0001
cfDNAme								
5. De Borre, 2023	<34	10-15	-	0.75	<0.0001	56% (61)	24% (136)	<0.0001
						38% (61)	10% (136)	<0.0001

cfRNA: AUC, DR & FPR

	PE (wks)	Blood (wks)	Markers	AUC	P	DR (n)	FPR (n)	P
cfmRNA								
1. Farina, 2010	All	10-14	FLT1	0.87	<0.001	45% (11)	5% (88)	<0.0001
	All	10-14	ENG	0.88	<0.001	36% (11)	5% (88)	<0.0005
	All	10-14	TGFβ1	0.84	<0.001	27% (11)	5% (88)	<0.01
2. Zanello, 2014	≥34	14-18	PLAC1	0.71	<0.001	30% (43)	10% (200)	<0.0005
3. Weiner, 2022	All	16-20	NAPT	0.65	<0.005	30% (22)	10% (192)	<0.01
	<34	16-20	NAPT & APOA	0.89	<0.0001	50% (6)	10% (192)	<0.05
4. Ramussen, 2022	<37	16-27	Seven	0.82	<0.0001	59% (72)	10% (452)	<0.0001
cfmiRNA								
5. Hromadnikova, 2017	All	10-13	miR5175p	0.70	<0.05	43% (21)	14% (58)	<0.01
6. Zhang, 2017	All	12-20	miR942	0.72	<0.0001	65% (26)	31% (52)	<0.005
7. Hromadnikova, 2019	All	10-13	miR5175p	0.63	<0.05	28% (43)	10% (102)	<0.01
			miR520a5p	0.70	<0.0005	42% (43)	10% (102)	<0.0001
			miR5255p	0.70	<0.0005	40% (43)	10% (102)	<0.0001
			All three	0.72	<0.001	44% (43)	10% (102)	<0.0001
cfmRNA and non-coding								
8. Moufarrej, 2022	All	5-16	Eighteen	0.72	NR	46% (36)	10% (96)	<0.0001
	<37	5-16	Eighteen	0.81	NR	55% (12)	10% (93)	<0.0001

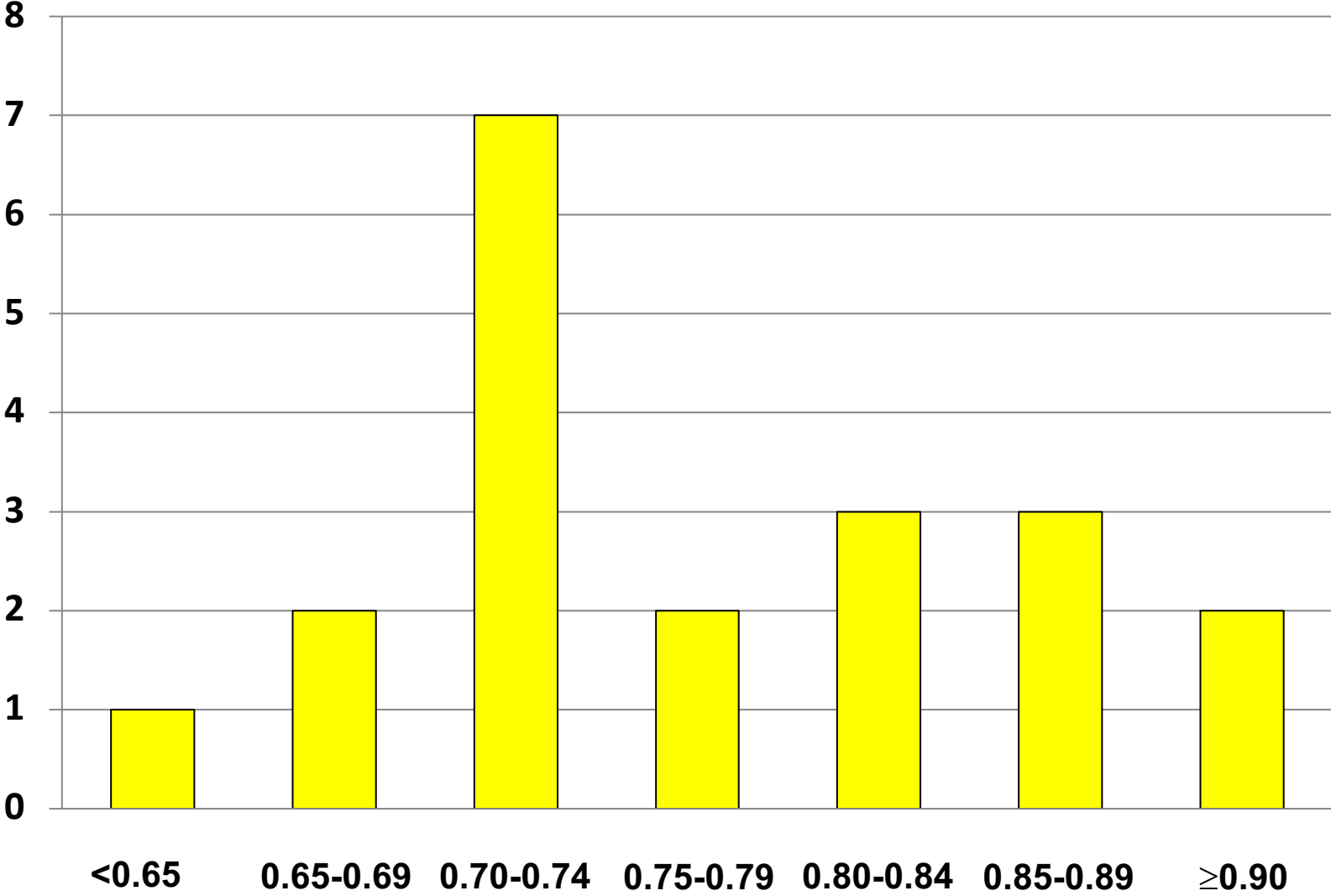
cfRNA: DR & FPR

	PE (wks)	Blood (wks)	Markers	DR (n)	FPR (n)	P
cfmRNA						
1. Tarca, 2021	<34	11-17	MMP11, SLC6A2, III18BP	83% (12)	6% (32)	<0.0001
cfmiRNA						
2. Murakami, 2018	All	<20	miR5153p	85% (13)	7% (44)	<0.0001
			miR517a	85% (13)	25% (44)	<0.0002
			miR517	100% (13)	20% (44)	<0.0001
			miR518b	100% (13)	25% (44)	<0.0001

Combined: AUC, DR & FPR

	PE (wks)	Blood (wks)	AUC	P	DR (n)	FPR (n)	P
1. De Borre, 2023							
cfDNAme pattern	<34	10-15	0.75	<0.0001	38% (61)	10% (136)	<0.0001
Prior risk			0.80	<0.0001	28% (61)	10% (136)	<0.002
Combined			0.85	<0.0001	57% (61)	10% (136)	<0.0001
2. Kim, 2016							
Total cfDNA, HYP2	All	1T	0.68	<0.05	45% (14)	10% (53)	<0.005
					33% (14)	5% (53)	<0.005
MS-PAPP-A			0.70	<0.0005	34% (14)	10% (53)	<0.05
					23% (14)	5% (53)	<0.05
Combined			0.82	<0.0001	65% (14)	10% (53)	<0.0001
					47% (14)	5% (53)	<0.0001
3. Weiner, 2022							
cfmRNA, NAPT	All	16-20	0.65	<0.005	30% (22)	10% (192)	<0.01
MAP			0.68	<0.001	31% (22)	10% (192)	<0.005
Combined			0.77	<0.0001	38% (22)	10% (192)	<0.0005
cfmRNA, NAPT & APOA1	<34	16-20	0.89	<0.0001	50% (6)	10% (192)	<0.05
MAP			0.73	<0.01	33% (6)	10% (192)	0.07
Combined			0.92	<0.0001	67% (6)	10% (192)	<0.0001

Reported AUC



Combined: AUC, DR & FPR

	PE (wks)	Blood (wks)	AUC	P	DR (n)	FPR (n)	P
1. De Borre, 2023							
cfDNAme pattern	<34	10-15	0.75	<0.0001	38% (61)	10% (136)	<0.0001
Prior risk			0.80	<0.0001	28% (61)	10% (136)	<0.002
Combined			0.85	<0.0001	57% (61)	10% (136)	<0.0001
2. Kim, 2016							
cfDNA, HYP2	All	1T	0.68	<0.05	45% (14)	10% (53)	<0.005
					33% (14)	5% (53)	<0.005
Maternal serum PAPP-A			0.70	<0.0005	34% (14)	10% (53)	<0.05
					23% (14)	5% (53)	<0.05
Combined			0.82	<0.0001	65% (14)	10% (53)	<0.0001
					47% (14)	5% (53)	<0.0001
3. Weiner, 2022							
cfmRNA, NAPT	All	16-20	0.65	<0.005	30% (22)	10% (192)	<0.01
MAP			0.68	<0.001	31% (22)	10% (192)	<0.005
Combined			0.77	<0.0001	38% (22)	10% (192)	<0.0005
cfmRNA, NAPT & APOA1	<34	16-20	0.89	<0.0001	50% (6)	10% (192)	<0.05
MAP			0.73	<0.01	33% (6)	10% (192)	0.07
Combined			0.92	<0.0001	67% (6)	10% (192)	<0.0001



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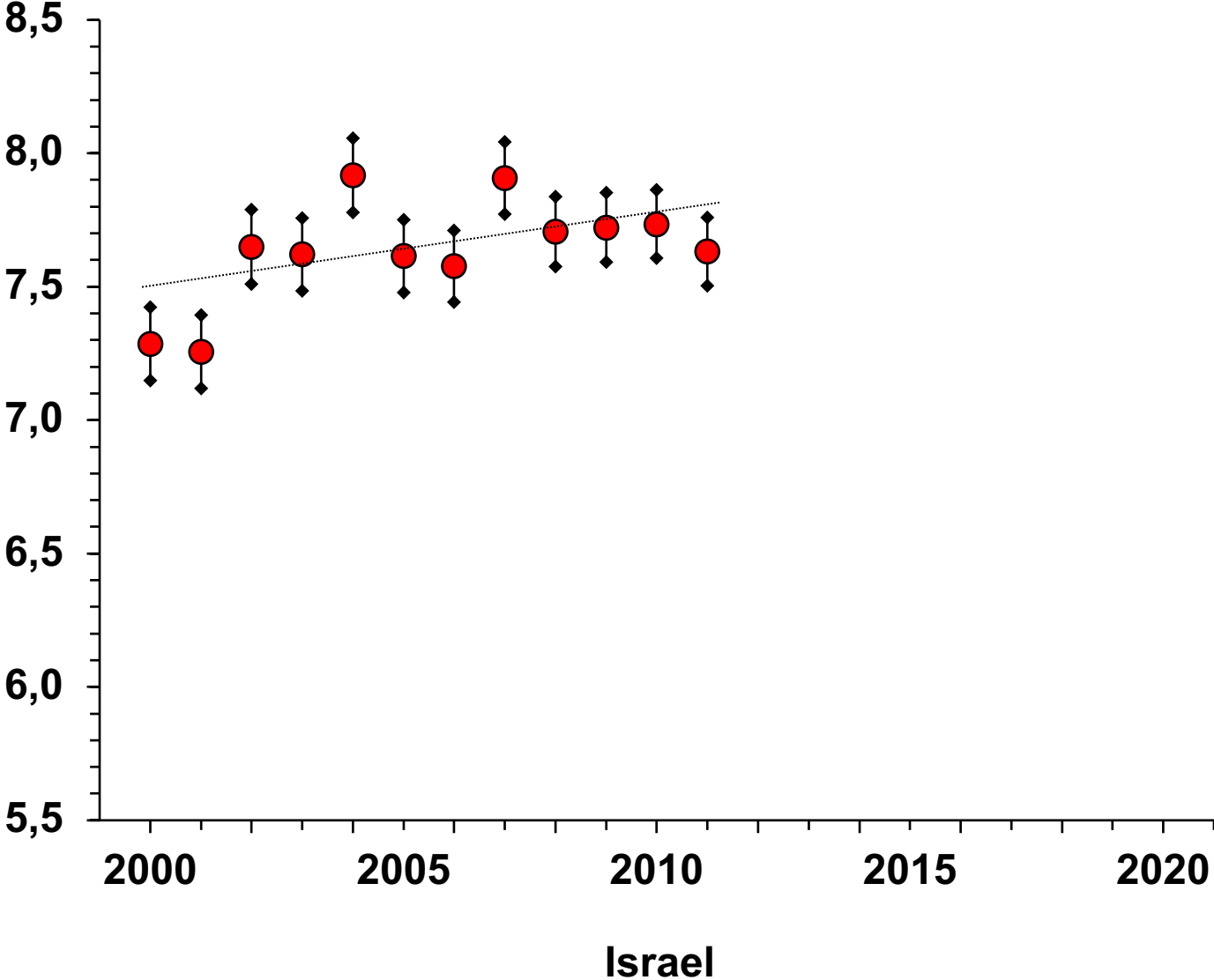
ENP / INBON



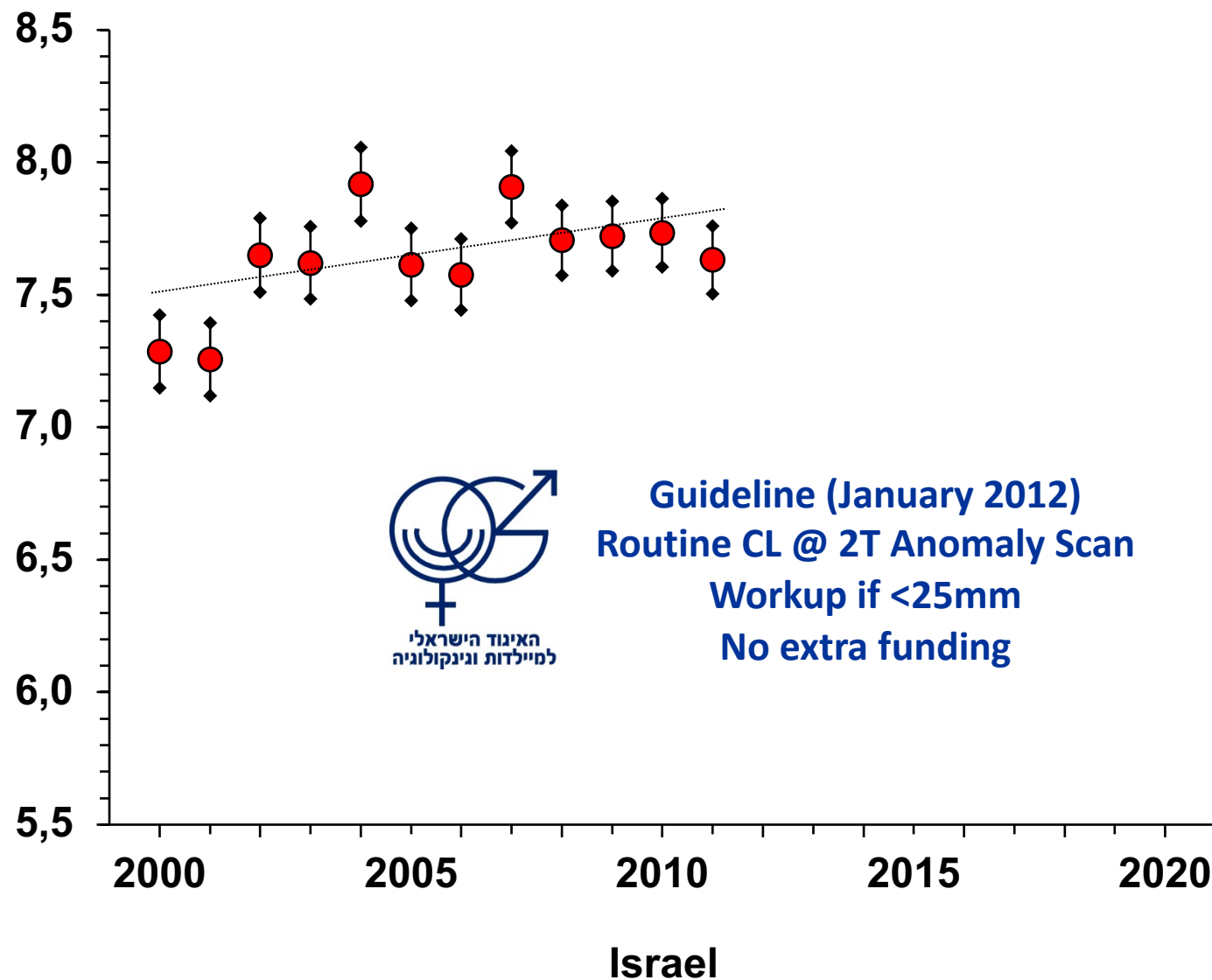
Cervical length



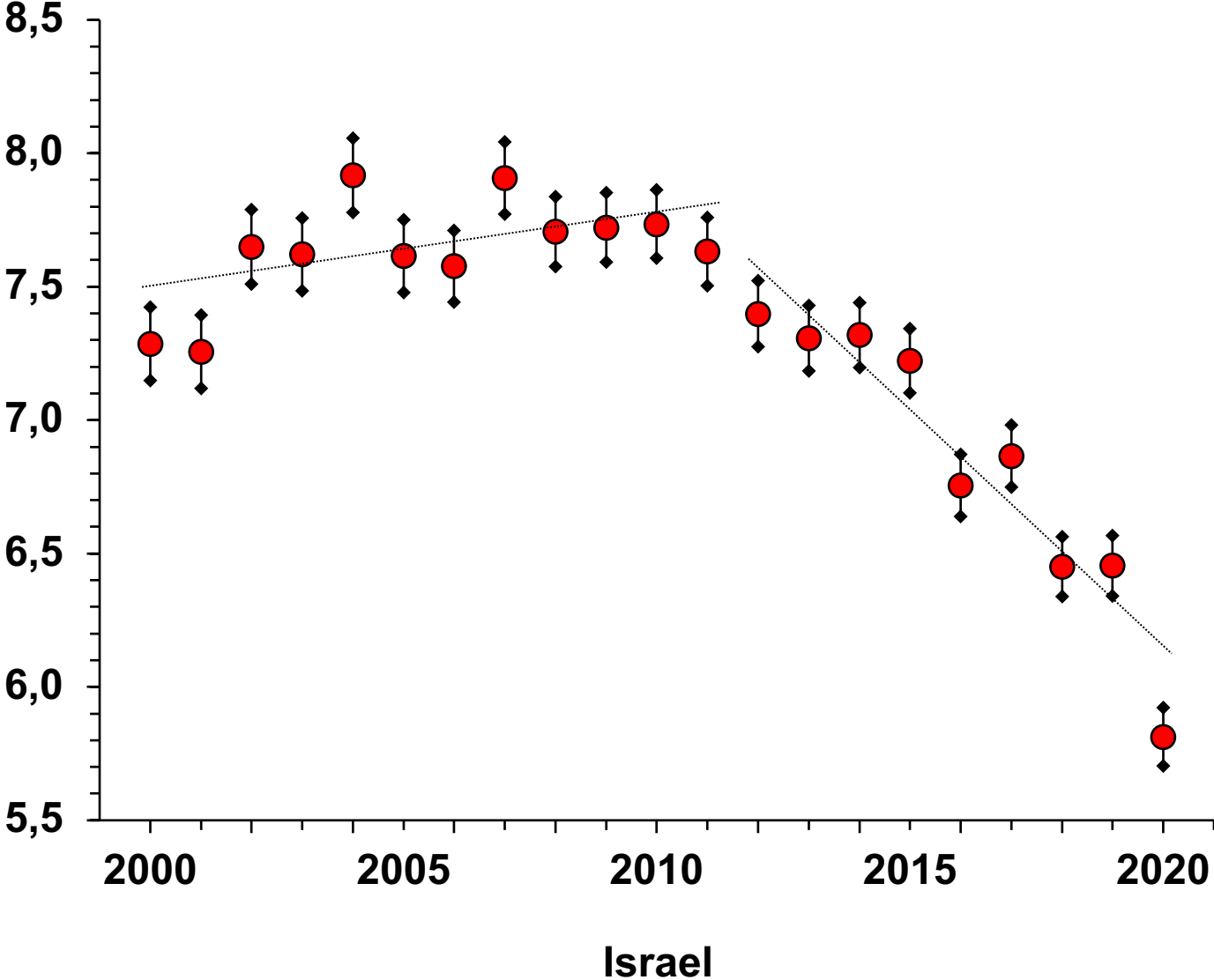
PTB prevalence (%)



PTB prevalence (%)



PTB prevalence (%)





Total cfDNA

1/1 increased

cffDNA

1/3 increased

Fetal fraction

2/6 reduced

cfRNA: AUC, DR & FPR

	PTB (wks)	Blood (wks)	Markers	AUC	P	DR (n)	FPR (n)	P
cfmRNA								
1. Camunas-Soler, 2022	<35	12-23	Twenty five	0.80	<0.0001	76% (46)	8% (194)	<0.0001
2. Weiner, 2022	<37	16-20	PSME2, Let7g	0.58	<0.05	21% (73)	10% (192)	<0.02
	≤32	16-20	PSME2, Let7g	0.76	<0.0001	50% (30)	10% (192)	<0.0001
3. Weiner, 2023	≤32	12-14	PSME2, APOA1	0.72	<0.001	41% (40)	10% (20)	<0.02
cfmiRNA								
4. Hromadnikova, 2022	<37	10-13	Six	0.81	<0.001	53% (41)	10% (80)	<0.0001



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