The Predictors Studies (1, 2 & 3)

A comparison of tests for high grade CIN in women with abnormal smears and in a screening population

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Aim

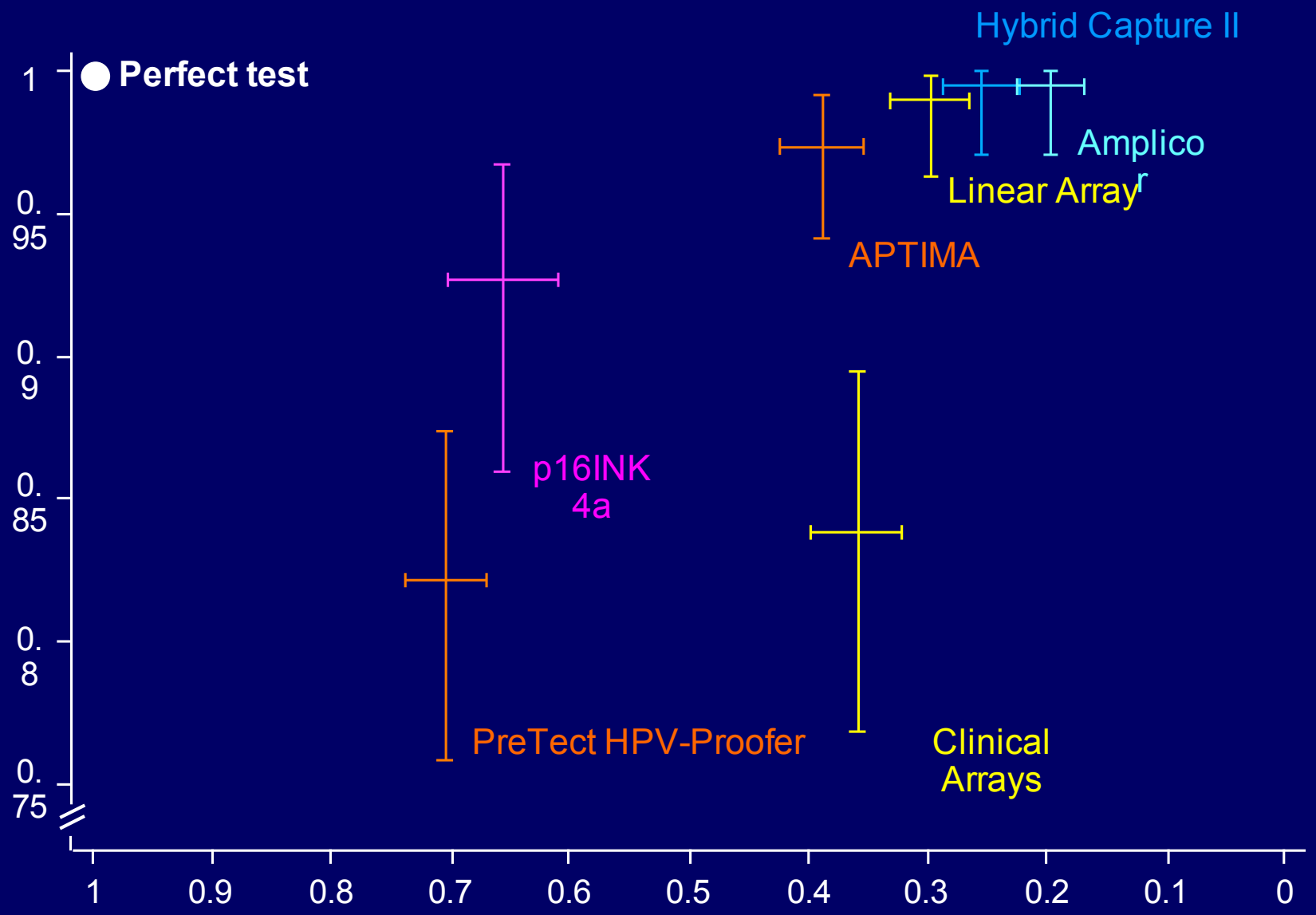
To evaluate and compare the sensitivity and specificity of several adjunctive tests for the detection of high-grade disease (CIN2+ and CIN3+) in a referral population

Tests evaluated – Predictors 1

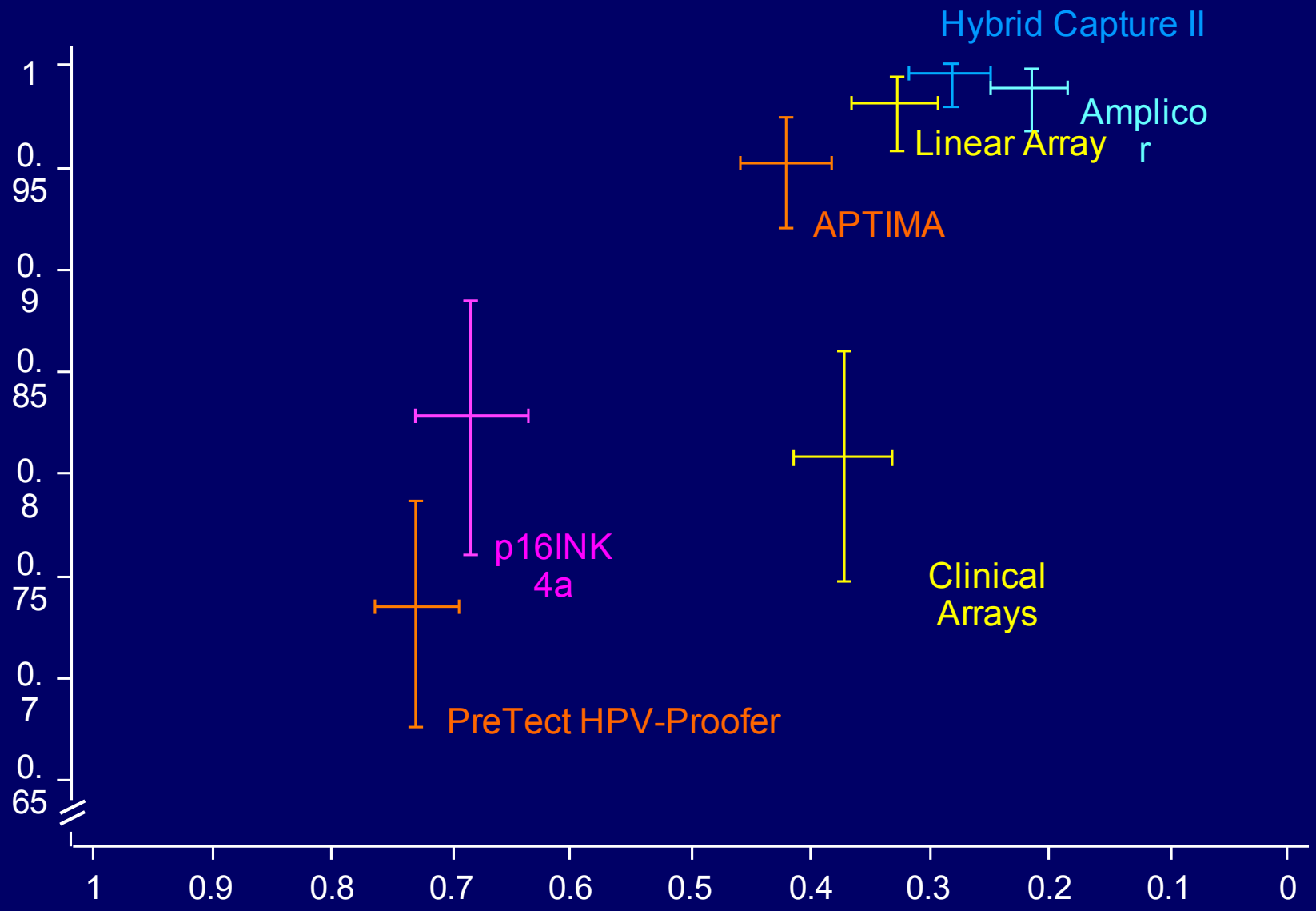
(From a liquid PreservCyt® sample)

- Hybrid Capture II (Digene)
- Amplicor (Roche)
- PreTect HPV-Proofer (NorChip)
- APTIMA HPV assay (Gen-Probe)
- Linear Array (Roche)
- Clinical Arrays (Genomica)
- p16INK4a immunocytochemistry (MTM) (on a subset)

Summary graph – Detection of CIN3+



Summary graph – Detection of CIN2+



Tests evaluated – Predictors 2

Repeat Cytology

DNA-Based Detection Assays

Hybrid Capture II (Qiagen)

Partial Typing tests

Cobas (Roche)

Real-time PCR (Abbott)

BD HPV test (BD)

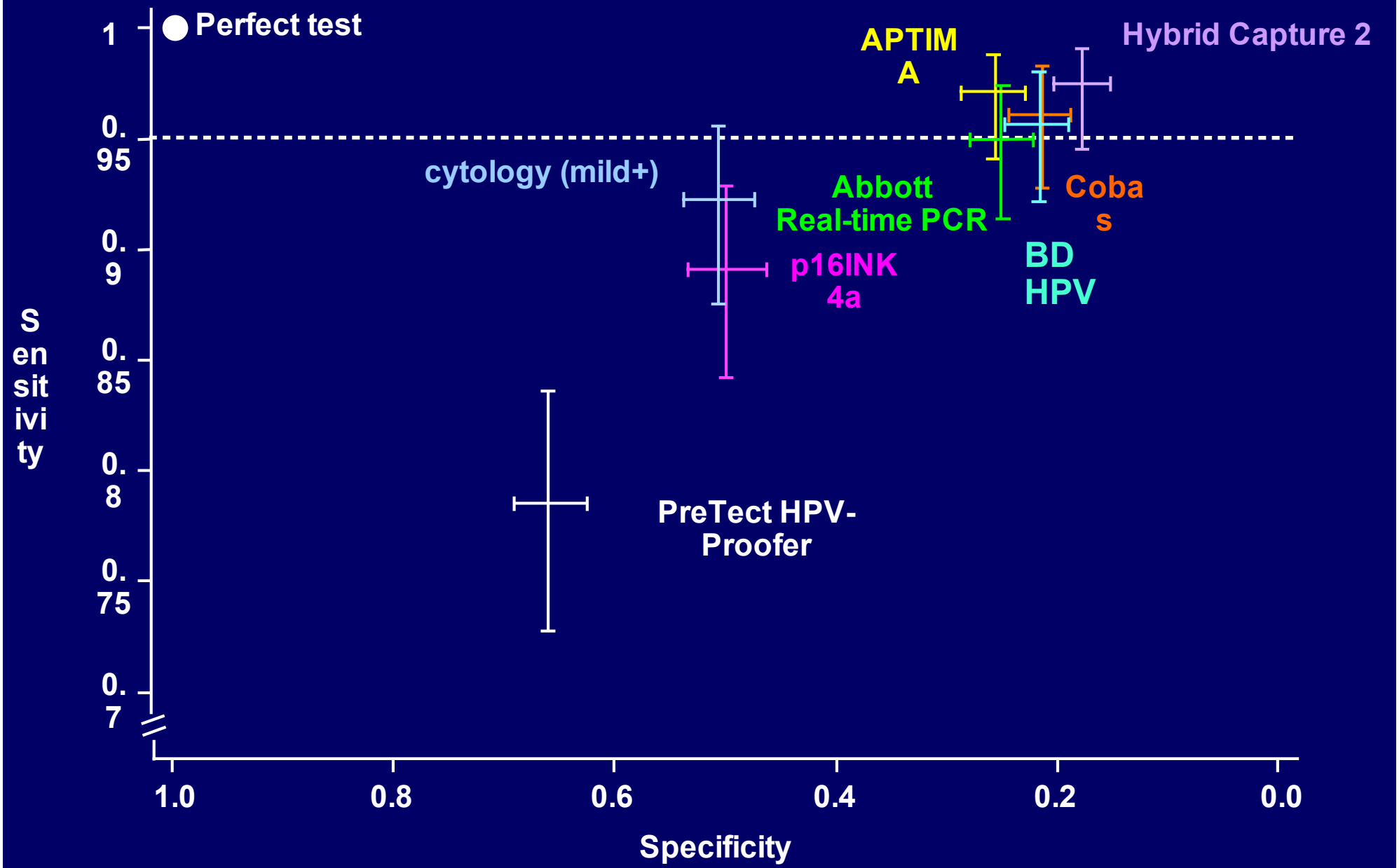
RNA-Based Detection Assays

PreTect HPV-Proofer (Norchip)

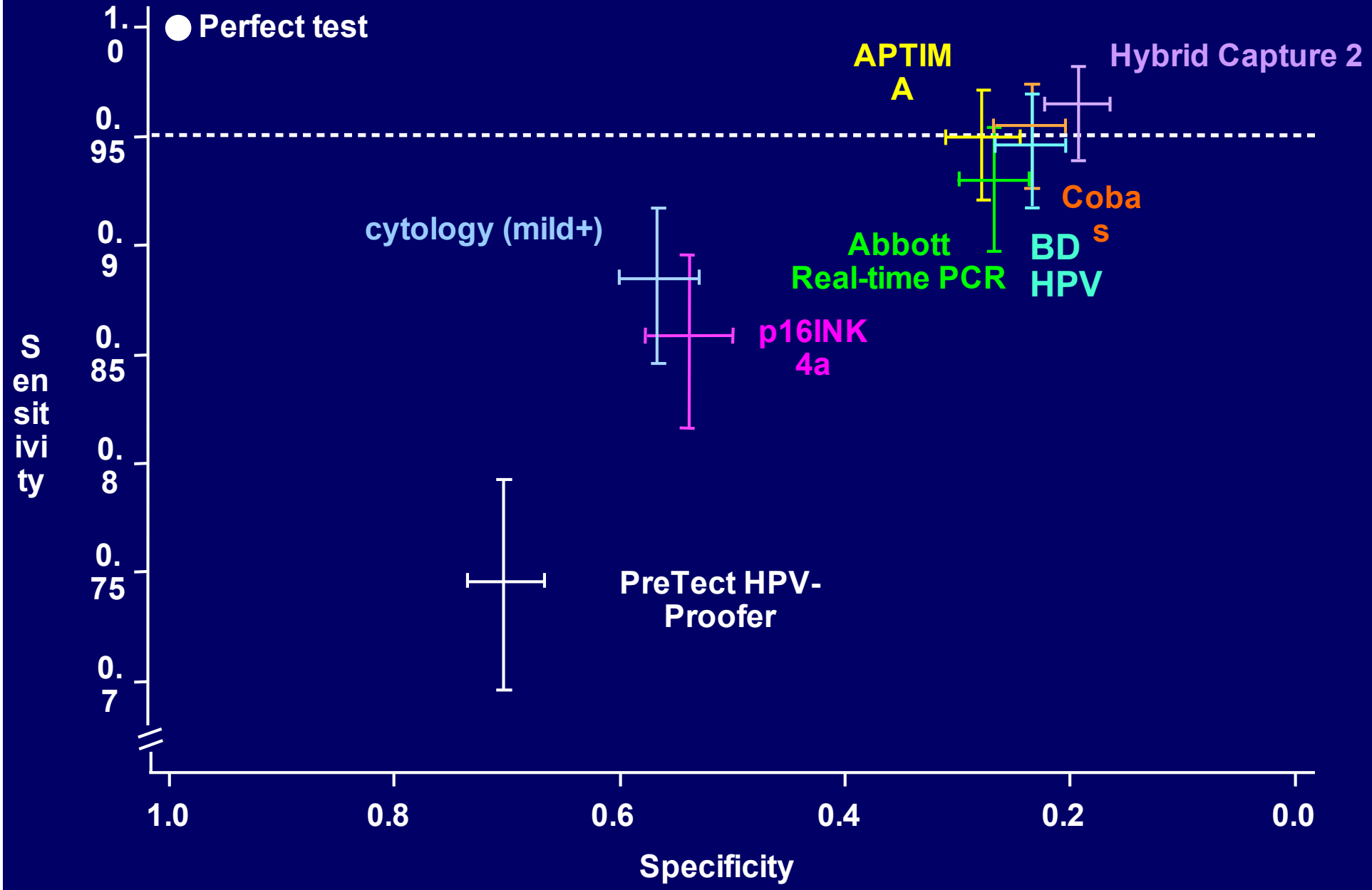
APTIMA (Gen-Probe)

p16INK4a (mtm)

Summary graph – Detection of CIN3+



Summary graph – Detection of CIN2+



Kappa and Discordant Pairs

	Hybrid Capture 2	Cobas	Real-time PCR	BD HPV	APTIMA	PreTect HPV-Proofer	p16INK4a
Hybrid Capture 2	-	0.64	0.65	0.67	0.69	0.20	0.23
Cobas	(69, 35)* 2.0 (1.3, 3.1)	-	0.86	0.87	0.73	0.26	0.25
Real-time PCR	(88, 21) 4.2 (2.6, 7.1)	(39, 8) 4.9 (2.2, 12.1)	-	0.87	0.77	0.30	0.28
BD HPV	(67, 28) 2.4 (1.5, 3.9)	(22, 19) 1.2 (0.6, 2.3)	(8, 37) 0.2 (0.1, 0.5)	-	0.78	0.27	0.25
APTIMA	(83, 13) 6.4 (3.5, 12.5)	(63, 28) 2.3 (1.4, 3.6)	(43, 39) 1.1 (0.7, 1.7)	(55, 22) 2.5 (1.5, 4.3)	-	0.29	0.32
PreTect HPV-Proofer	(438, 11) 39.8 (22.0, 80.4)	(405, 8) 50.6 (25.4, 118.1)	(378, 13) 29.1 (16.8, 55.1)	(404, 9) 44.9 (23.4, 98.9)	(380, 18) 21.1 (13.2, 36.0)	-	0.26
p16INK4a	(294, 33) 8.9 (6.2, 13.2)	(273, 46) 5.9 (4.3, 8.3)	(255, 59) 4.3 (3.2, 5.8)	(272, 49) 5.6 (4.1, 7.7)	(246, 51) 4.8 (3.6, 6.7)	(117, 250) 0.5 (0.4, 0.6)	-

Kappa and Discordants for HPV 16

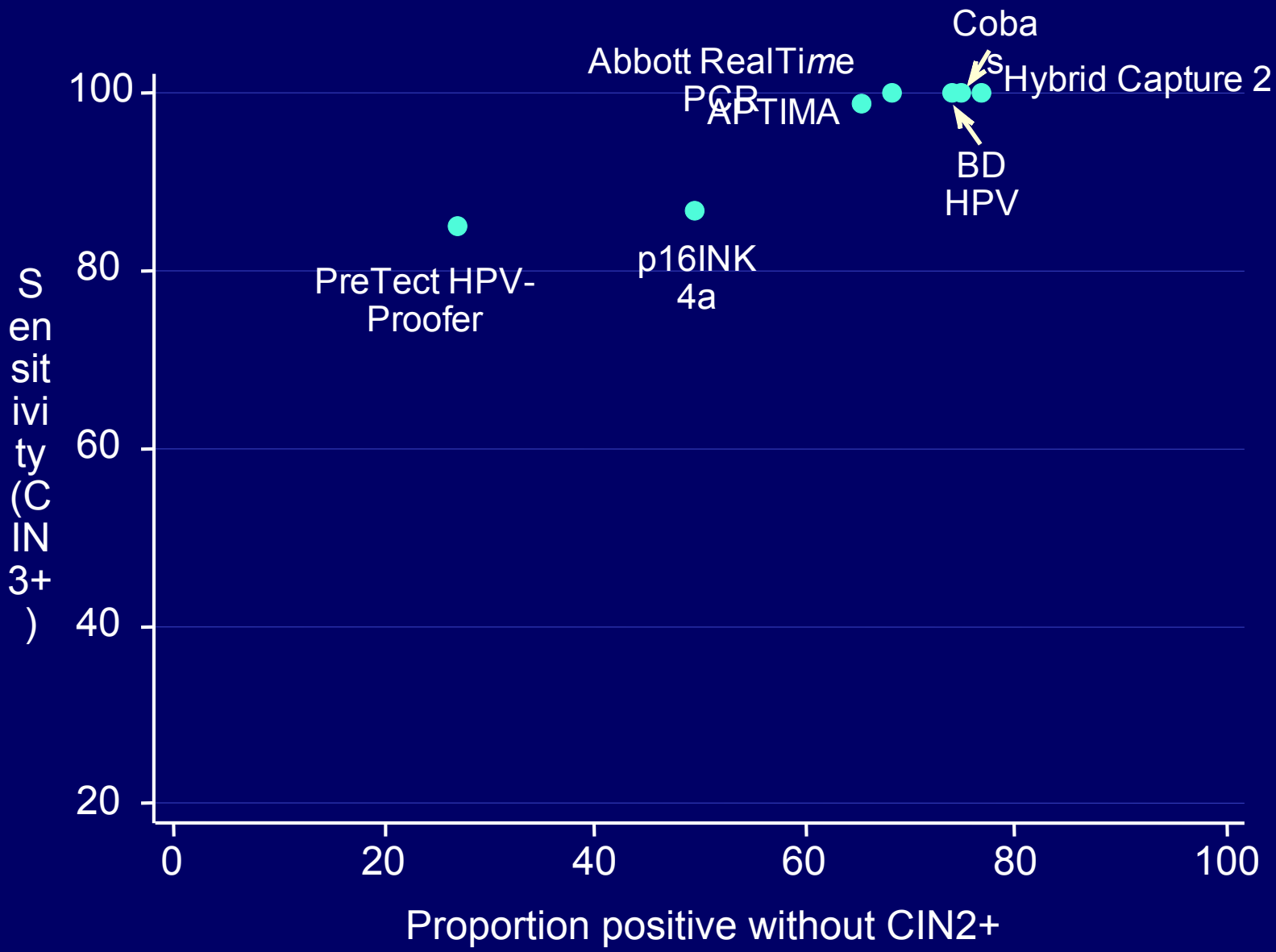
	Cobas	Real-time PCR	BD HPV	APTIMA	PreTect HPV-Proofer
Cobas	-	0.96	0.96	0.94	0.76
Real-time PCR	(16, 2)* 8.0 (1.9, 71.7)	-	0.96	0.94	0.78
BD HPV	(16, 2) 8.0 (1.9, 71.7)	(10, 10) 1.0 (0.4, 2.7)	-	0.96	0.79
APTIMA	(22, 4) 5.5 (1.9, 22.0)	(14, 9) 1.6 (0.6, 4.1)	(11, 7) 1.6 (0.6, 4.8)	-	0.78
PreTect HPV-Proofer	(67, 37) 1.8 (1.2, 2.8)	(54, 38) 1.4 (0.9, 2.2)	(53, 37) 1.4 (0.9, 2.2)	(48, 37) 1.3 (0.8, 2.0)	-

Results restricted to low grade cytology

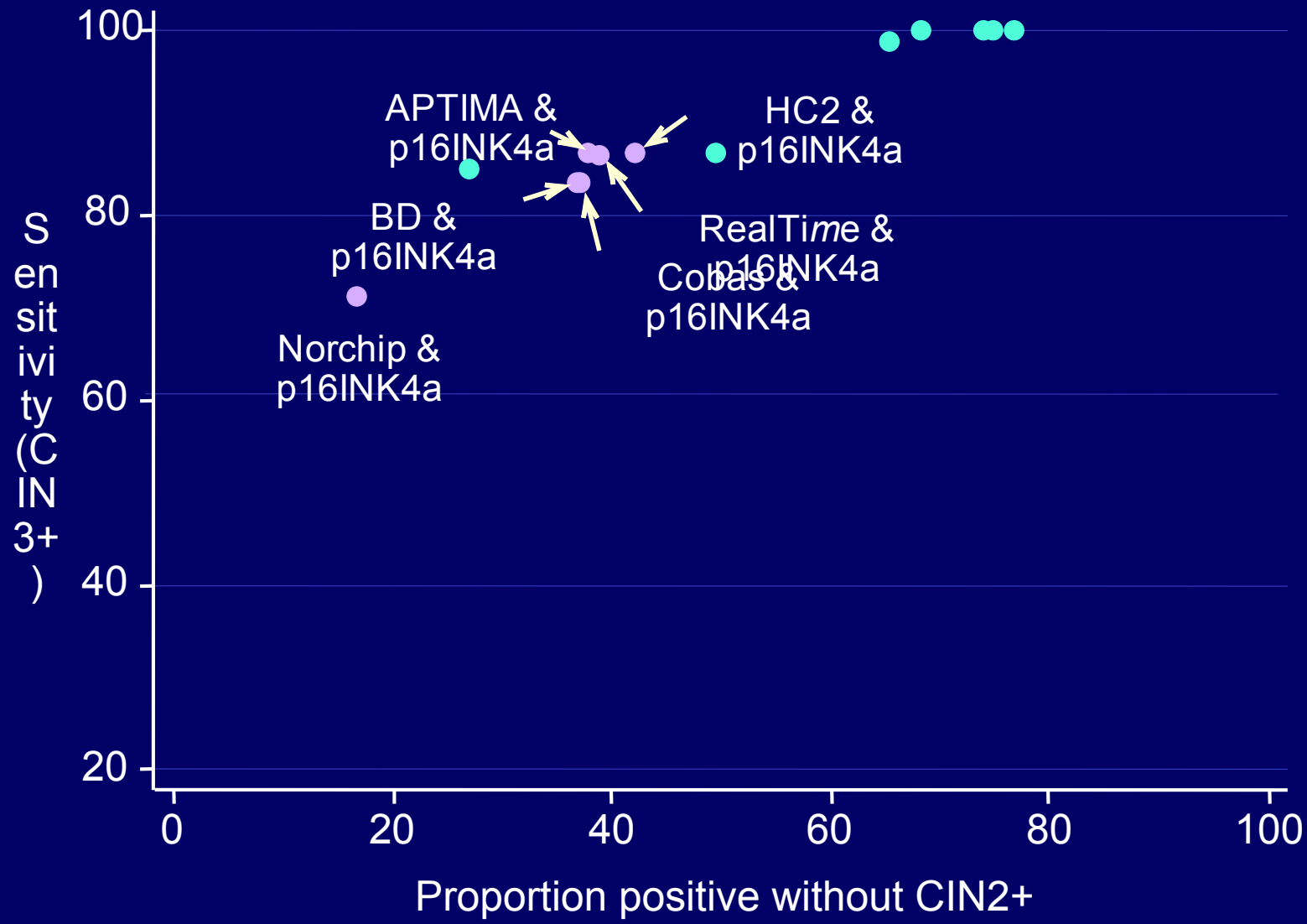
It is well established that low grade cytology has poor positive predictive value

Triage tests are needed to improve specificity to minimise over-referral
(including HPV DNA, HPV RNA, HPV typing and p16 tests)

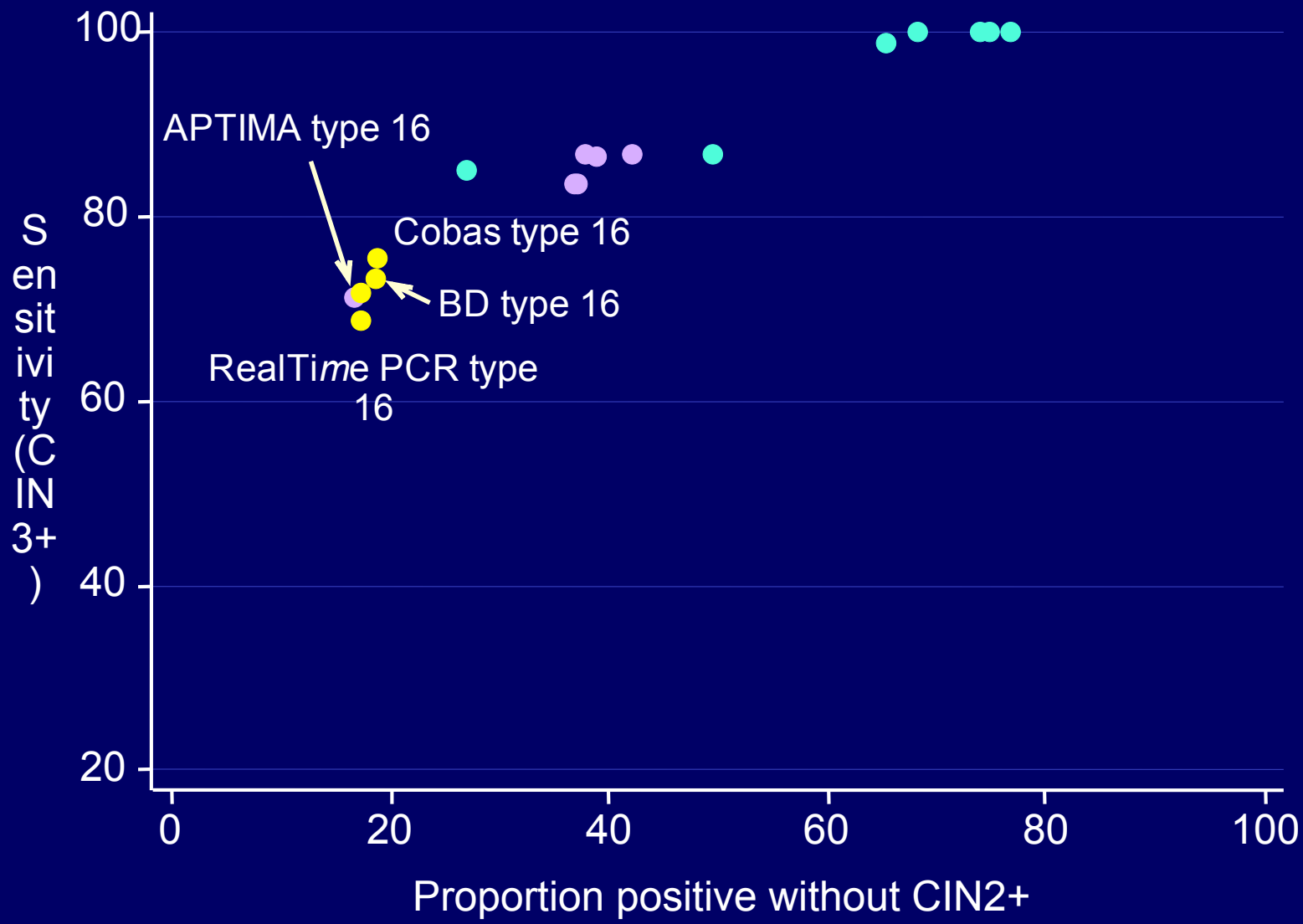
Individual Tests



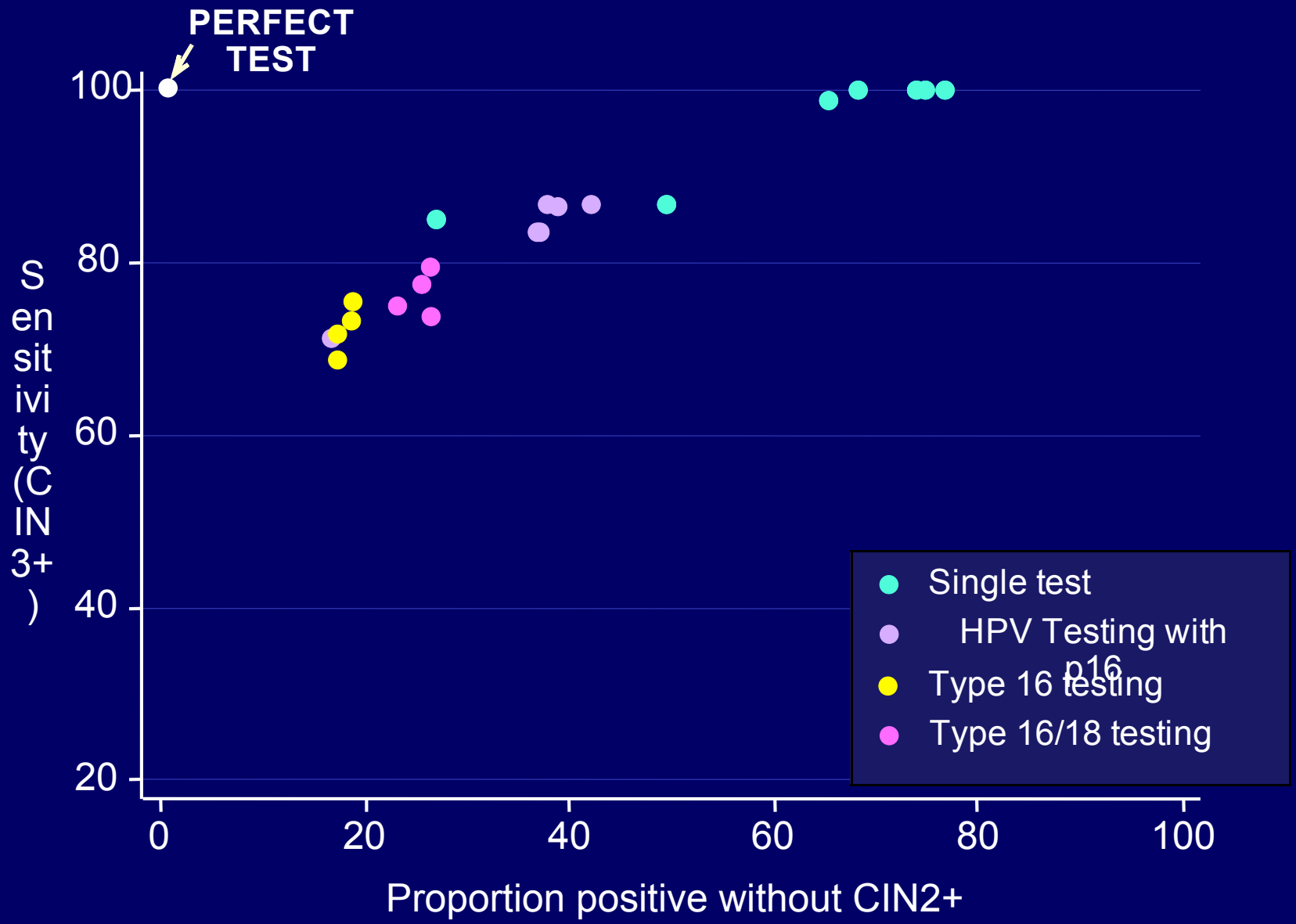
HPV tests plus p16



HPV type 16


100
80
60
40
20
Sensitivity (CIN 3+)
APTIMA type 16
Cobas type 16
BD type 16
RealTime PCR type 16
0
20
40
60
80
100
Proportion positive without CIN2+

HPV 16 alone or 16/18 typing



Conclusions

- **Five HPV tests had a very high sensitivity when considered in a triage setting**
  - **(Abbott RealTi*me* PCR, Hybrid Capture 2, Cobas, BD HPV, APTIMA)**
- **These highly sensitive tests could reduce the number of referrals to colposcopy by 20 - 30%**
- **Other triage strategies could reduce the number of unnecessary referrals further but missing between 15 – 30% of CIN3+**
  - **Such strategies would need to be combined with early recall**

A comparison of HPV tests in a Screening Population

The Predictors study

Phase 3

Aim

To evaluate and compare the sensitivity and specificity of several adjunctive tests for the detection of high-grade disease (CIN2+ and CIN3+) in a screening population

Methods

Residual material from a PreservCyt screening sample in 6000 women attending for routine screening

- All samples received in one cytology lab from October 2009 to May 2010
- Results not used for patient management
- No pathology review or follow up of HPV positive / cytology negative women

Worst (local) histology

	Freq.	%
Not taken	5,881	98.0
Unsatisfactory	1	0.02
Normal	2	0.03
HPV only	38	0.6
Borderline	2	0.03
CIN I	36	0.6
CIN II	21	0.4
CIN III	17	0.3
CGIN high grade	1	0.02
Invasive squamous carcinoma	1	0.02
TOTAL	6,000	100.0

40 (0.7%) CIN2+

Tests Evaluated

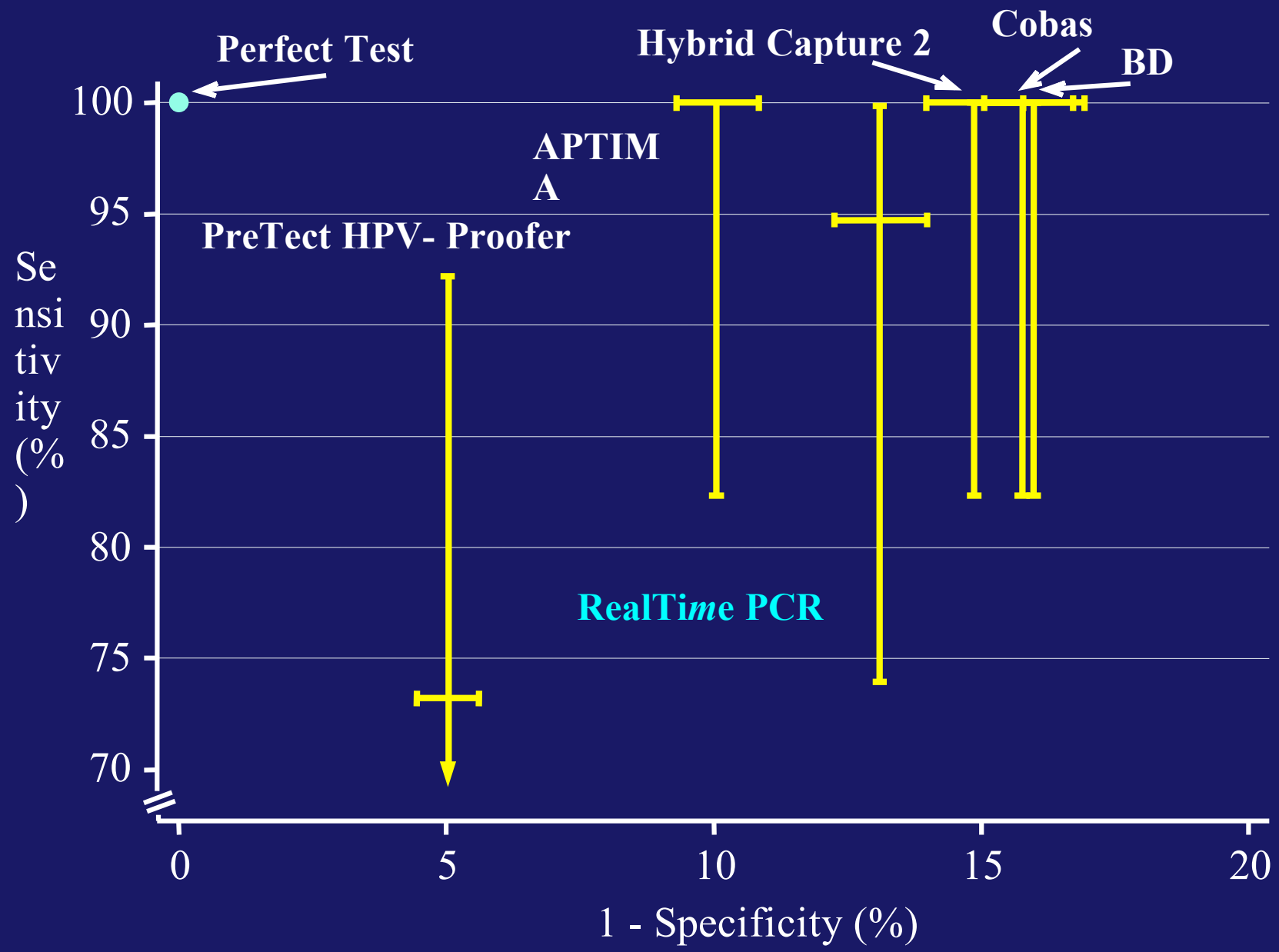
DNA-Based Detection Assays
Hybrid Capture II (Qiagen)

Partial Typing tests

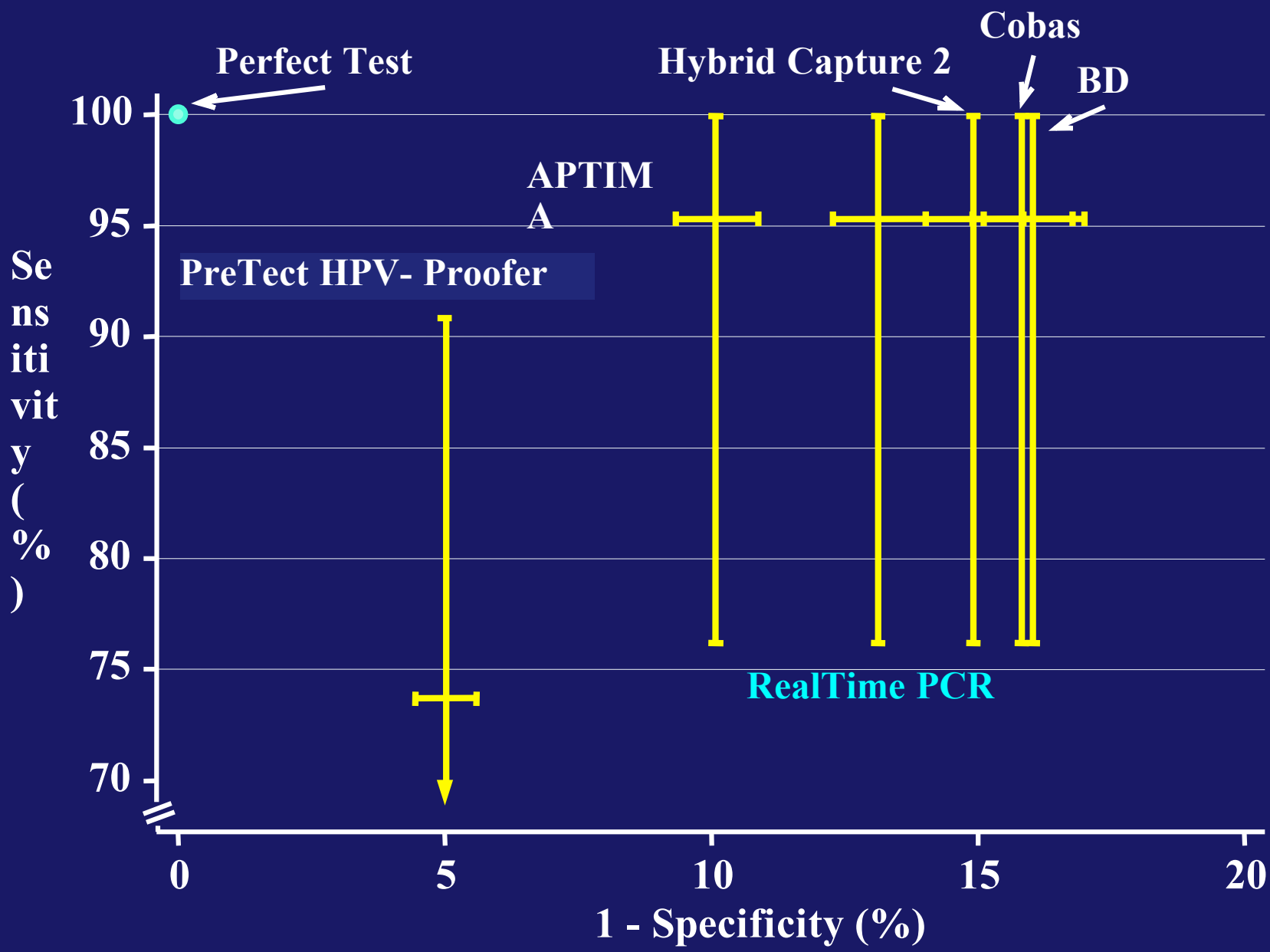
Cobas (Roche)
RealTime PCR (Abbott)
BD HPV test (BD)

RNA-Based Detection Assays
APTIMA (Gen-Probe)
PreTect HPV-Proofer (Norchip)

Summary graph - Detection of CIN3+



Summary graph - Detection of CIN2



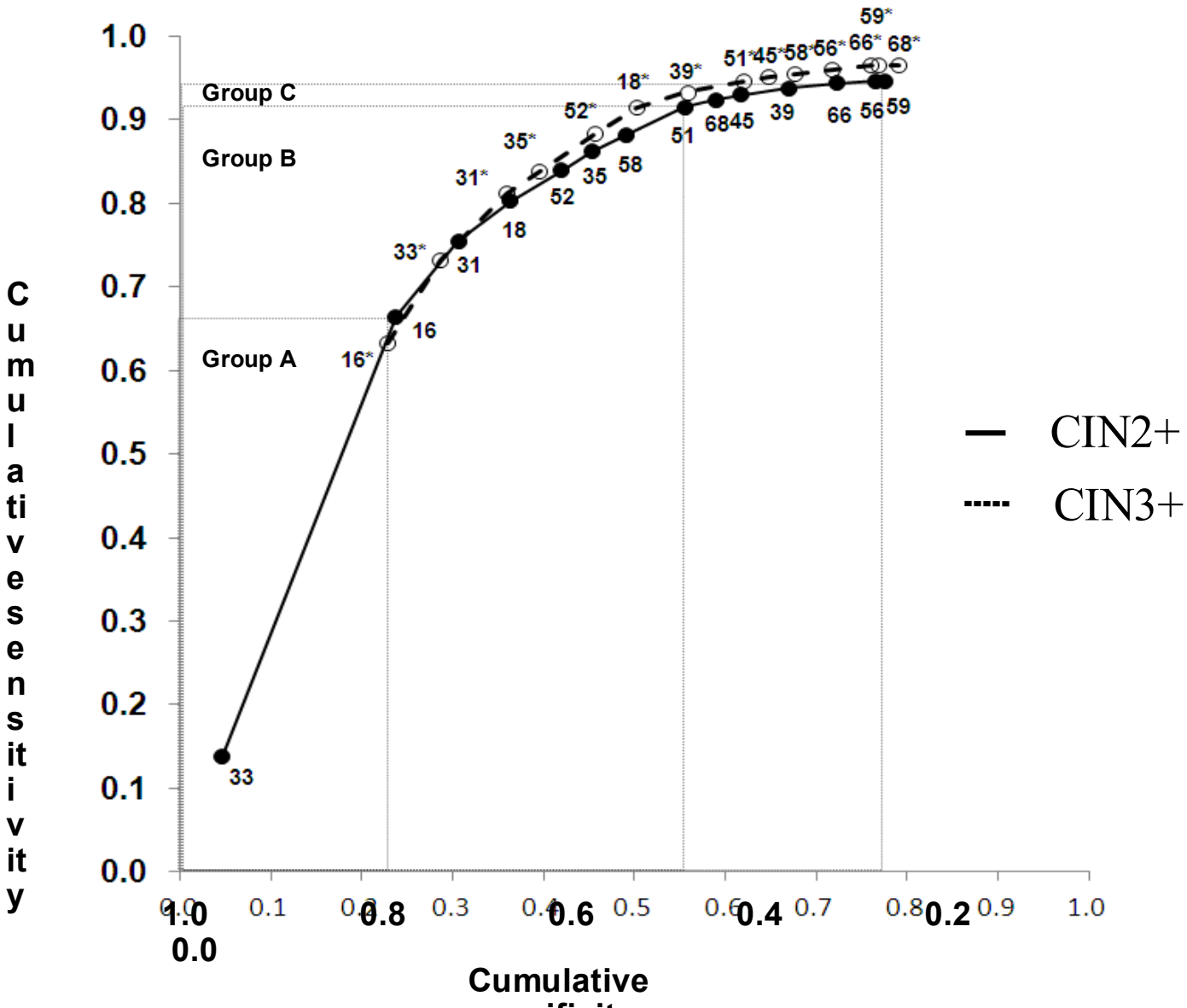
Kappas and Discordant Pairs –HPV 16

	BD HPV	Roche Cobas	Abbott Real Time PCR	Gen-Probe Aptima	Norchip PreTect HPV-Proofer
BD HPV	-	0.863	0.920	0.830	0.620
Roche Cobas	(4, 46) 0.1 (0.0, 0.2)	-	0.881	0.742	0.544
Abbott Real Time PCR	(8, 19) 0.4 (0.2, 1.0)	(38, 7) 5.4 (2.4, 14.4)	-	0.794	0.600
Gen-Probe Aptima	(45, 4) 11.3 (4.1, 43.1)	(84, 1) 84.0 (14.7, 3356.8)	(57, 5) 11.4 (4.6, 36.4)	-	0.697
Norchip PreTect HPV-Proofer	(72, 30) 2.4 (1.5, 3.8)	(112, 29) 3.9 (2.5, 6.0)	(83, 30) 2.8 (1.8, 4.4)	(36, 34) 1.1 (0.6, 1.7)	-

HPV Screening Strategies

Role of Typing

ROC curve of cumulative sensitivity and specificity genotypes are ordered according to PPV



3 Groups According to PPV
Based on referral patients

- Group A - Types 16 & 33
  - Very High Risk
- Group B - Types 31,18*, 52, 35, 58
  - High Risk
  - Type 18 important due to endocervical lesions
- Group C - Types 51, 68, 45*, 39, 66,56, 59
  - Intermediate Risk