Using all the data: Immunoassay signal-to-cutoff values provide useful information that should be considered in HIV diagnostic algorithms

KP Delaney, M Pentella, B Bennett, and K Landgraf for the CDC/APHL HIV Steering Committee

The findings and conclusions in this presentation are those of the authors and do not necessarily represent the views of the Centers for Disease Control and Prevention or the Association of Public Health Laboratories

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Michele Owen

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Debra Candal

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PHLs

Sheryl Coons

Missouri DOH and Senior Services

Brian Louie

SF Public Health Laboratory

Kay Hermon

Kansas DHEKS

Arthur Kazianis

MA Hinton State Laboratory

Berry Bennett

FL Bureau of Laboratories

Outline

- Background
- Study objectives
- Methods
- Lots of results
- A few conclusions
- Next steps

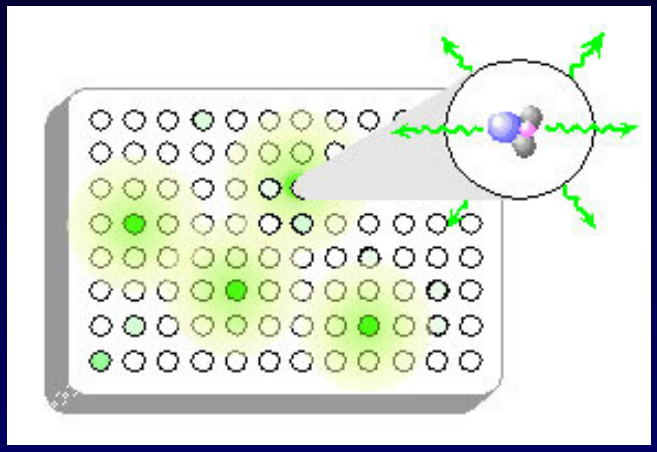
Background: ‘S/CO’?

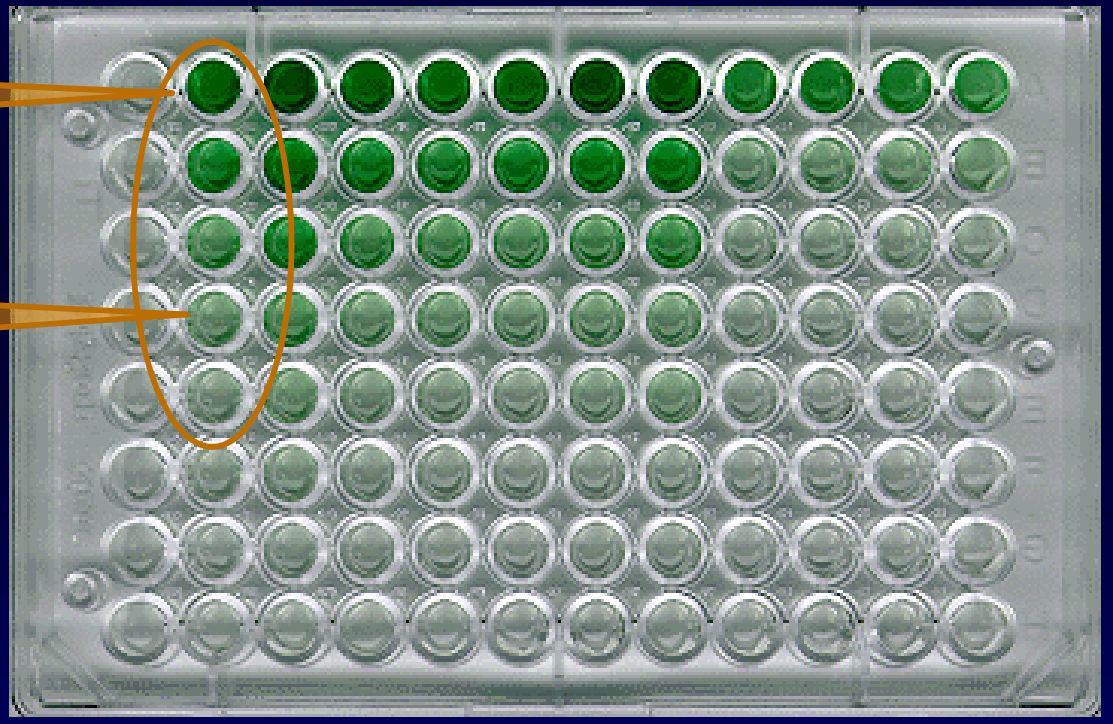
What do we mean by S/CO?

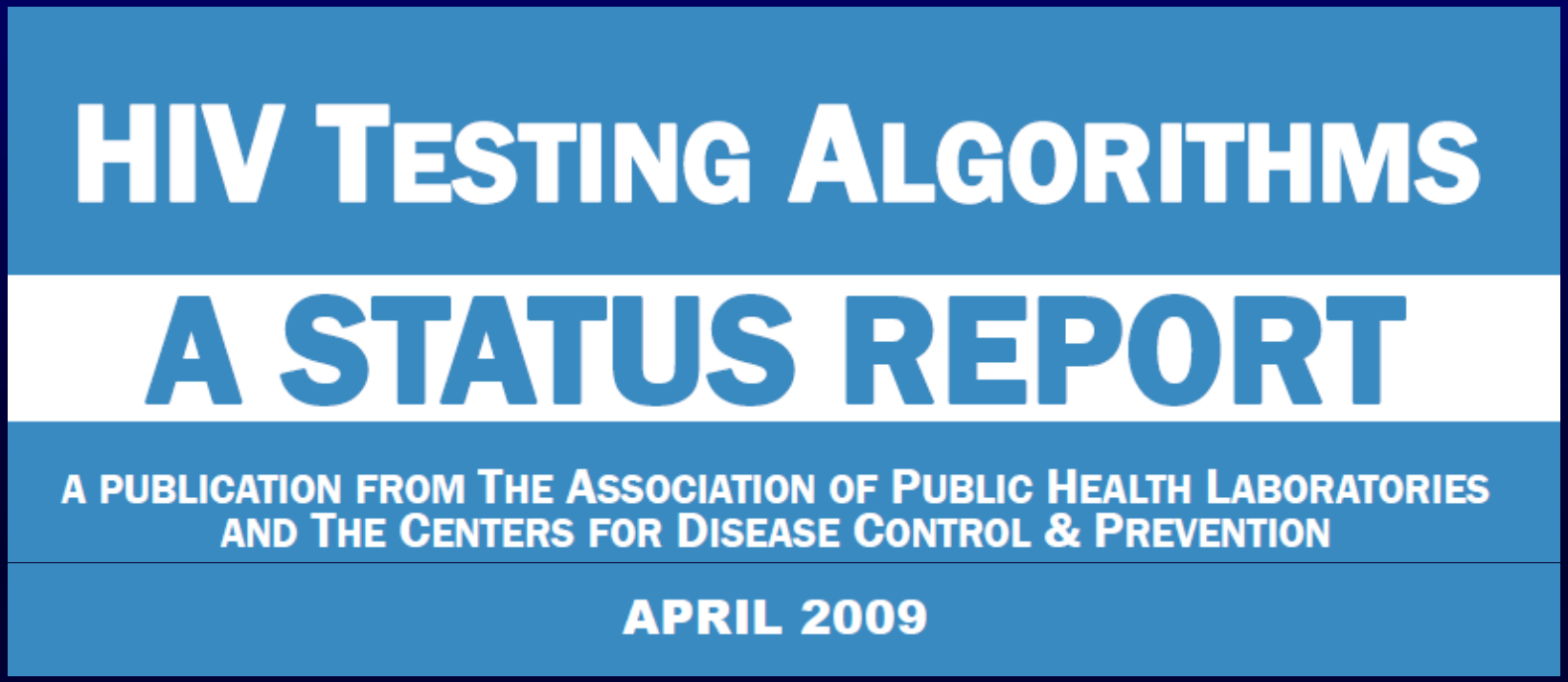
Signal-to-Cutoff

Is there a difference between this?

And this?

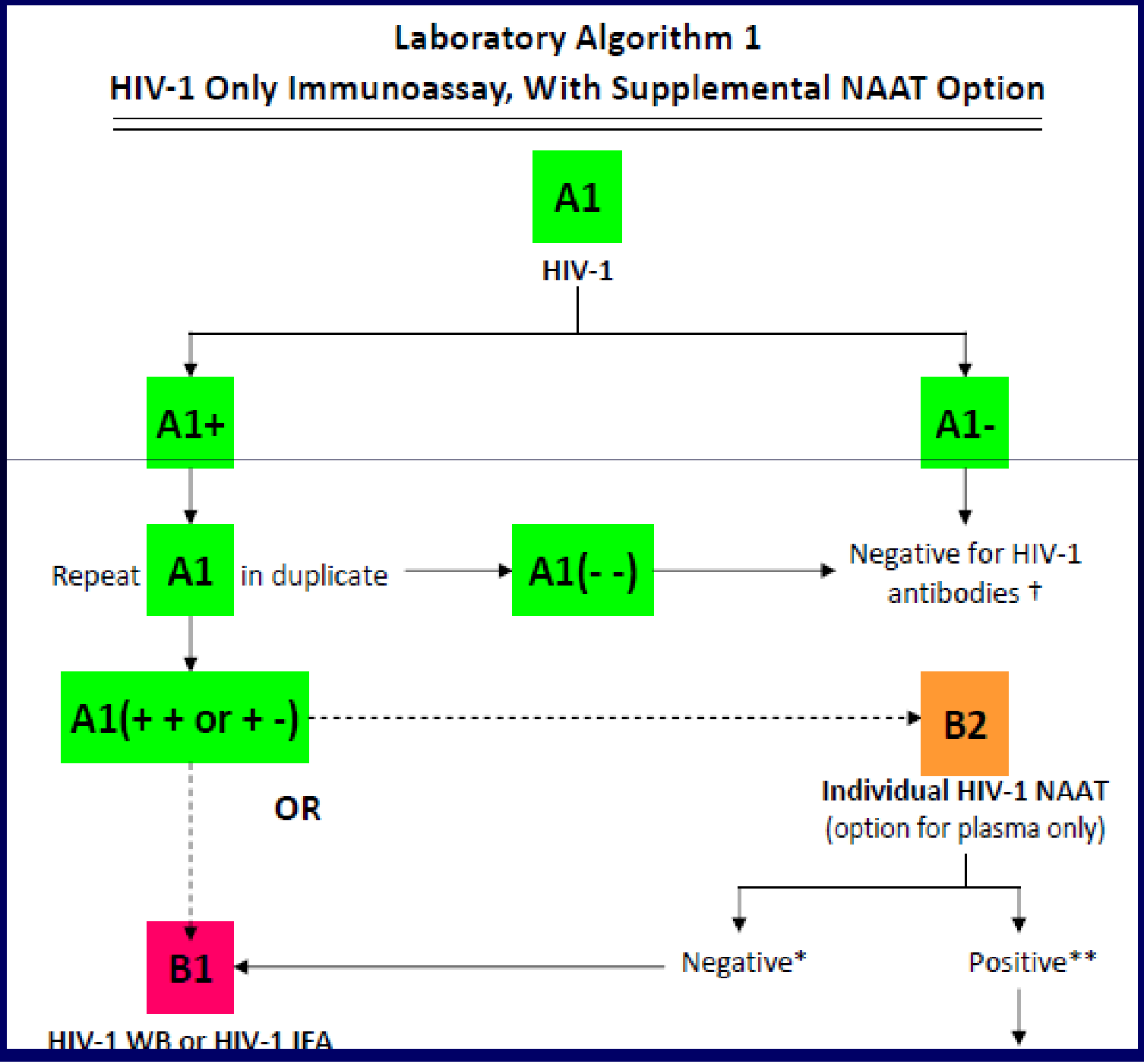




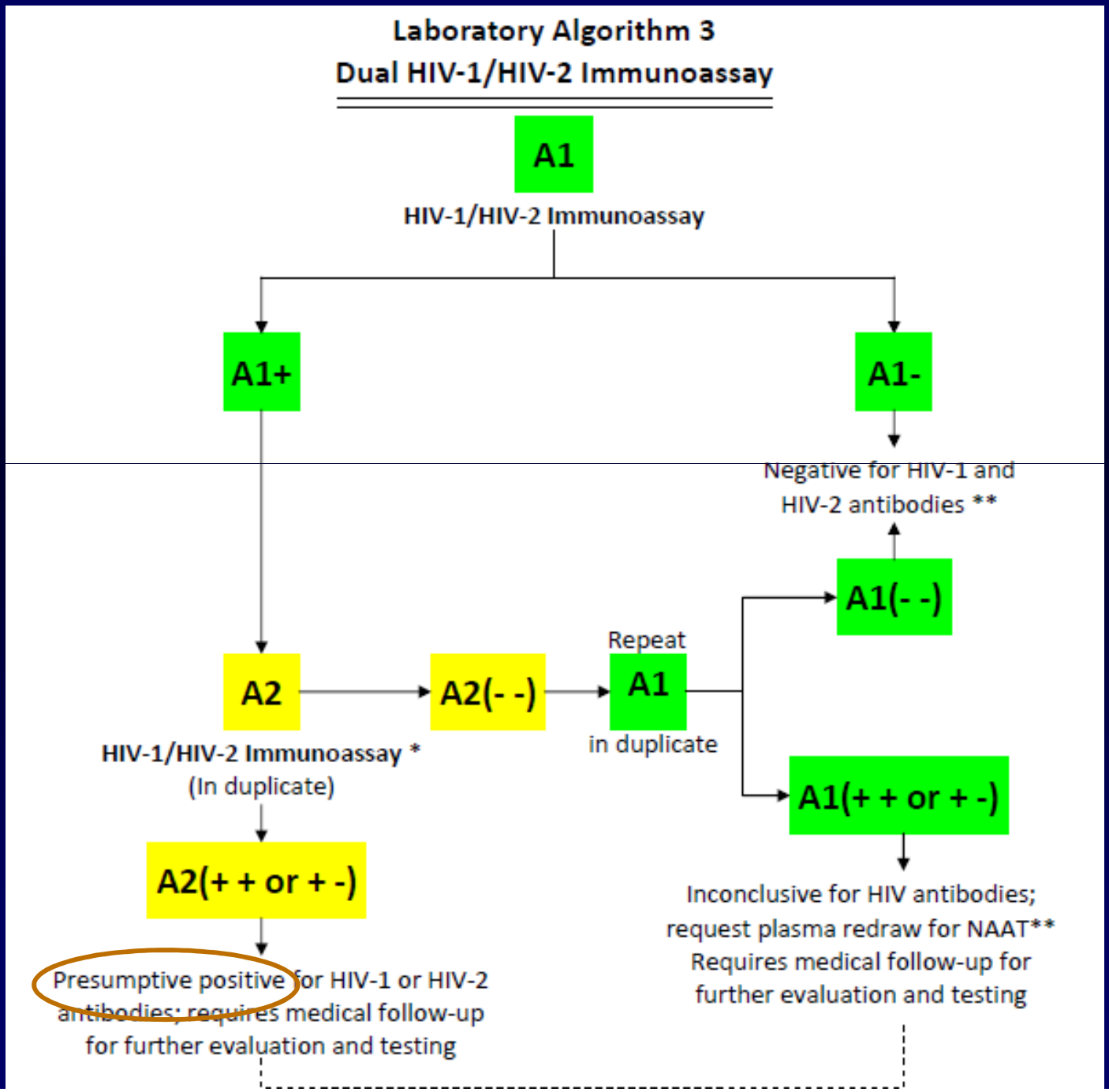


- The “Status Report” provides 3 algorithms incorporating laboratory-based immunoassays (IAs)
  - Also lists data needs ‘to validate’ the algorithms

Current (as of 1989) algorithm



Proposed laboratory algorithm 3



Status report data needs

- S/CO values for initially-reactive A1 and for repeat testing *(LA 1&2)*
- S/CO values for both A1 and A2 to validate whether this additional information can be used to improve interpretation of the algorithm *(LA 3)*

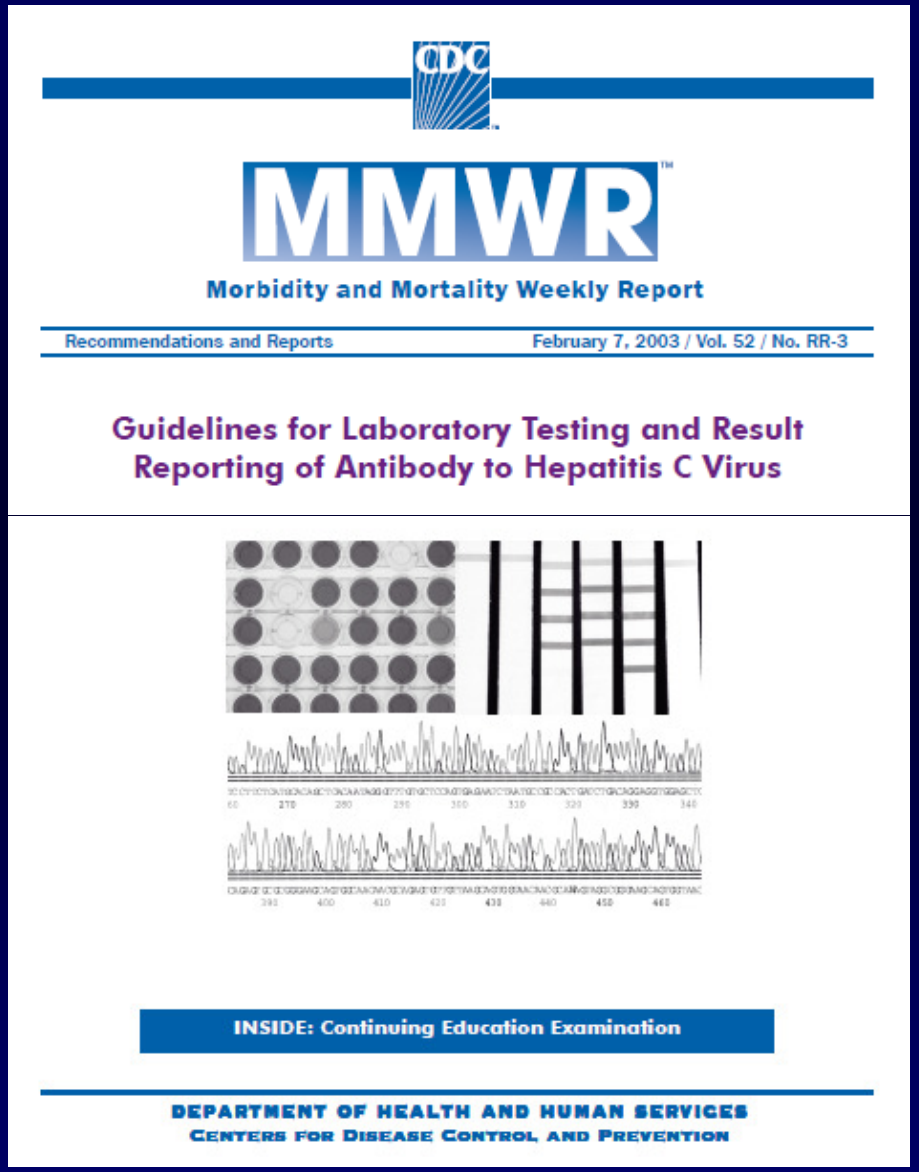
The ‘real’ need?

- Data and/or modifications to the algorithm are needed to advance the “presumptive positive” interpretation of concordant results to a more definitive laboratory-based positive result.

Can S/CO data help meet this goal?

Hepatitis C algorithms

"Use of S/CO ratios minimizes the amount of supplemental testing that needs to be performed while improving the reliability of reported test results."



http://www.cdc.gov/hepatitis/HCV/LabTesting.htm#section1

Study objectives

- Characterize initial S/CO values of HIV IAs
- Consider S/CO values of repeated IAs and evaluate the benefit of repeating initially reactive IAs
- Compare S/CO results when repeating the same IA to results of a different IA

Methods: Data sources

- Public Health Laboratory (PHL) data
  - 5 PHLS have submitted data
    - FL, MO, KA, MA, SF
  - All use the BioRad HIV-1/2 plus O

Data sources

- Specimens from CDC
  - Specimens from a field evaluation of HIV rapid tests conducted in Los Angeles June 2005-August 2007
  - Tested at CDC, and 2 external laboratories January 2008-present
    - BioRad GS HIV 1/2 *plus* O
    - Abbott Architect AG/AB
    - Abbott HIV 1/2 AB
    - Ortho VITROS Anti-HIV 1 & 2 Assay
    - Siemens ADVIA Centaur HIV 1/O/2 Enhanced

Categorization of specimens, based on IA and confirmatory results

Initial IA Result	Repeat IA result(s)	Western Blot result	APTIMA HIV-1 Qualitative RNA result	Category
Negative	Not done	Not done	Negative*	1) Negative
Reactive	Negative	Not done**	Negative*	2) False-positive IA
Reactive	Reactive	Negative	Negative	2) False-positive IA
Reactive	Reactive	Indeterminate	Negative/Positive	3) Indeterminate
Reactive	Reactive	Negative	Positive	4) Recent Infection
Reactive	Reactive	Positive		5) Positive

*16 member pools

** Western blot results available for CDC specimens with a reactive result on ANY IA

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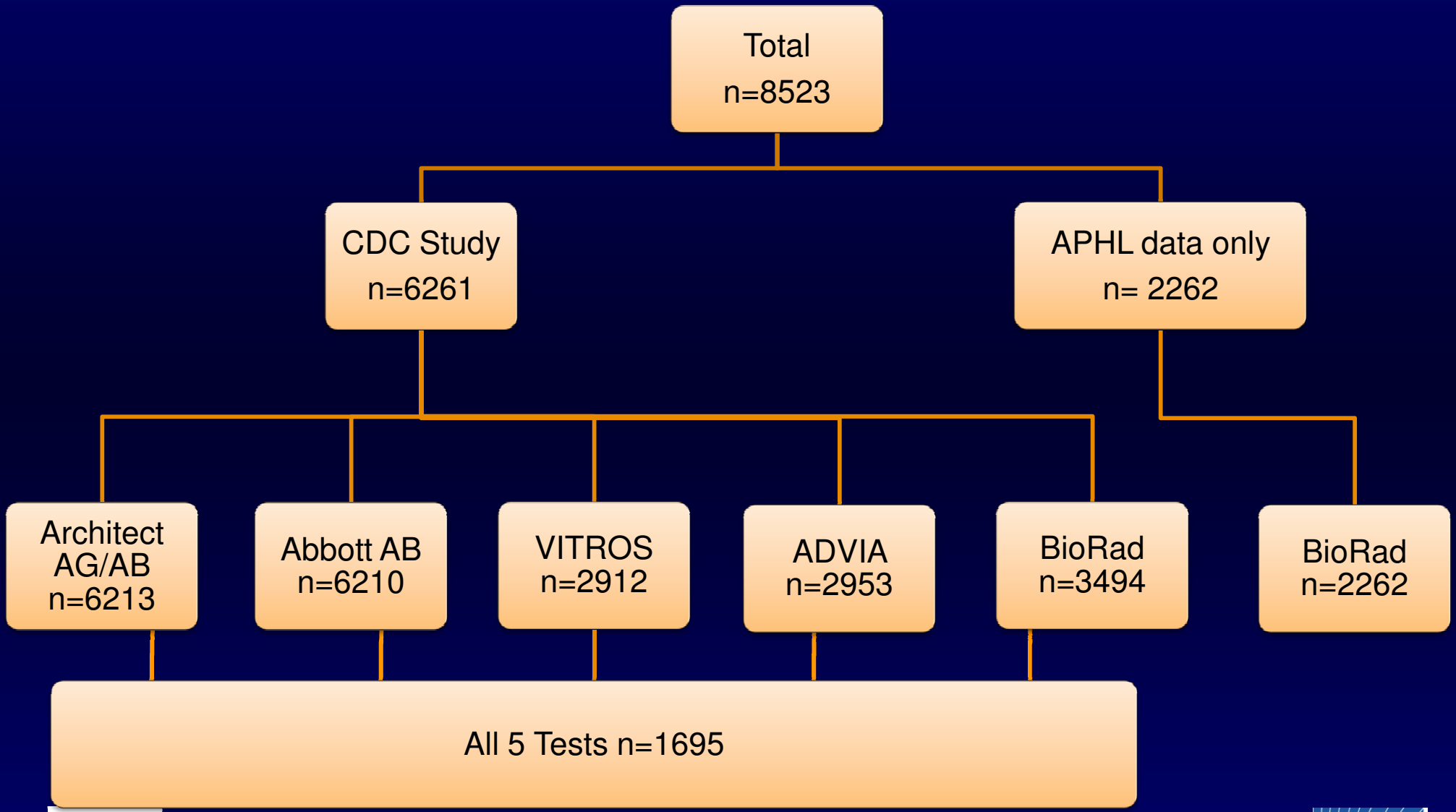
Categorization of specimens, based on IA and confirmatory results

Initial IA Result	Repeat IA result(s)	Western Blot result	APTIMA HIV-1 Qualitative RNA result	Category
Negative	Not done	Not done	Negative*	1) Negative
Reactive	Negative	Not done**	Negative*	2) False-positive IA
Reactive	Reactive	Negative	Negative	2) False-positive IA
Reactive	Reactive	Positive		5) Positive

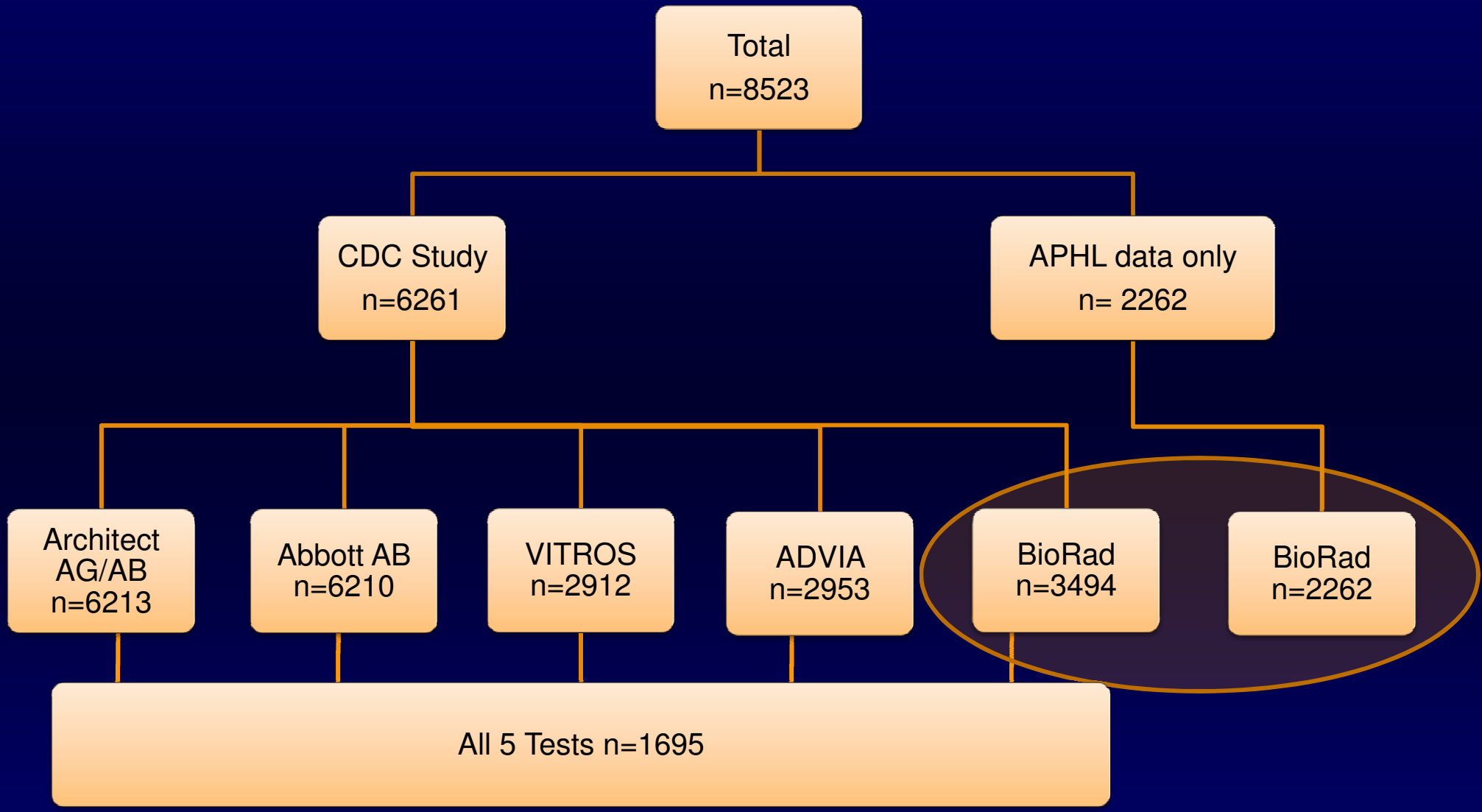
- Compared median and range of S/CO values of true and false-positive specimens

Results

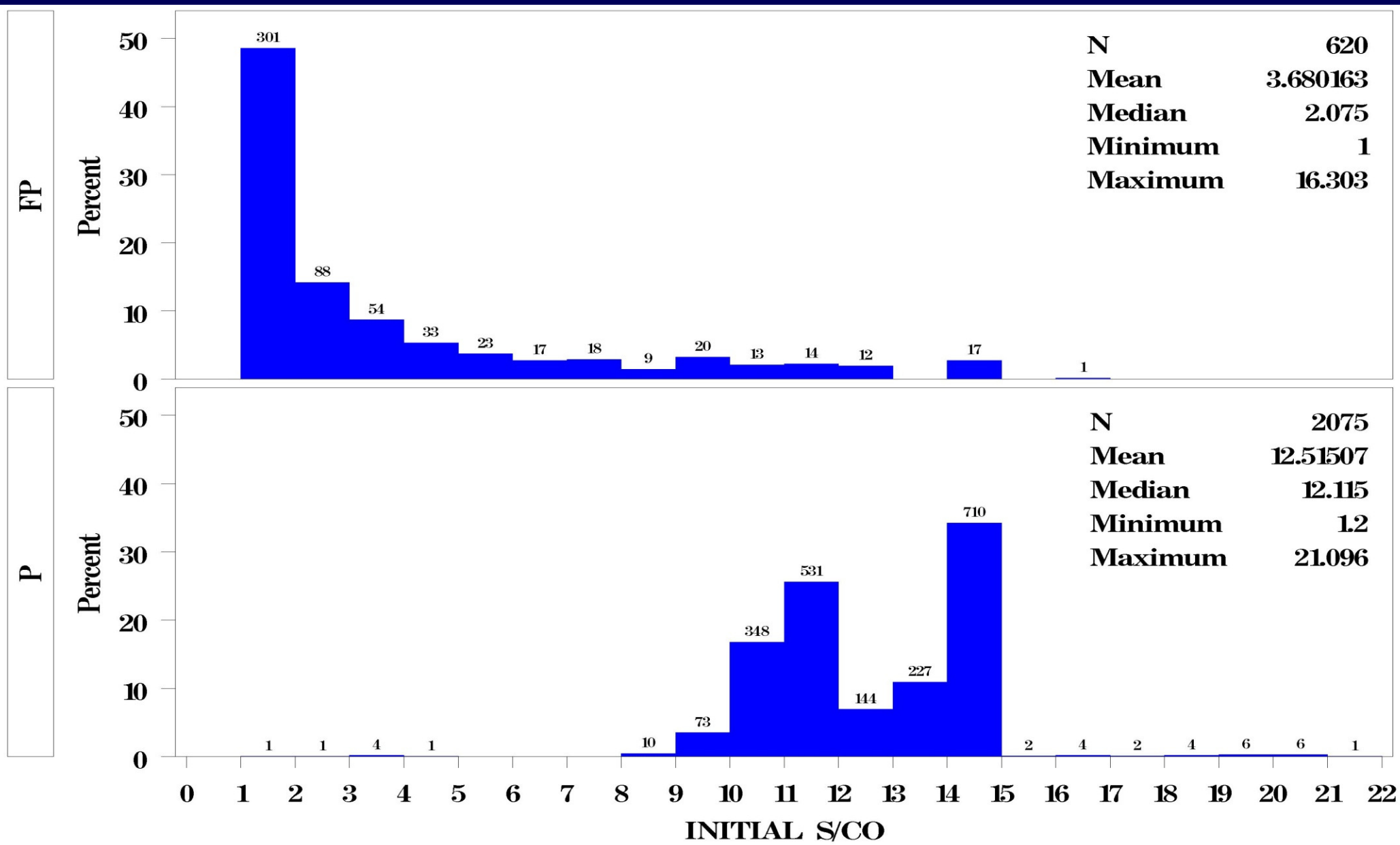
Number of specimens tested, by test type



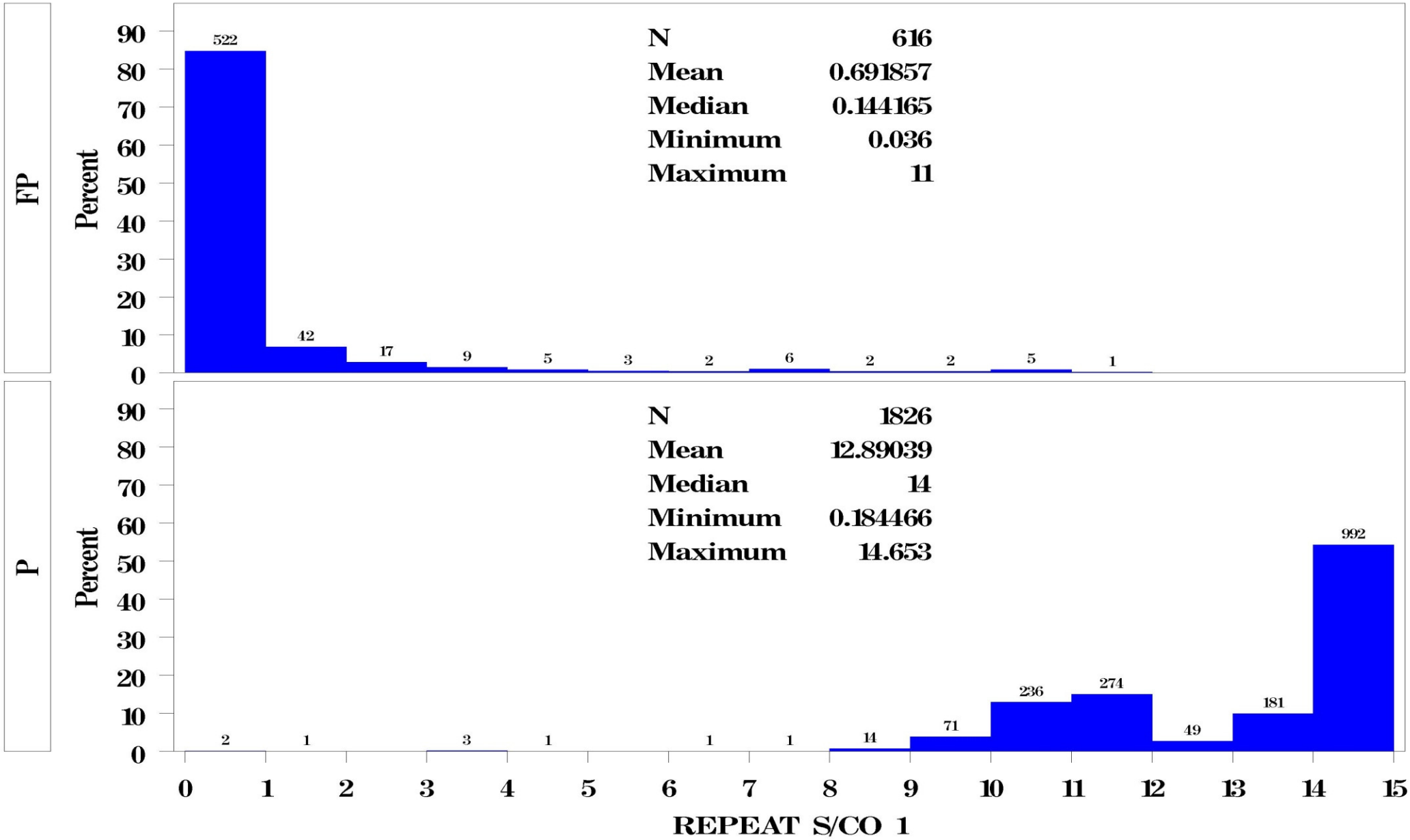
Number of specimens tested, by test type



S/CO distribution of initial BioRad IA test results



S/CO distribution of repeat BioRad IA test results

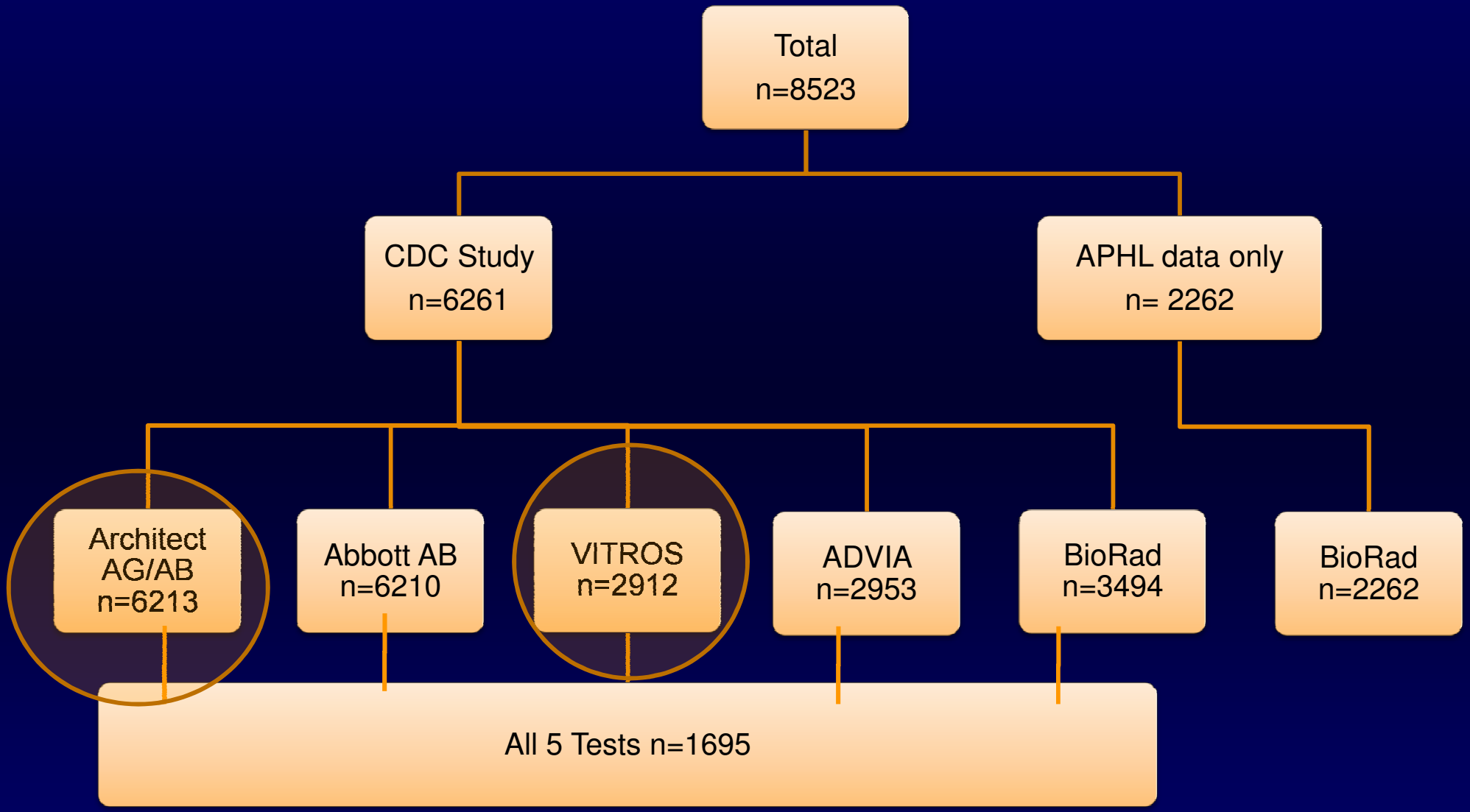


What did we learn from the S/CO of BioRad initial and repeat results?

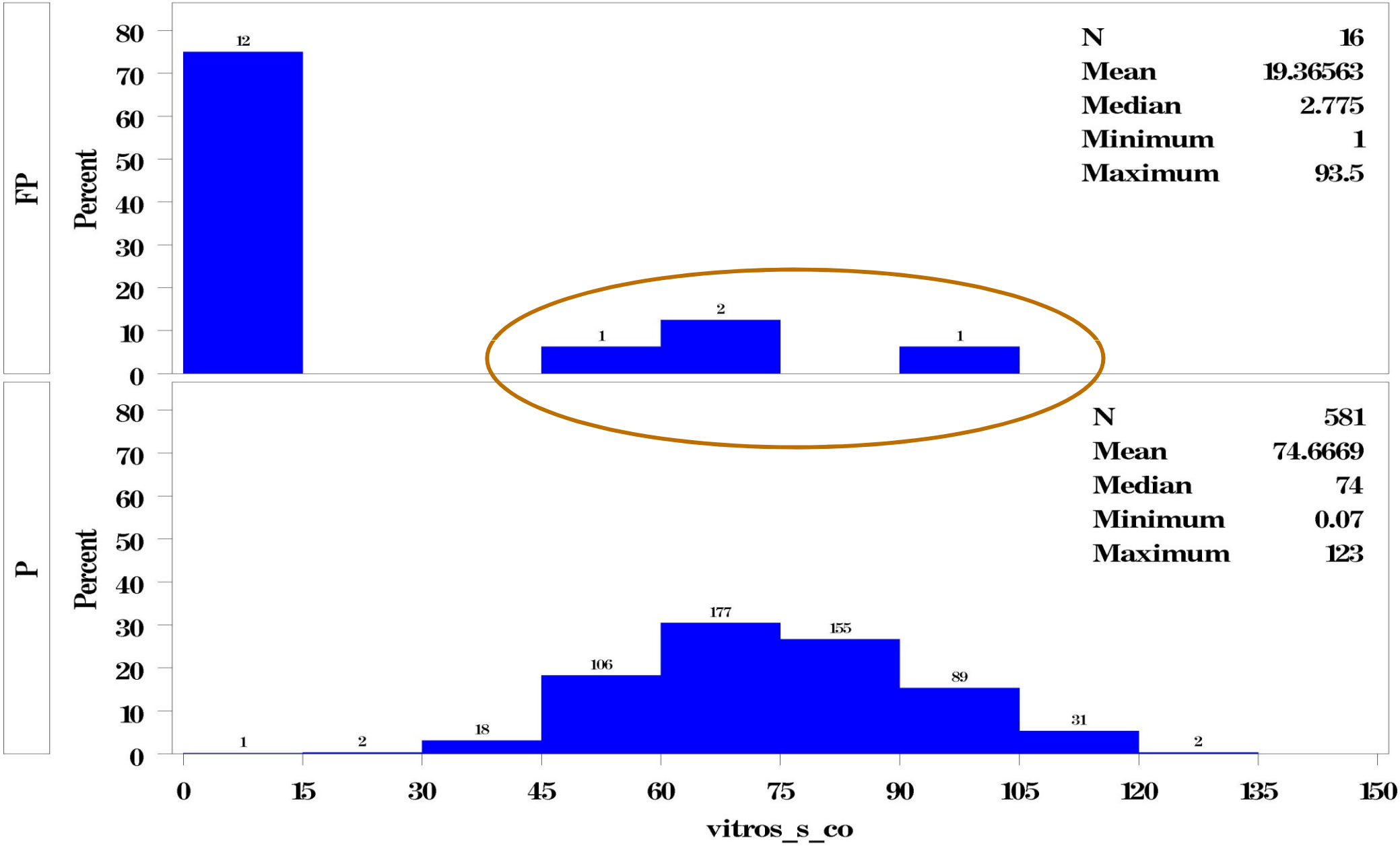
- Initial BioRad results
  - 57/620 (10%) false-positive specimens and
  - 1985/2075 (97%) positive specimens

  had a S/CO > 10
- Repeat S/CO data were available for 636 false-positive specimens
  - 630 (>99%) of specimens had a repeat S/CO < 10.
  - 94 (15%) had RR results
- No follow-up or other data to know which RR specimens might represent false-negative WB

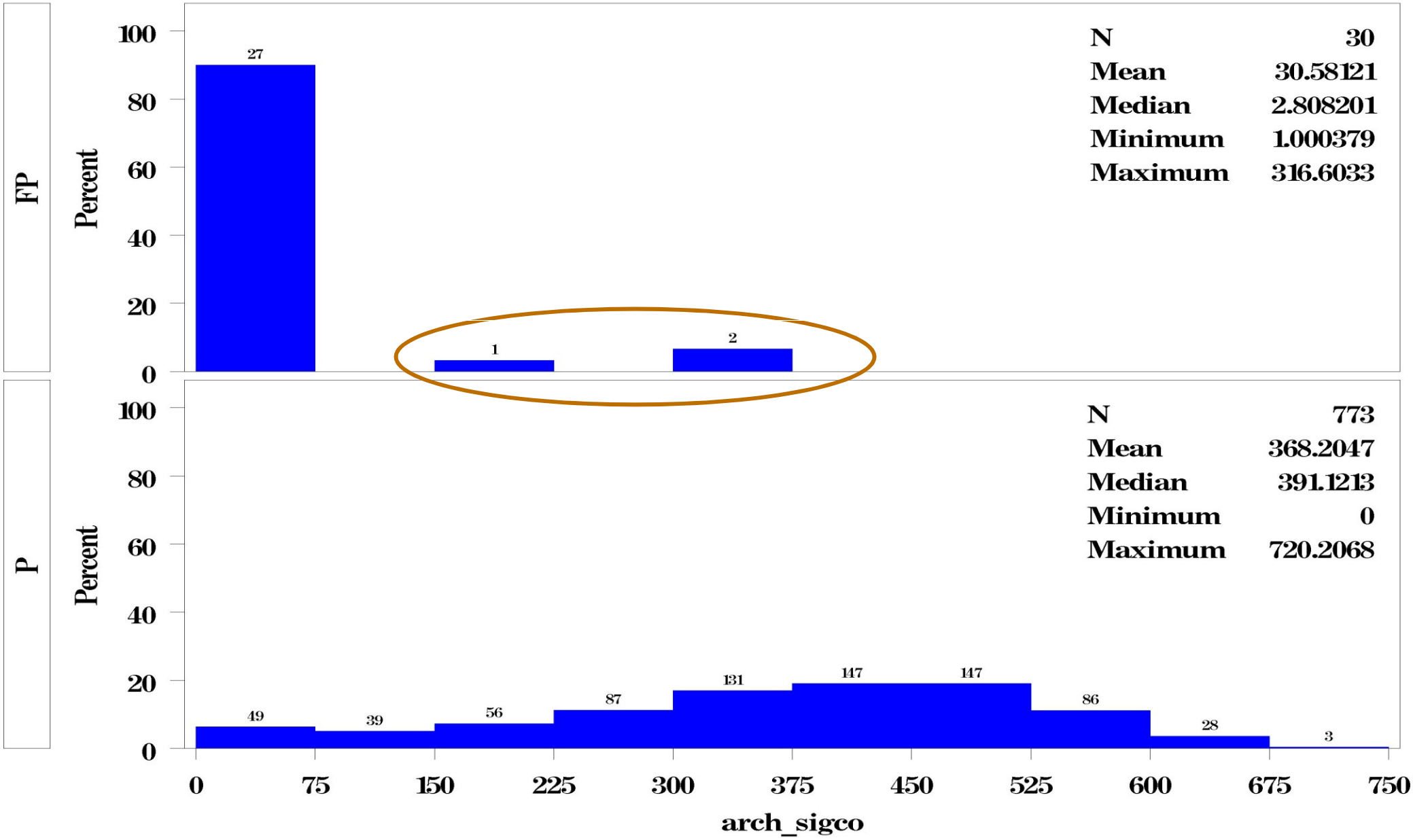
Number of specimens tested, by test type



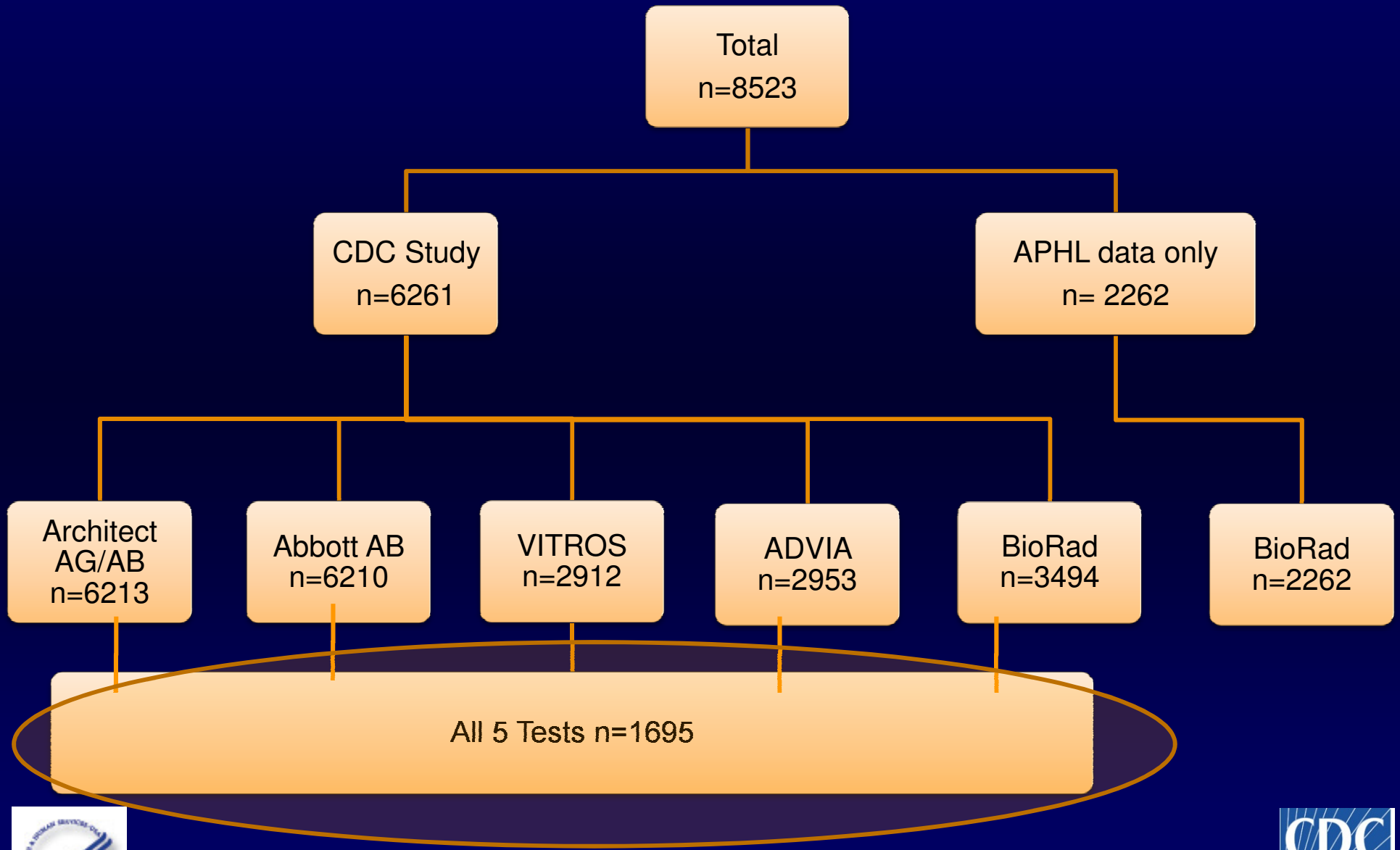
S/CO of the VITROS HIV 1-2 IA



S/CO of the Architect Ag/Ab IA



Results


Total
n=8523
CDC Study
n=6261
APHL data only
n= 2262
Architect
AG/AB
n=6213
Abbott AB
n=6210
VITROS
n=2912
ADVIA
n=2953
BioRad
n=3494
BioRad
n=2262
All 5 Tests n=1695

Of 1695 specimens, 105 were false-positive on at least one test; 9 had reactive results on >1 IA

WB	VITROS	ADVIA	ARCHITECT	ABBOTT AB	BioRad	Frequency
N	Neg	Neg	Neg	Neg	Neg	1311
N	Neg	Neg	Neg	Neg	Pos	74
N	Neg	Neg	Neg	Pos	Neg	10
N	Neg	Neg	Pos	Neg	Neg	6
N	**Neg**	**Neg**	**Pos**	**Neg**	**Pos**	**1**
N	**Neg**	**Neg**	**Pos**	**Pos**	**Neg**	**2**
N	Neg	Pos	Neg	Neg	Neg	2
N	**Neg**	**Pos**	**Pos**	**Pos**	**Neg**	**1**
N	Pos	Neg	Neg	Neg	Neg	4
N	**Pos**	**Pos**	**Neg**	**Neg**	**Neg**	**3**
N	**Pos**	**Pos**	**Neg**	**Pos**	**Neg**	**1**
N	**Pos**	**Pos**	**Pos**	**Pos**	**Neg**	**1**
P	Pos	Pos	Neg	Pos	Pos	1
P	Pos	Pos	Pos	Pos	Pos	278

Of those 9, all but one had low S/CO values on all tests…

VITROS	ADVIA	ARCHITECT	Abbott HIV AB	BioRad
6.52	7.89	0.566	3.2353	0.355
0.40	0.74	1.888	1.4538	-0.032
62.40	50.00	305.987	18.3333	0.48
0.43	1.75	3.444	8.7167	0.254
5.22	4.37	0.183	0.1557	0.162
3.74	1.34	0.132	0.2049	0.278
0.08	0.05	1.770	0.1597	1.409
0.04	0.05	1.125	1.2689	0.385
1.05	1.78	0.106	0.2288	0.15

This specimen had a highly reactive (S/CO> 13) test result when BioRad was repeated at CDC

VITROS	ADVIA	ARCHITECT	Abbott HIV AB	BioRad
6.52	7.89	0.566	3.2353	0.355
0.40	0.74	1.888	1.4538	-0.032
62.40	50.00	305.987	18.3333	0.48
0.43	1.75	3.444	8.7167	0.254
5.22	4.37	0.183	0.1557	0.162
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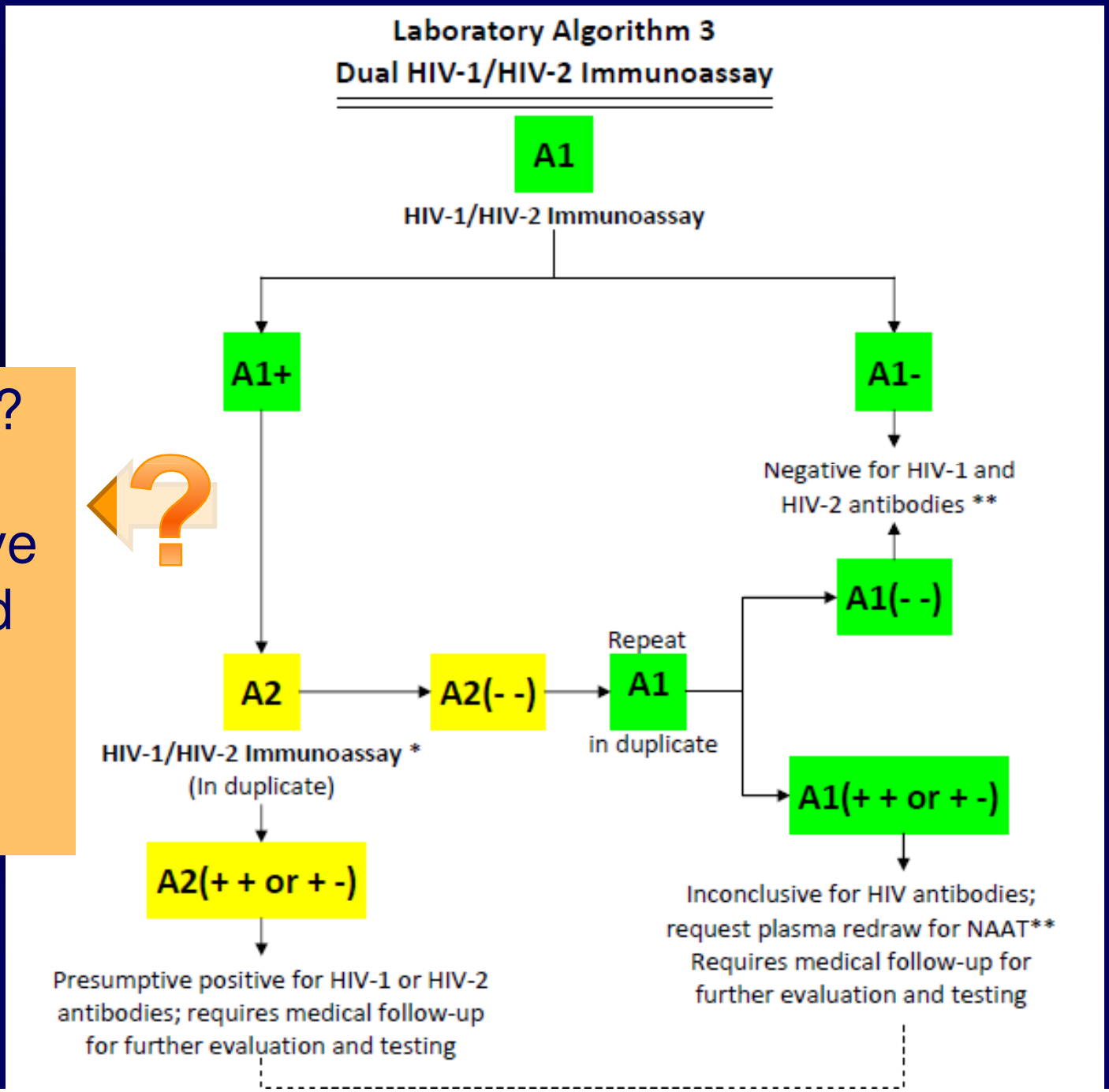
0.08	0.05	1.770	0.1597	1.409
0.04	0.05	1.125	1.2689	0.385
1.05	1.78	0.106	0.2288	0.15

Summary

- All 5 IAs included in this evaluation had
  - Wide separation between true and false- positive results
  - Weakly reactive results on some WB-positive specimens
    - Most early infections are also weakly reactive on IAs
  - Strongly reactive results on false-positive specimens
    - We don't know if some of these are true positive…
- Only 1/1695 (0.05%) specimen was highly reactive on more than 1 IA
    - This specimen was repeatedly-reactive and WB-positive when retested

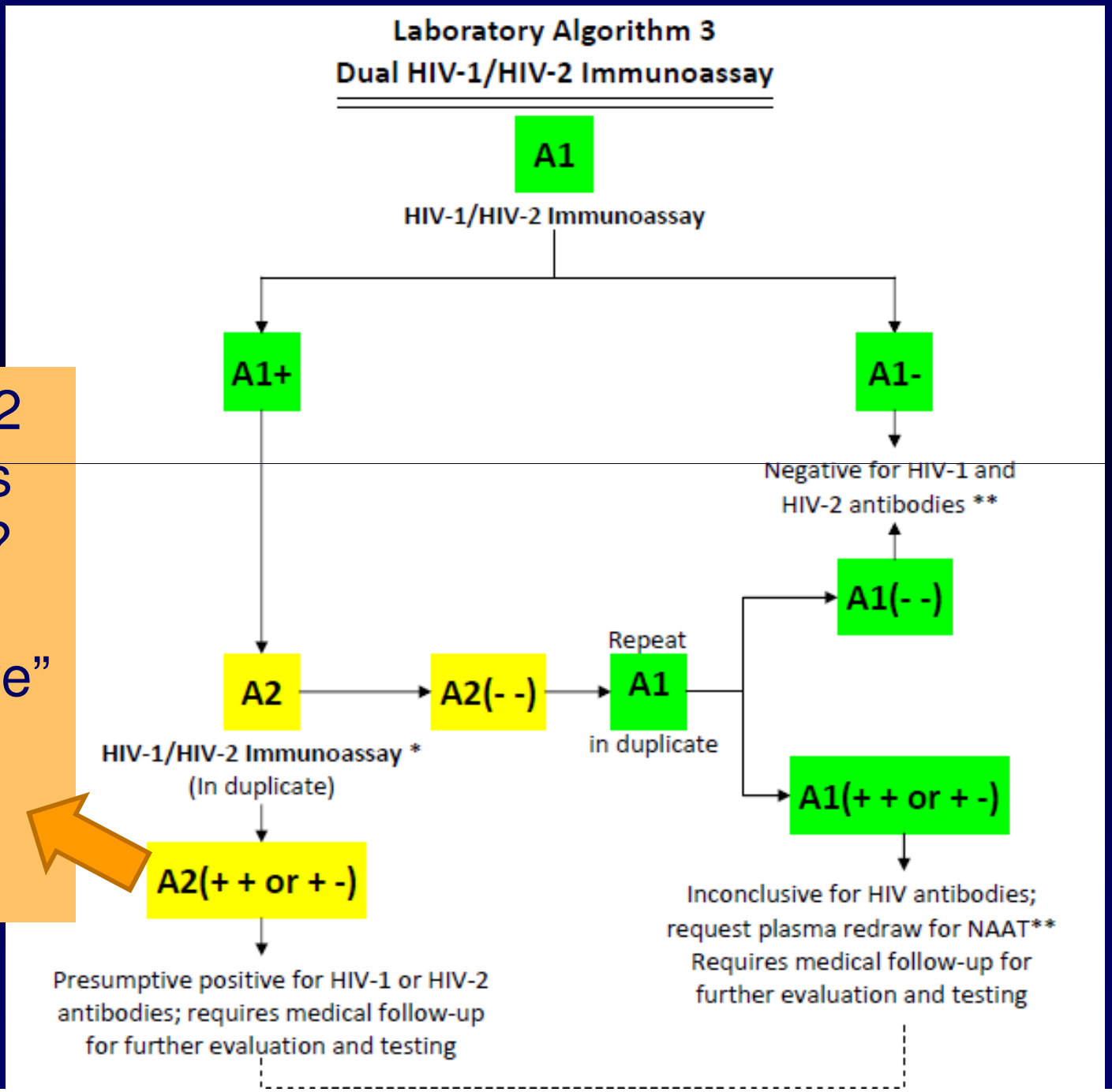
Revisiting the algorithms

If S/CO > ??
Consider "presumptive positive and refer to medical follow-up?"



Revisiting the algorithms

If S/CO on 2 different IAs > ?? and ?? report as "HIV-positive" and refer to medical follow-up



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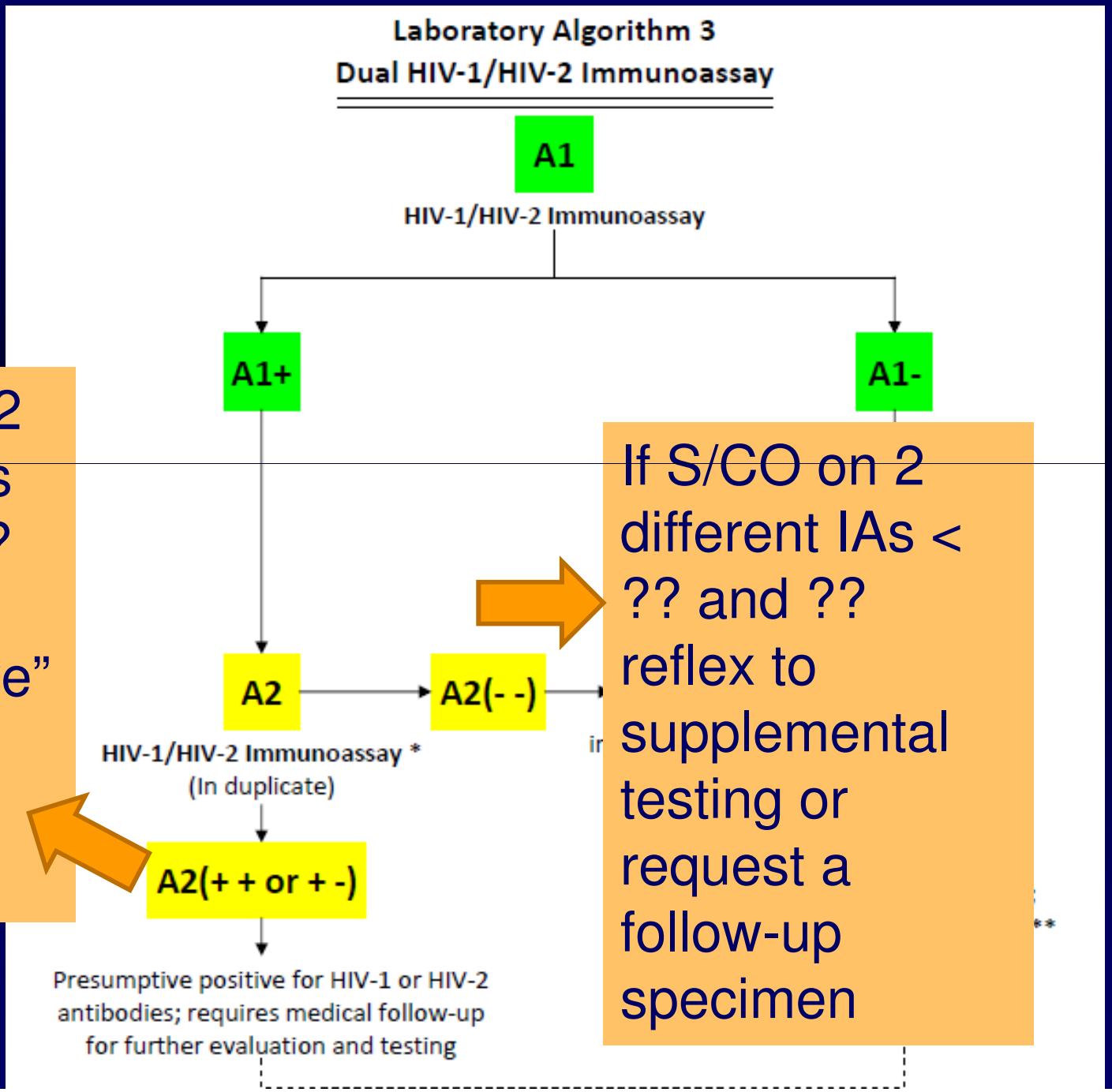
Revisiting the algorithms



If S/CO on 2 different IAs > ?? and ?? report as "HIV-positive" and refer to medical follow-up

If S/CO on 2 different IAs < ?? and ?? reflex to supplemental testing or request a follow-up specimen

Next Steps?

- Is this worth continuing to pursue?
  - It seems likely that we can limit the amount of supplemental testing by incorporating S/CO data in the algorithms
- Need determine an appropriate cut-off value for each IA
  - Will be testing a large sample of specimens with false-positive results at a National reference laboratory

Next Steps?

- What additional data do we need?
  - More results on multiple IAs for falsely-reactive specimens
  - Additional seroconversion panels and early infection specimens
    - S/CO values on these specimens are similar to those for false-positive specimens
  - If the algorithm required sending all specimens with weakly reactive results for supplemental testing, that might be OK?!?

Next Steps?

- What additional data do we need?
  - Data comparing S/CO data for multiple IAs to rapid test results
    - It seems unlikely that most laboratories would be able to support to large IA systems
    - Rapid tests should be sensitive enough to detect true positive specimens with high S/CO values

Questions??