WESTGARD QC

GETTING TO SIX SIGMA FOR UNAIDS 90-90-90

In order to achieve 90-90-90, We need The Truth, the Whole Truth, and Nothing but the Truth

WWW.WESTGARD.COM

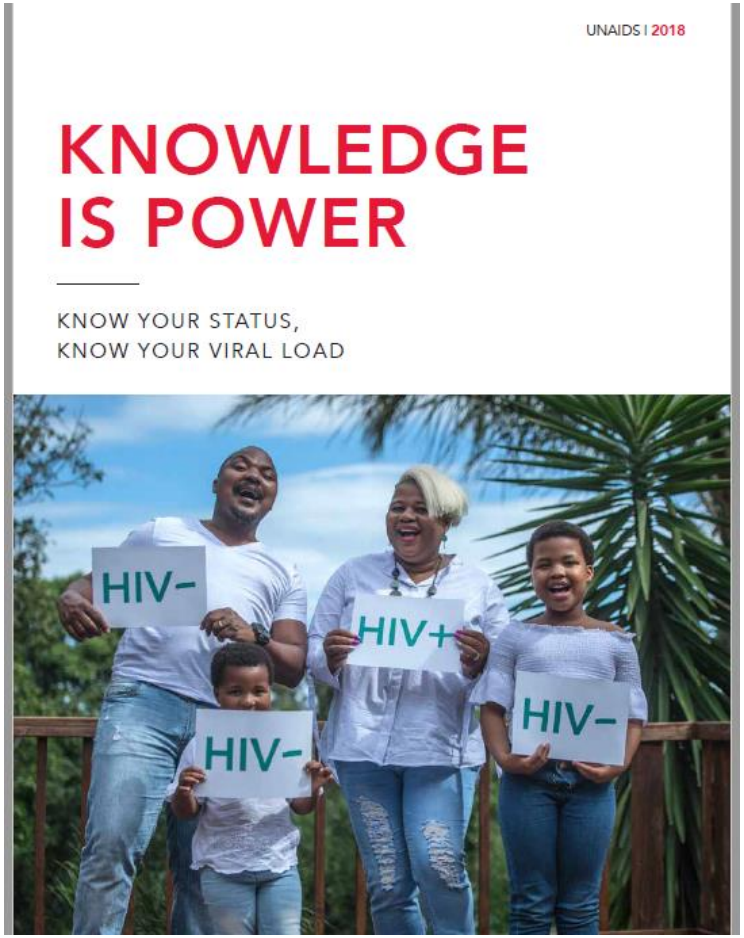
GOALS

1. Know your Sigma – Know the Quality of the Results you're reporting

2. Adjust your QC rules, controls, and frequency to the Sigma of your method

3. If you can't afford the QC, you can't afford the method - demand better

UNAIDS 90-90-90 REPORT: IGNORANCE IS POWERLESSNESS



Knowledge of Acceptable Analytical Quality of Viral Load Testing is ***absent***

The report is very good at identifying obstacles to getting tested and acting on test results

There is little discussion of whether the results themselves are correct

THE WESTGARDS, ALL THE WESTGARDS, AND NOTHING BUT THE WESTGARDS

Father knows best!

"*The*" Westgard

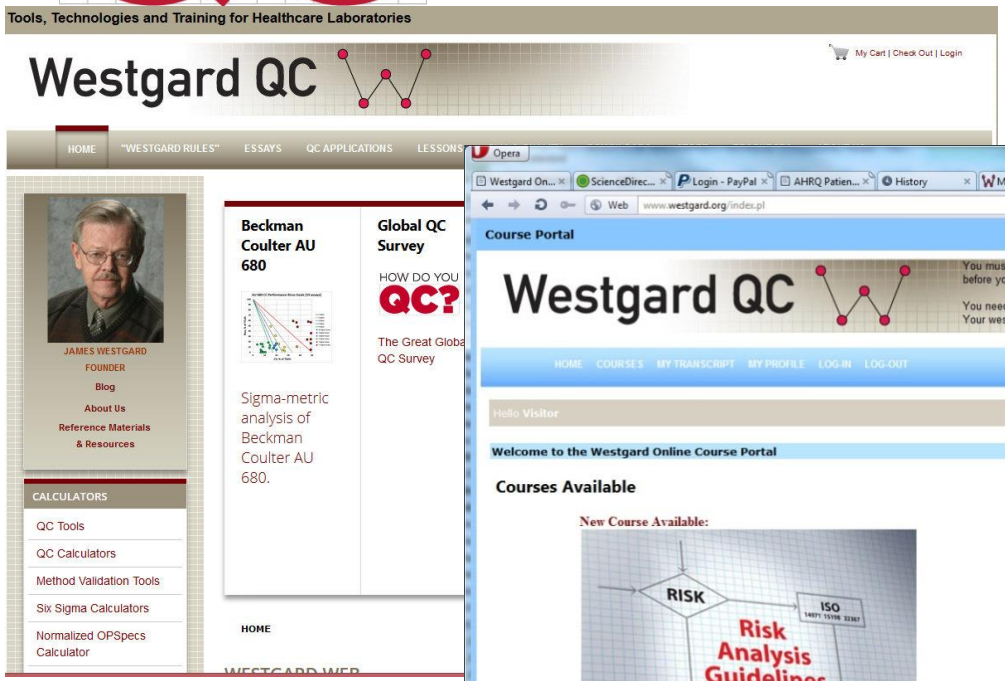
- 40+ years at the University of Wisconsin
- "Westgard Rules"
- Method Validation
- Critical-Error graphs
- OPSpecs

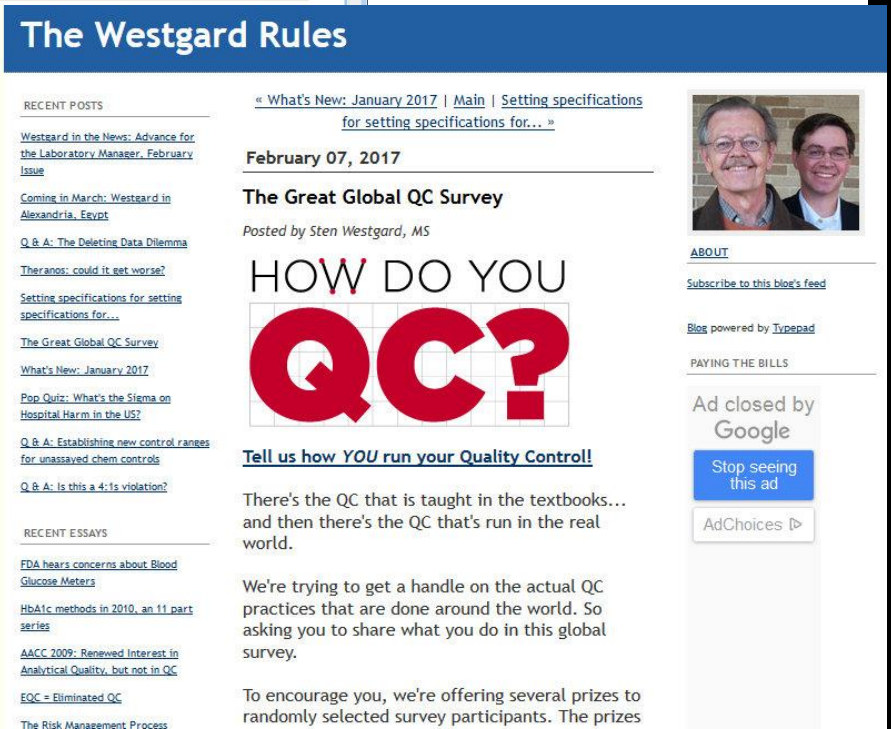
Son knows better?

"A" Westgard

- 25 years at Westgard QC
- Publishing
- Web
- Blog
- course portal

WESTGARD WEB



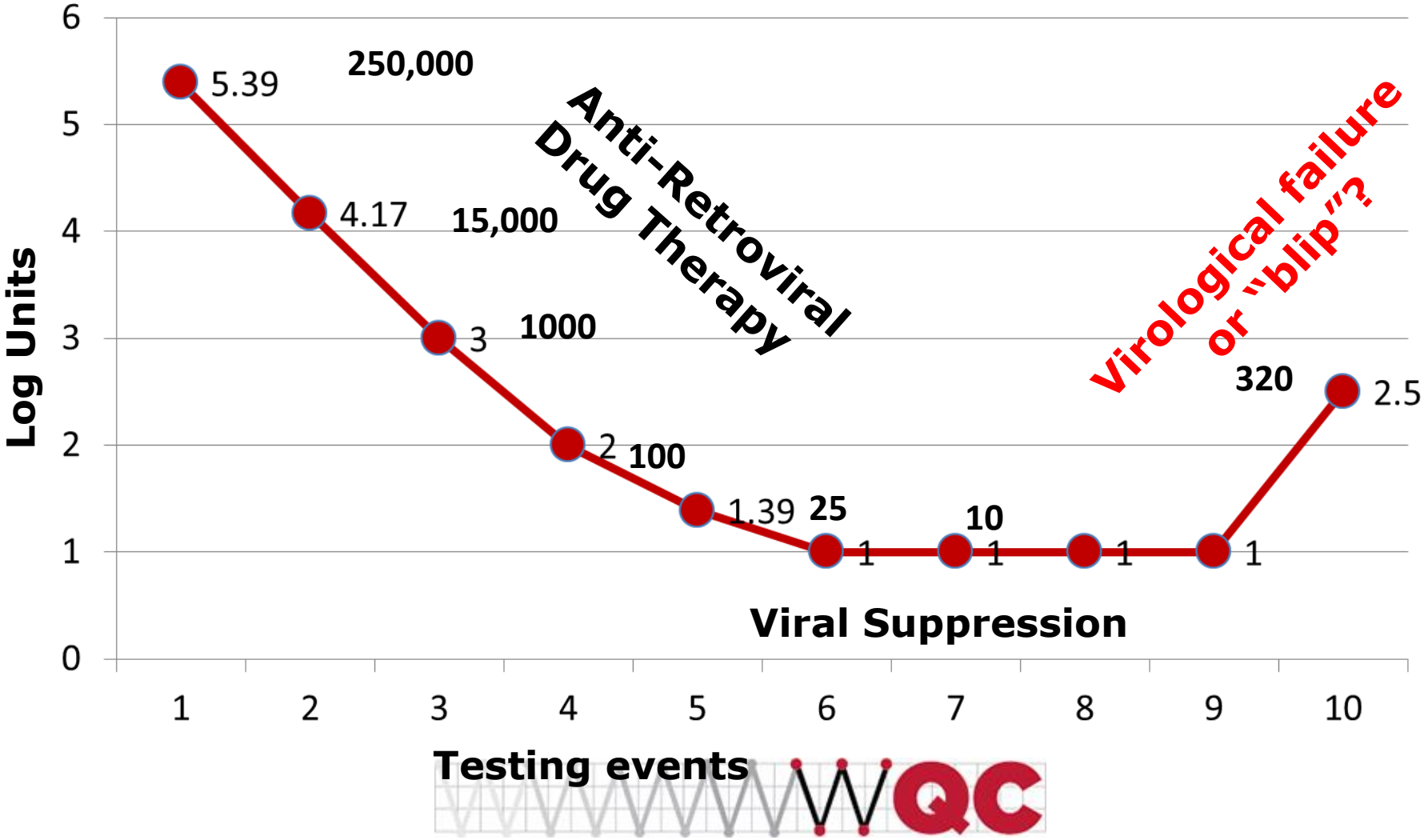


Website:
>60,000 members
>3 million views
>600+ essays,
guest essays,
lessons,
QC applications,
references resources

Course Portal:
Training in QC, Method Validation, Risk Analysis, Quality Management

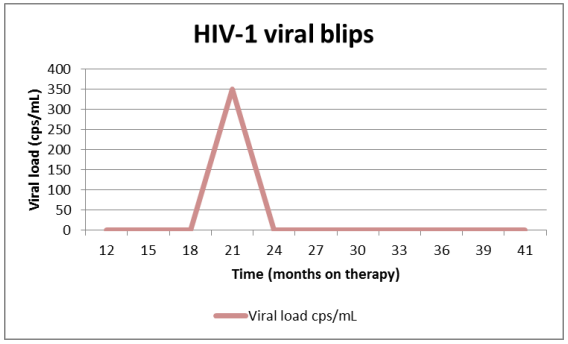
Blog:
>400 Short articles
Q&A

THE VIRAL LOAD ARV CHALLENGE



HOW OFTEN DO YOU REPEAT TESTS IN ORDER TO FIGURE OUT WHETHER THERE'S A "BLIP" IN THE PATIENT? – OR THE QC?

Reference	Blip range	Method A v1	Method A v2	Method B
Briggs	40-1000 cps/mL	65.2% (161/247)	45.3% (112/247)	7.7% (19/247)
Taylor	50-1000 cps/mL	NA	22.8% (85/373)	1.9% (1/52)
McKinnon	50-200 cps/ml	NA	6.5% (5/77)	0%



Viral Blip = A temporary, detectable increase in the amount of HIV in the blood (viral load) that occurs after antiretroviral therapy (ART) has effectively suppressed the virus to an undetectable level.

THE TRUTH, THE WHOLE TRUTH, AND NOTHING BUT THE TRUTH FOR 90-90-90

- ***The Truth*** *requires that a test be related to the disease process of interest and that the interpretative guidelines be understood in terms of the quality (or limits of variation) required for the test.*

- *For* ***the Whole Truth*** *to be known, the test must be measured by a reliable method having the proper specifications for precision and accuracy.*

- *To provide* ***Nothing but the Truth****, a test result should not be confounded by unknown or undisclosed factors, such as changes in the subject due to biological variation or changes in the method due to lack of stability and quality control.*

THE TRUTH, UNAIDS 90-90-90

- ***The Truth*** *requires that a test be related to the disease process of interest and that the interpretative guidelines be understood in terms of the quality (or limits of variation) required for the test.*
- Core Laboratory testing may be better, but impractical for Low and Middle Income Countries
- Infrastructure of centralized laboratory testing is lacking
- Patients are too often far away from central labs

- Point-of-Care Viral Load Testing is necessary
- **How good do these tests need to be?**

THE TRUTH, WHO 90-90-90 FOR PERFORMANCE SPECIFICATION

- ***The Truth ...****the quality (or limits of variation) required for the test.*
- Quality Standard for Viral Load Testing is NOT standardized

• 50 copies/mL	EACS, DAIG, French HIV, GeSIDA, Italy
• 200 copies/mL	IAS-USA, British HIV
•1000 copies/mL	UNAIDS 90-90-90 cut-off; India NACO

- Even a cut-off is not enough.

- **How much *error* is allowed for a VL assay?**

THE TRUTH, WHO 90-90-90 FOR PERFORMANCE SPECIFICATION

- ***The Truth ...****the quality (or limits of variation) required for the test.*
- Converting Cut-offs into Decision Intervals
- ART failure – viraemia – resistance

• 50 to 200 copies/mL	300% allowable error
• 200 to 1000 copies/mL	400% allowable error
• 1.7 to 2.301 log	35.88% allowable error; log (0.61)
• 2.301 to 3.0 log	29.97% allowable error; log (0.69)

THE TRUTH, WHO 90-90-90 FOR PERFORMANCE SPECIFICATION

- ***The Truth ...****the quality (or limits of variation) required for the test.*
- Converting Cut-offs into Decision Intervals
- ART failure – viraemia – resistance

• 1.7 to 2.301 log	35.88% allowable error; log (0.61)
• 2.301 to 3.0 log	29.97% allowable error; log (0.69)

- **30% allowable error may be the most practical goal for 90-90-90**

- **What are the components within the allowable error?**

THE WHOLE TRUTH FOR 90-90-90

- *For **the Whole Truth** to be known, the test must be measured by a reliable method having the proper specifications for precision and accuracy.*

- Allowable Error, better defined as Allowable Total (Analytical) Error, TEa

- A combination of both imprecision and inaccuracy (bias, lack of trueness),TEa is well-known and long used in laboratories

- Amply defined for biochemistry, hematology, etc. parameters by all EQA programs and many governments (USA, Germany, China, etc.) but not for VL testing

THE WHOLE TRUTH FOR 90-90-90 – WHAT IS RELIABLE?

- *For **the Whole Truth** to be known, the test must be measured by a **reliable method** having the proper specifications for precision and accuracy.*

- If we know TEa, Bias, and CV, we can calculate performance on a Six Sigma scale (Sigma-metric)

- High Sigma-metric indicates analytical reliability

- Low Sigma metric indicates analytical variability

TESTING FOUNDATION MUST BE BUILT ON CORRECT RESULTS

From UNAIDS 2018 Knowledge is Power Report:

The five Cs of testing

Consent: HIV testing is a choice, and an individual's decision to take an HIV test must always be voluntary. People being offered testing for HIV must give informed consent and have the right to refuse testing without consequences.

Confidentiality: Testing services must be confidential. Test results and the content of discussions between the person tested and the testing provider, counsellor and/or other health-care workers cannot be disclosed to anyone else without the consent of the person tested.

Counselling: Appropriate and high-quality brief pretest information and post-test counselling needs to be tailored to the person, and the test results must be available.

Correct results: HIV test results delivered to individuals must be accurate and communicated to the person tested, unless that person subsequently decides that they do not wish to receive the results.

Connections: Linkages to HIV prevention, treatment, and care and support services should be supported through concrete and well-resourced patient referral, support and/or tracking systems *(23)*.

How do we know and assure that the results are correct?

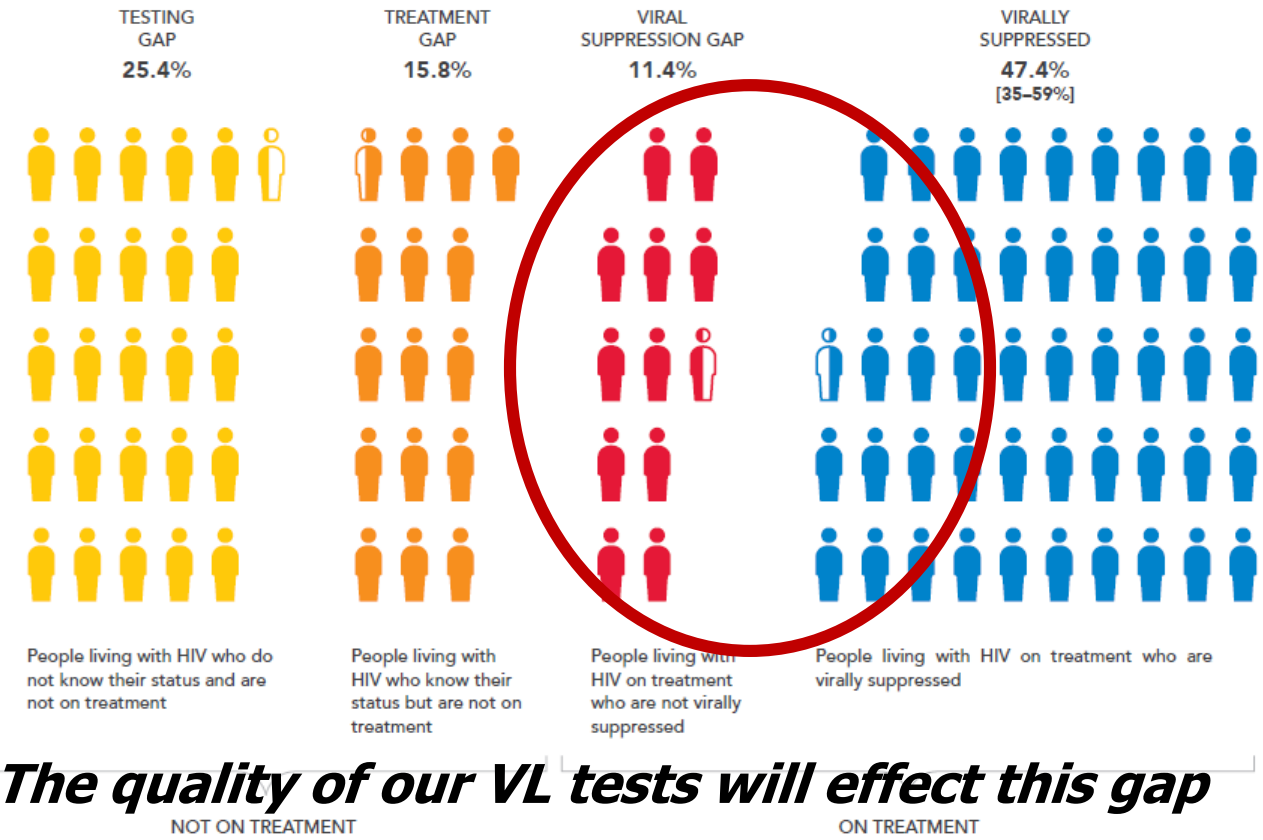
WESTGARD QC

ANALYTICAL QUALITY WILL DIRECTLY IMPACT NUMBERS OF PATIENTS WHO ARE OR ARE NOT VIRALLY SUPPRESSED.

From UNAIDS 2018 Knowledge is Power Report:

Three gaps on the path to viral suppression

Figure 6. Knowledge of status, treatment and viral suppression gaps, global, 2017



The quality of our VL tests will effect this gap

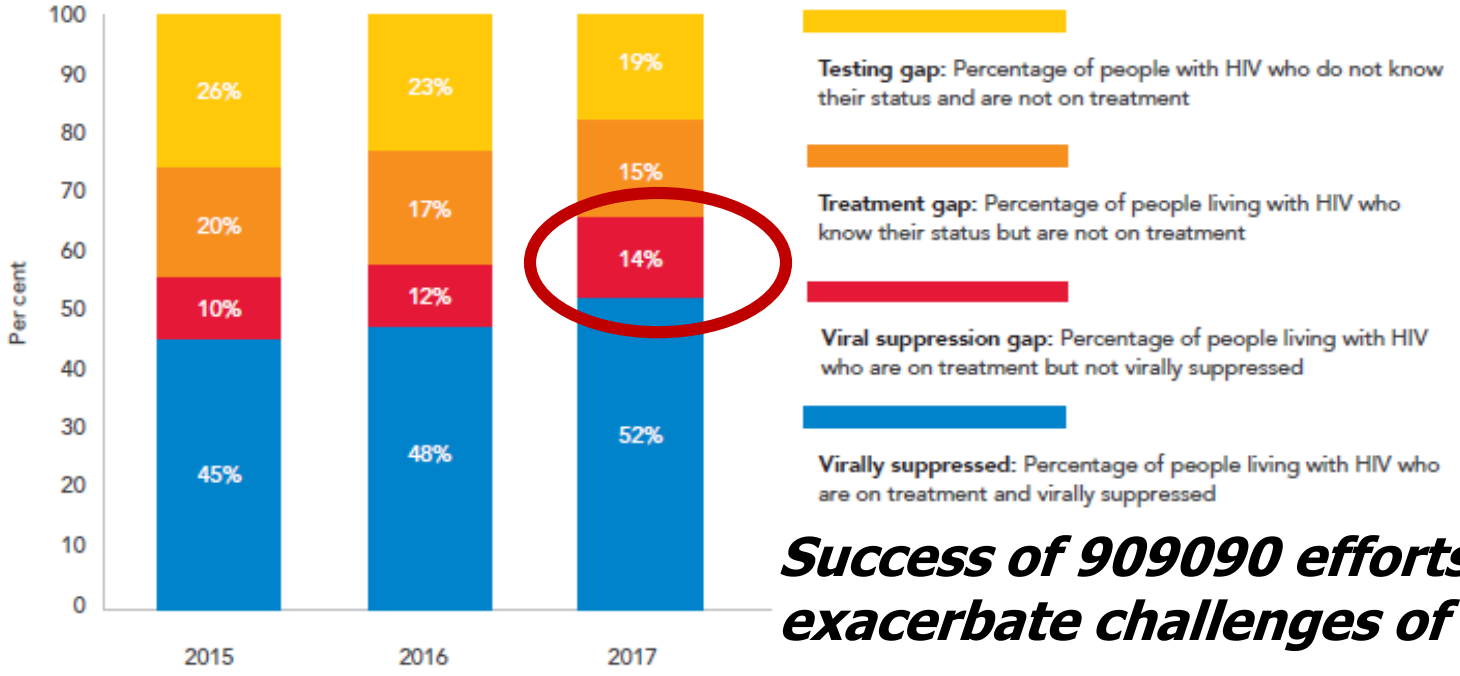
IN AFRICA, THE VIRAL SUPPRESSION GAP IS LARGER AND GROWING

From UNAIDS 2018 Knowledge is Power Report:

Figure 9. Trends vary among regions

Knowledge of status, treatment and viral suppression gaps, two regions, 2015–2017

EASTERN AND SOUTHERN AFRICA



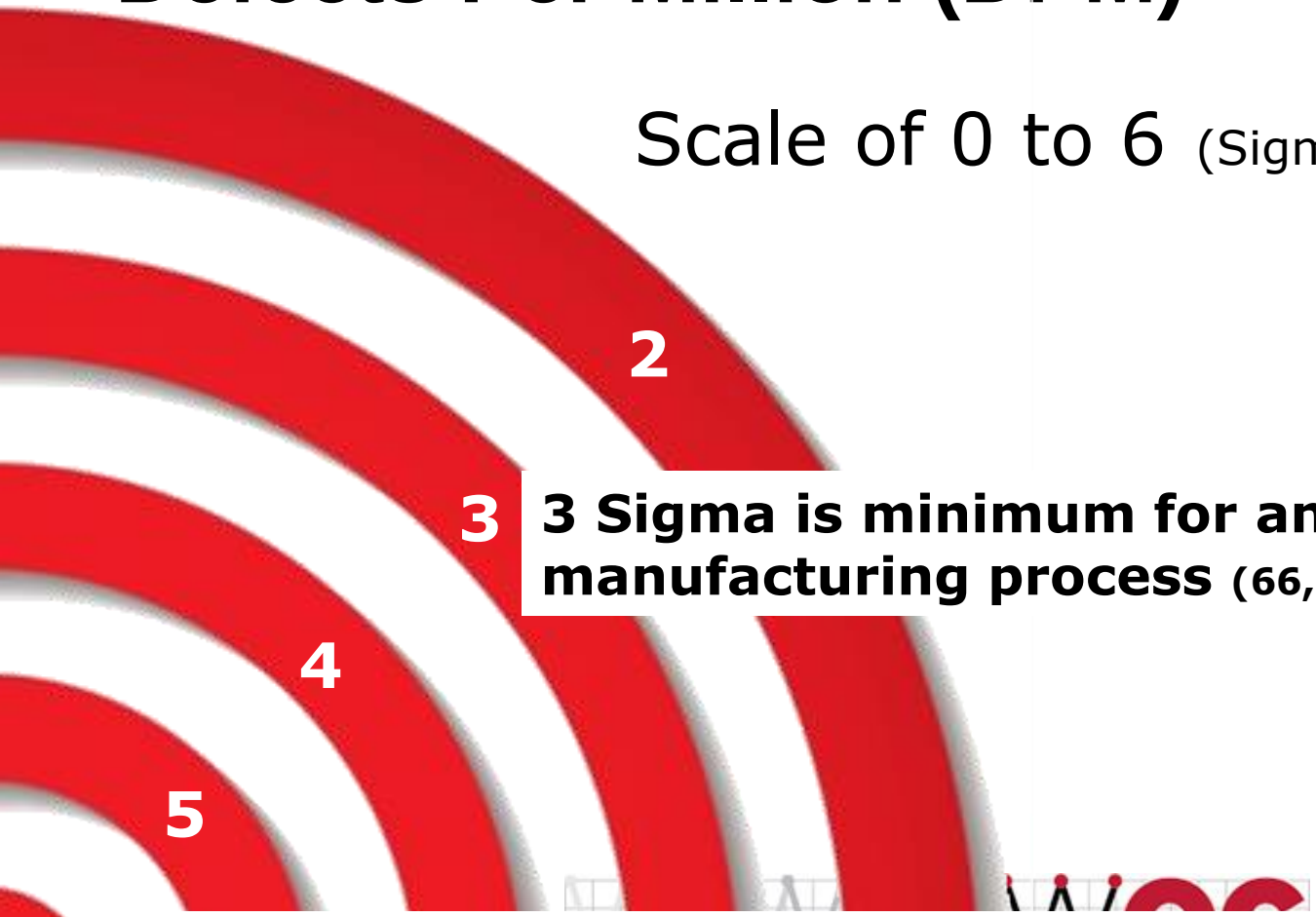
Source: UNAIDS special analysis, 2018.

Success of 909090 efforts will exacerbate challenges of VL testing

SIX SIGMA: TELLS US WE HAVE A TARGET TO HIT

Defects Per Million (DPM)

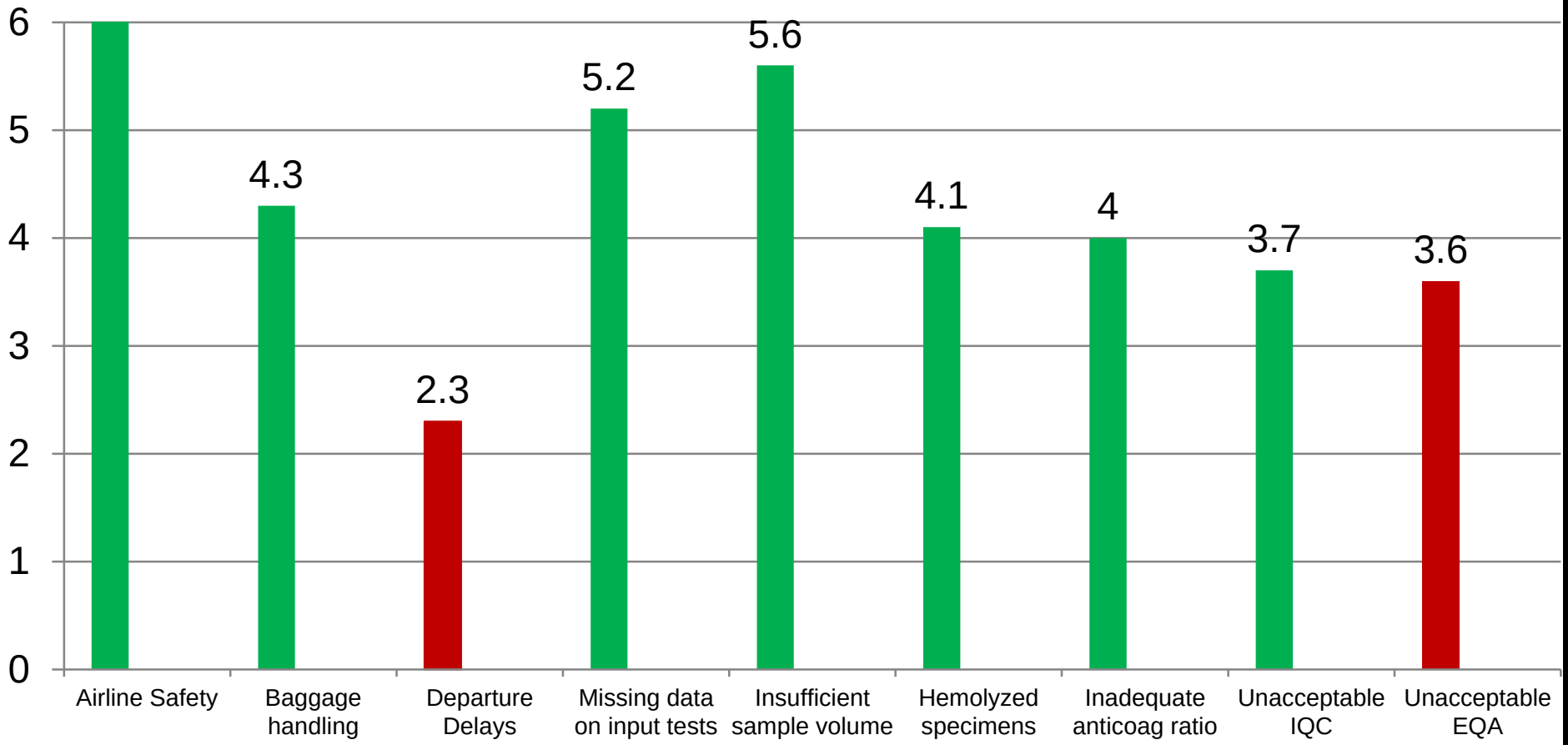
Scale of 0 to 6 (Sigma short-term scale)



3 Sigma is minimum for any business or manufacturing process (66,807 dpm)

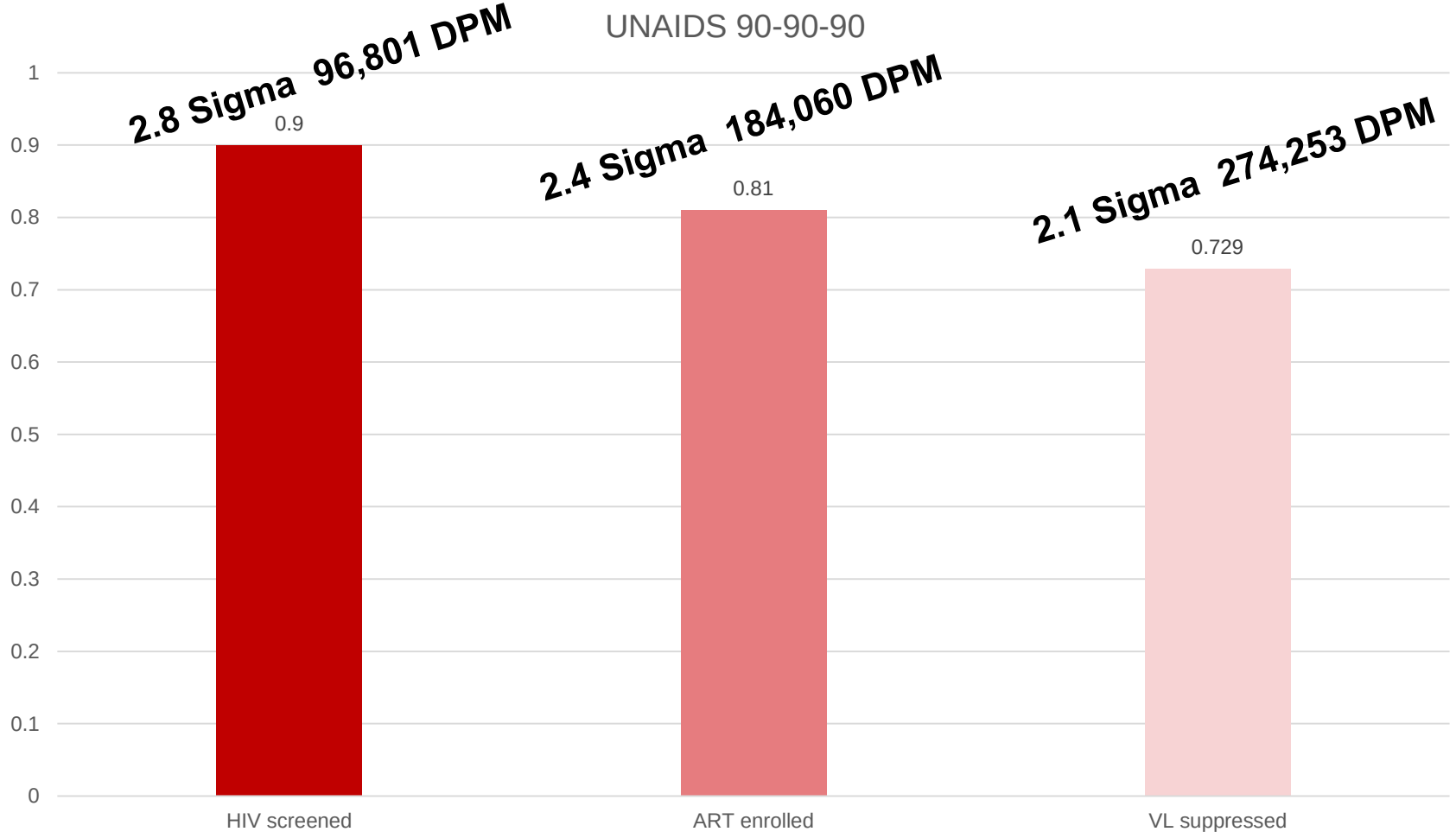
World Class Performance (3.4 DPM)

SIGMA METRICS OF COMMON PROCESSES (US) AND LABORATORY PROCESSES (ITALY)

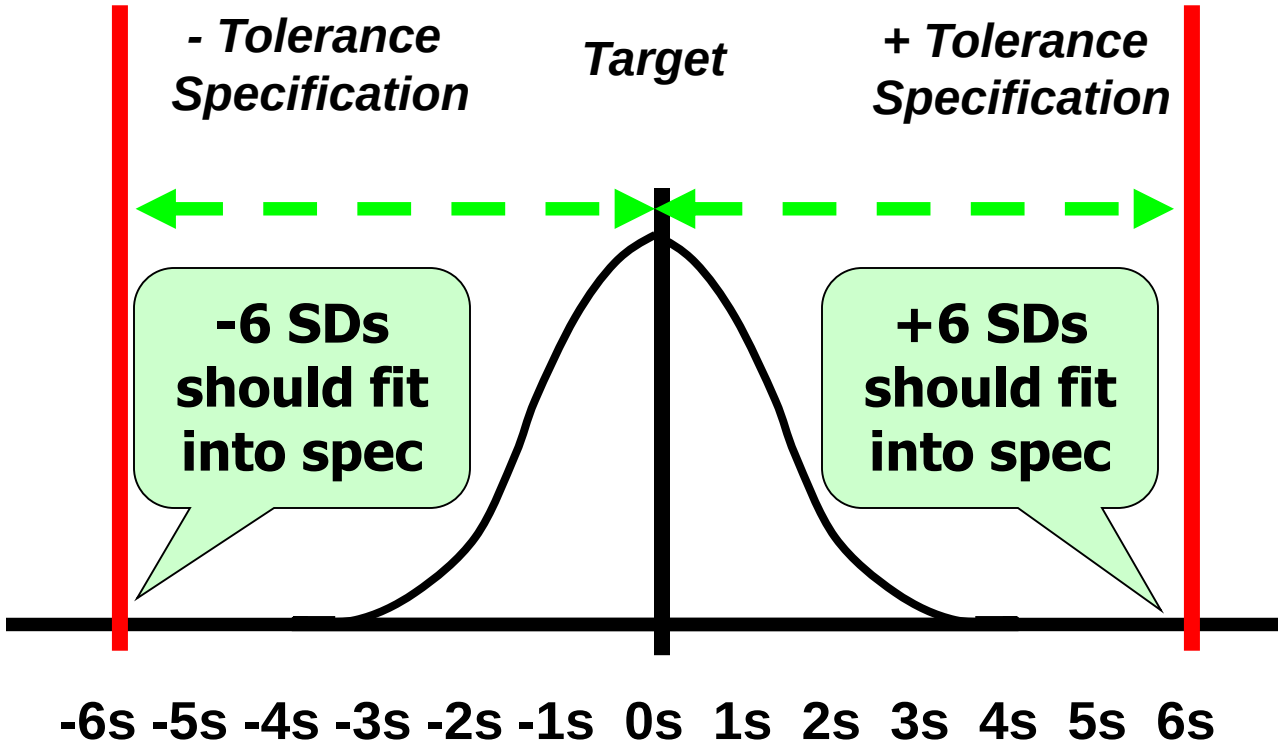


Sources: Quality Indicators in Laboratory Medicine: Experience of a Large Laboratory. L. Sciacoelli, A. Aita A. Padoan. M. Plebani, Abstract 0962, 2014 IFCC World Lab Istanbul

UNAIDS 90-90-90 IN A SIX SIGMA CONTEXT



WHAT DOES SIX SIGMA ACTUALLY MEAN?



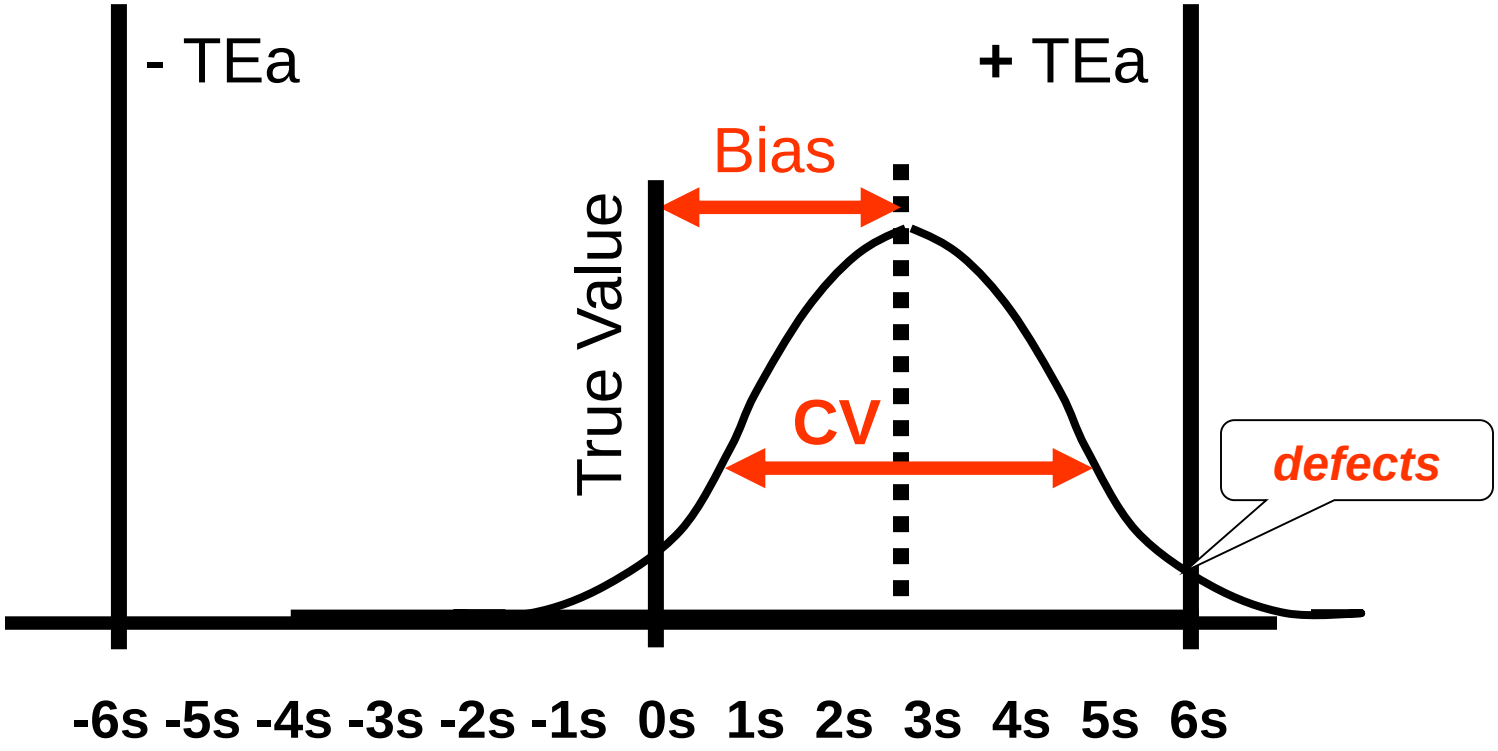
HOW DO WE MEASURE (SIX) SIGMA PERFORMANCE?

Measure Variation – Use existing data

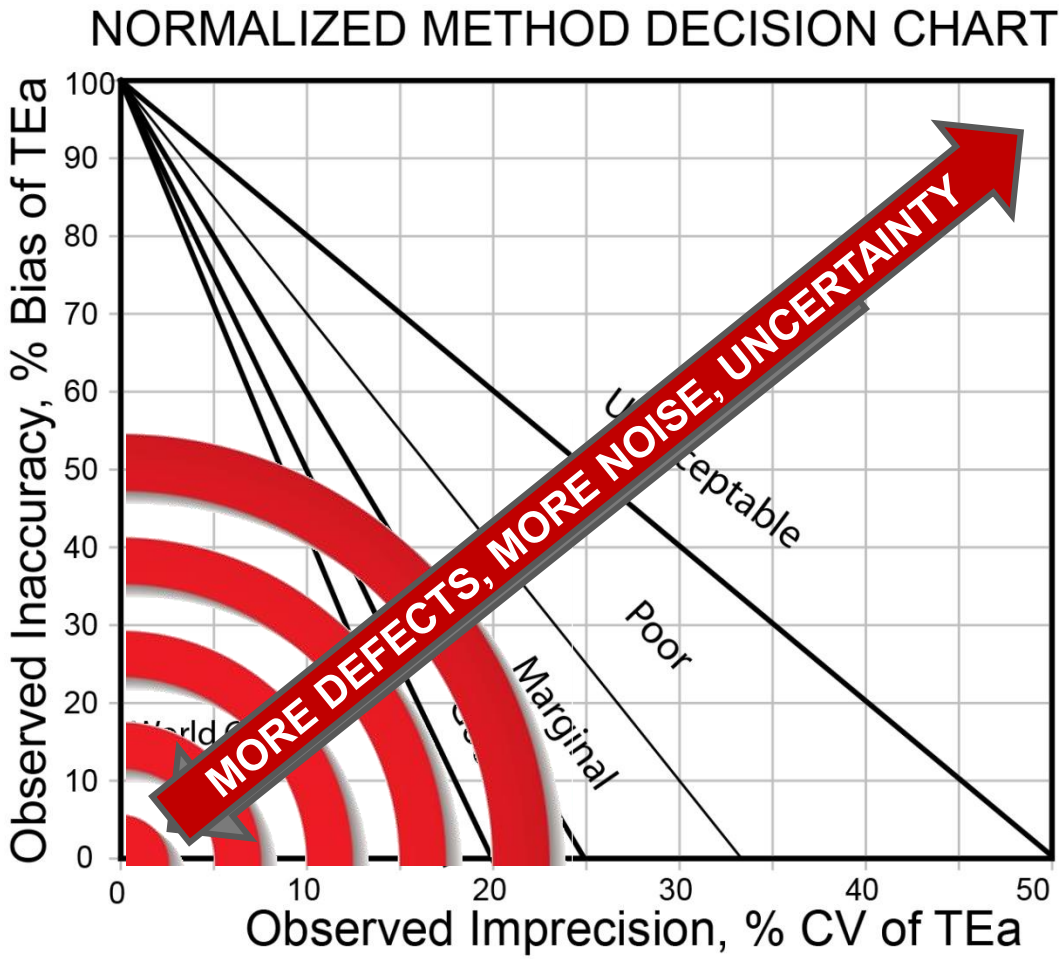
- Can we measure imprecision (CV)?
- Can we measure inaccuracy (bias)?
- ***Capture this data at critical medical decision levels - for ART, the cutoff for virological failure***

SIGMA METRIC EQUATION FOR ANALYTICAL PROCESS PERFORMANCE

Sigma-metric = (TE_a – Bias)/CV



AN EASIER WAY TO THINK ABOUT THE METHOD DECISION CHART



AN EXAMPLE OF HIV-1 VIRAL LOAD ASSAYS

JCM
Journals.ASM.org

Evaluation of the RealTime HIV-1, Xpert HIV-1, and Aptima HIV-1 Quant Dx Assays in Comparison to the NucliSens EasyQ HIV-1 v2.0 Assay for Quantification of HIV-1 Viral Load

Orna Mor,[a] Yael Gozlan,[a] Marina Wax,[a] Fernando Mileguir,[a] Avia Rakovsky,[a] Bina Noy,[b] Ella Mendelson,[a,c] Itzchak Levy[d]

National HIV Reference Laboratory, Central Virology Laboratory, Ministry of Health, Sheba Medical Center, Ramat-Gan, Israel[a]; Ilex Medical, Petach Tikva, Israel[b]; School of Public Health, Tel Aviv University, Tel Aviv, Israel[c]; Infectious Diseases Unit, Sheba Medical Center, Ramat-Gan, Israel[d]

HIV-1 RNA monitoring, both before and during antiretroviral therapy, is an integral part of HIV management worldwide. Measurements of HIV-1 viral loads are expected to assess the copy numbers of all common HIV-1 subtypes accurately and to be equally sensitive at different viral loads. In this study, we compared for the first time the performance of the NucliSens v2.0, RealTime HIV-1, Aptima HIV-1 Quant Dx, and Xpert HIV-1 viral load assays. Plasma samples ($n = 404$) were selected on the basis of their NucliSens v2.0 viral load results and HIV-1 subtypes. Concordance, linear regression, and Bland-Altman plots were assessed, and mixed-model analysis was utilized to compare the analytical performance of the assays for different HIV-1 subtypes and for low and high HIV-1 copy numbers. Overall, high concordance (>83.89%), high correlation values (Pearson r values of >0.89), and good agreement were observed among all assays, although the Xpert and Aptima assays, which provided the most similar outputs (estimated mean viral loads of 2.67 log copies/ml [95% confidence interval [CI], 2.50 to 2.84 log copies/ml] and 2.68 log copies/ml [95% CI, 2.49 to 2.86 log copies/ml], respectively), correlated best with the RealTime assay (89.8% concordance, with Pearson r values of 0.97 to 0.98). These three assays exhibited greater precision than the NucliSens v2.0 assay. All assays were equally sensitive for subtype B and AG/G samples and for samples with viral loads of 1.60 to 3.00 log copies/ml. The NucliSens v2.0 assay underestimated A1 samples and those with viral loads of >3.00 log copies/ml. The RealTime assay tended to

Brand A
Brand X
Brand N
Ref

Mor O, Gozlan Y, Max M et al 2015. Evaluation of the RealTime HIV-1, Xpert HIV-1 and Aptima HIV-1 Quant Dx assays in comparison to the NucliSens EasyQ HIV-1 2.0 asay for quantification of HIV-1 viral load. J Clin Microbiol 53:3458-3465.

AN EXAMPLE OF HIV-1 VIRAL LOAD ASSAYS

Brand N at the key decision level:

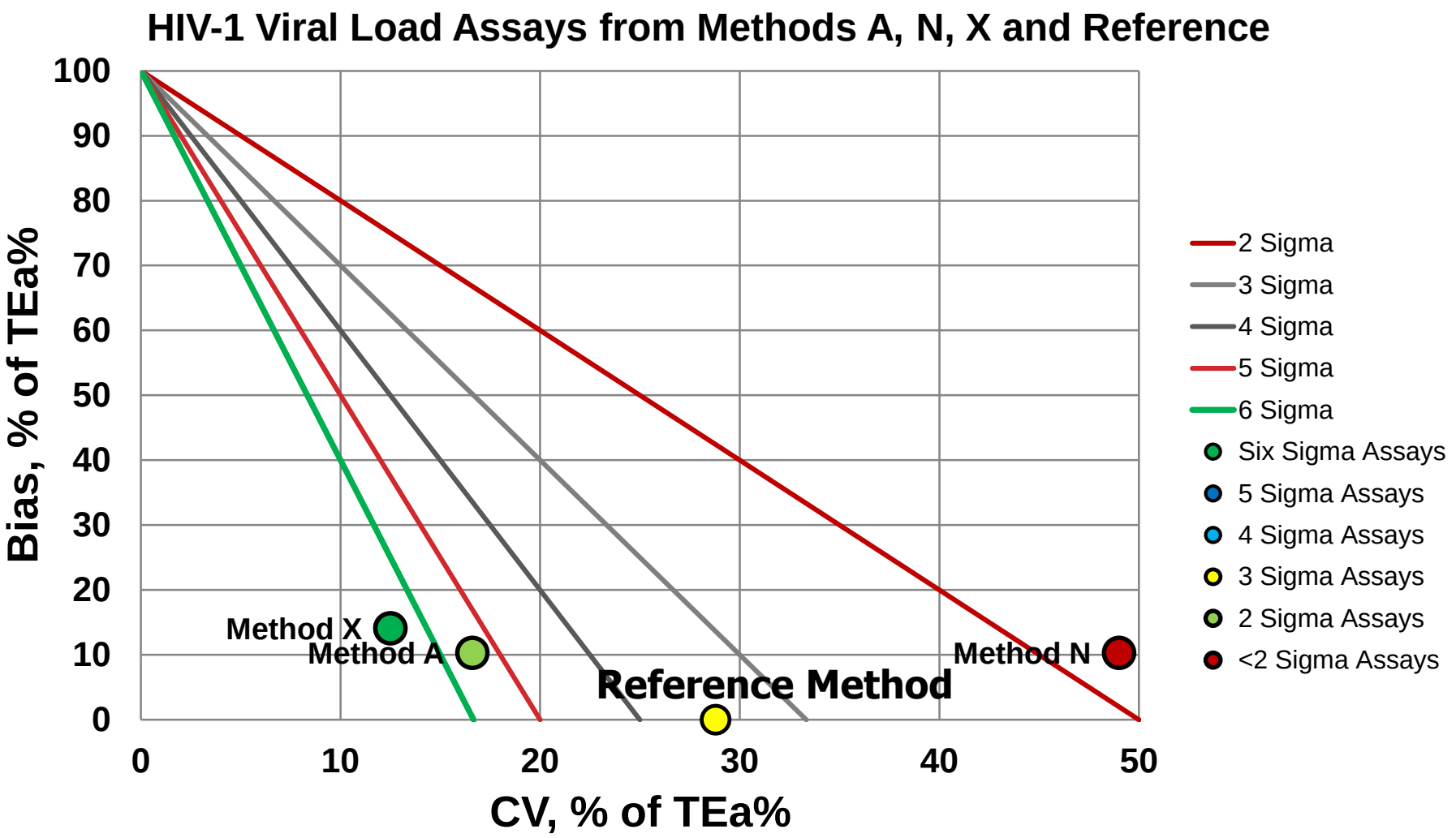
- 18.3% CV
- 3.08% Bias
- Sigma-metric = (30 – 3.08) / 18.3
  = 26.93 / 18.03
  = 1.47 Sigma

Brand X at the key decision level:

- 3.8% CV
- 4.23% Bias
- Sigma-metric = (30 - 4.23) / 3.8
  - =25.77 / 3.8
  - 6.78 Sigma

Mor O, Gozlan Y, Max M et al 2015. Evaluation of the RealTime HIV-1, Xpert HIV-1 and Aptima HIV-1 Quant Dx assays in comparison to the NucliSens EasyQ HIV-1 2.0 asay for quantification of HIV-1 viral load. J Clin Microbiol 53:3458-3465.

SIGMA PERFORMANCE OF HIV-1 VIRAL LOAD ASSAYS, 2015



ANOTHER EXAMPLE POC HIV VL ASSAY

JCM
Journals.ASM.org

Laboratory Evaluation of the Liat HIV Quant (IQuum) Whole-Blood and Plasma HIV-1 Viral Load Assays for Point-of-Care Testing in South Africa

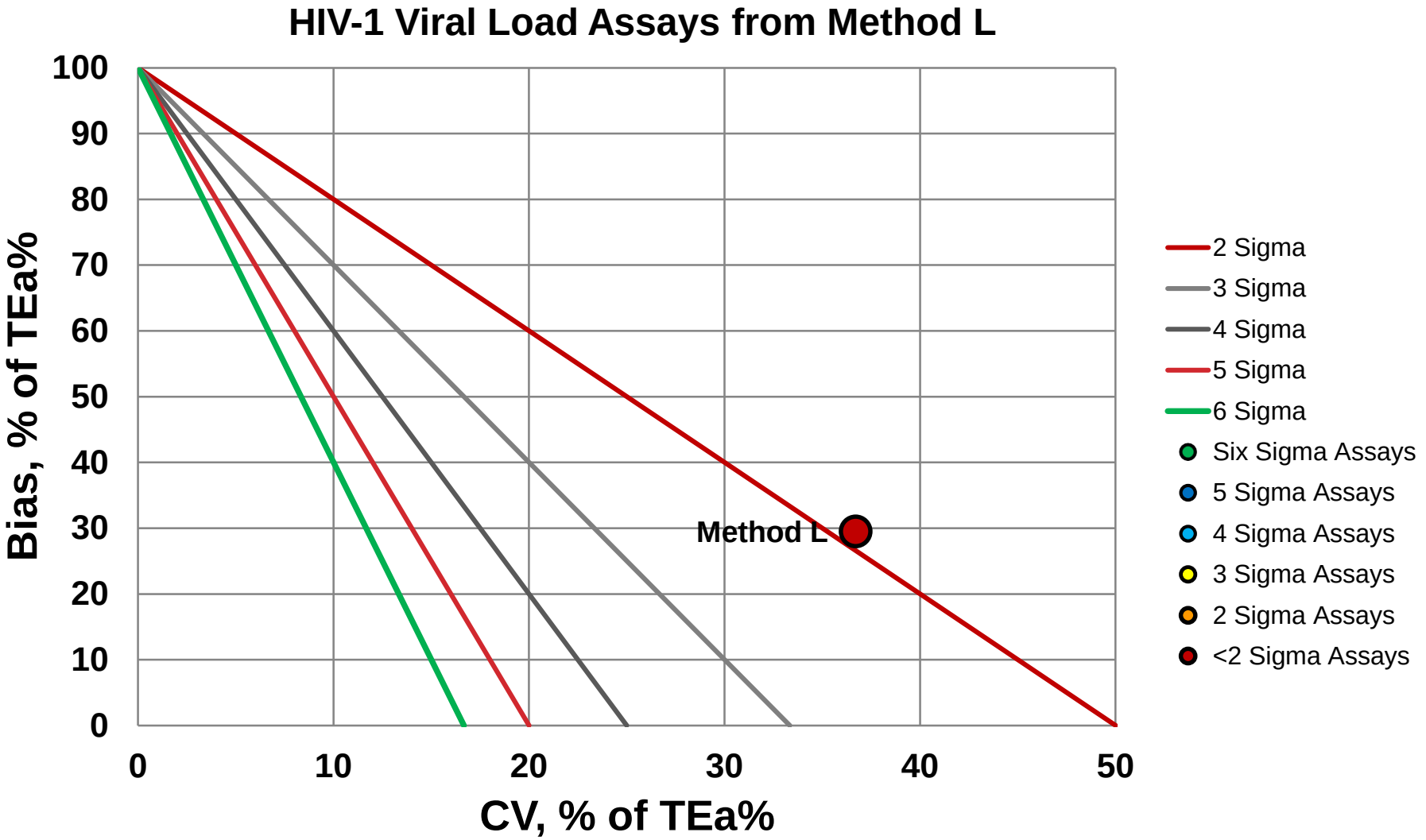
Lesley Scott,[a] Natasha Gous,[a] Sergio Carmona,[a,b] Wendy Stevens[a,b]

Department of Haematology and Molecular Medicine, School of Pathology, Faculty of Health Science, University of Witwatersrand, Johannesburg, South Africa[a]; National Health Laboratory Services, National Priority Program, Johannesburg, South Africa[b]

Point-of-care (POC) HIV viral load (VL) testing offers the potential to reduce turnaround times for antiretroviral therapy monitoring, offer near-patient acute HIV diagnosis in adults, extend existing centralized VL services, screen women in labor, and prompt pediatrics to early treatment. The Liat HIV Quant plasma and whole-blood assays, prerelease version, were evaluated in South Africa. The precision, accuracy, linearity, and agreement of the Liat HIV Quant whole-blood and plasma assays were compared to those of reference technologies (Roche CAP CTMv2.0 and Abbott RealTime HIV-1) on an HIV verification plasma panel ($n = 42$) and HIV clinical specimens ($n = 163$). HIV Quant plasma assay showed good performance, with a 2.7% similarity coefficient of variation (CV) compared to the Abbott assay and a 1.8% similarity CV compared to the Roche test on the verification panel, and 100% specificity. HIV Quant plasma had substantial agreement (p_c [concordance correlation] = 0.96) with Roche on clinical specimens and increased variability ($p_c = 0.73$) in the range of <3.0 log copies/ml range with the HIV Quant whole-blood assay. HIV Quant plasma assay had good linearity (2.0 to 5.0 log copies/ml; $R^2 = 0.99$). Clinical sensitivity at a viral load of 1,000 copies/ml of the HIV Quant plasma and whole-blood assays compared to that of the Roche assay ($n = 94$) was 100% (confidence interval [CI], 95.3% to 100%). The specificity of HIV Quant plasma was 88.2% (CI, 63.6% to 98.5%), and that for whole blood was 41.2% (CI, 18.4% to 67.1%). No virological failure (downward misclassification) was missed. Liat HIV Quant plasma assay can be interchanged with existing VL technology in South Africa. Liat HIV Quant whole-blood assay would be advantageous for POC early infant diagnosis at birth and adult adherence monitoring and needs to be evaluated further in this clinical context. LIAT cartridges currently require cold storage, but the technology is user-friendly and robust. Clinical cost and implementation modeling is required.

Scott L, Gous N, Carmona S, Stevens W, 2015. Laboratory evaluation of Liat HIV Quant (Iquum) whole blood and plasma HIV-1 viral load assays for point-of-care testing in South Africa. J Clin Microbiol 53:1616-1621.

METHOD L POC HIV VL PERFORMANCE



ANOTHER EXAMPLE POC HIV VL ASSAY

AMERICAN SOCIETY FOR MICROBIOLOGY | Journal of Clinical Microbiology

Evaluation of the Whole-Blood Alere Q NAT Point-of-Care RNA Assay for HIV-1 Viral Load Monitoring in a Primary Health Care Setting in Mozambique

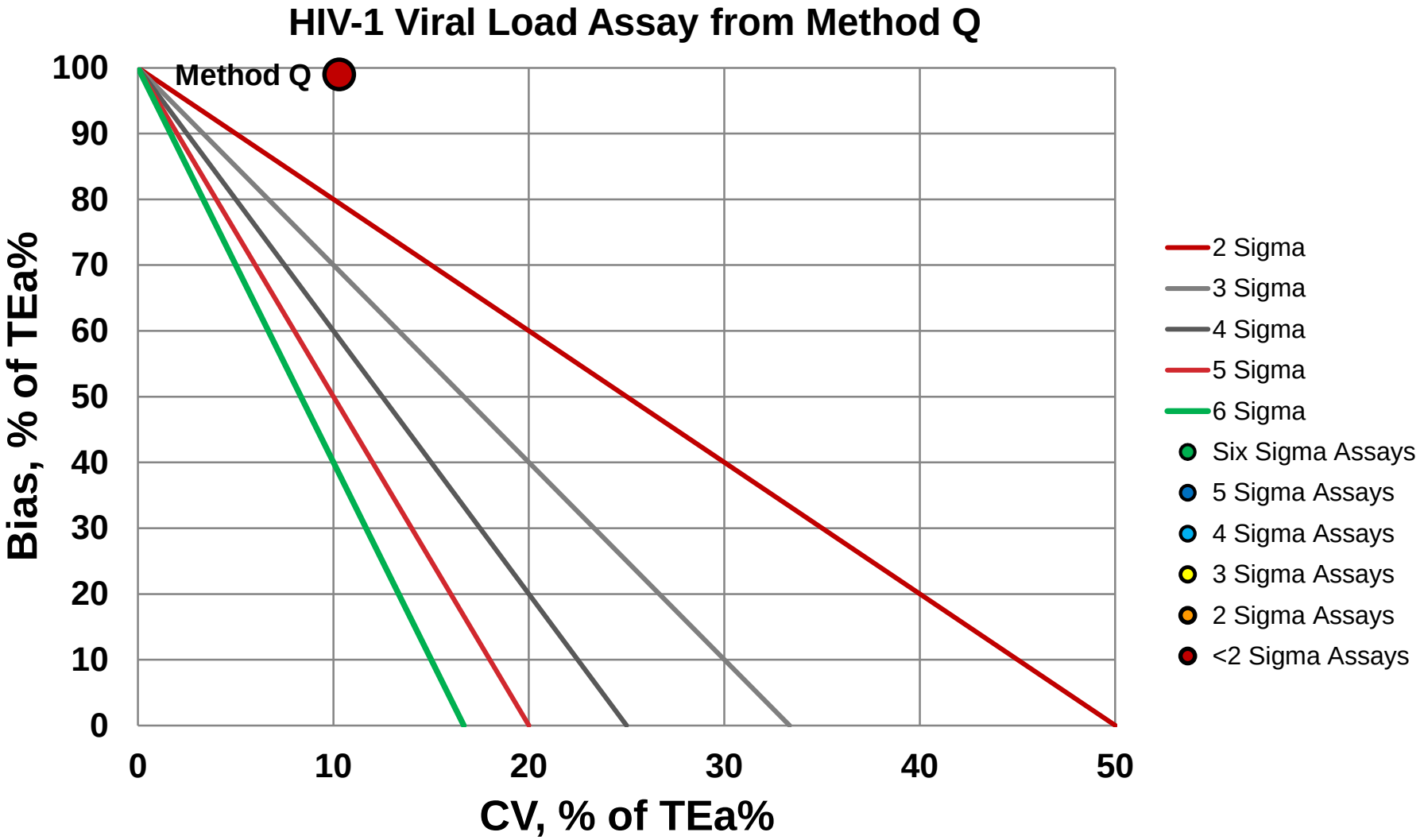
Ilesh V. Jani,[a] Bindiya Meggi,[a] Adolfo Vubil,[a] Nádia E. Sitoe,[a] Nilesh Bhatt,[a] Ocean Tobaiwa,[b] Jorge I. Quevedo,[b] Osvaldo Loquiha,[c] Jonathan D. Lehe,[b] Lara Vojnov,[b] Trevor F. Peter[b]

Instituto Nacional da Saúde, Maputo, Mozambique[a]; Clinton Health Access Initiative, Maputo, Mozambique[b]; Department of Mathematics and Informatics, Universidade Eduardo Mondlane, Maputo, Mozambique[c]

Viral load testing is the WHO-recommended monitoring assay for patients on HIV antiretroviral therapy (ART). Point-of-care (POC) assays may help improve access to viral load testing in resource-limited settings. We compared the performance of the Alere Q NAT POC viral load technology (Alere Technologies, Jena, Germany), measuring total HIV RNA using finger prick capillary whole-blood samples collected in a periurban health center, with that of a laboratory-based plasma RNA test (Roche Cobas Ampliprep/Cobas TaqMan v2) conducted on matched venous blood samples. The whole-blood Alere Q NAT POC assay produced results with a bias of 0.8593 log copy/ml compared to the laboratory-based plasma assay. However, at above 10,000 copies/ml, the bias was 0.07 log copy/ml. Using the WHO-recommended threshold to determine ART failure of 1,000 copies/ml, the sensitivity and specificity of the whole-blood Alere Q NAT POC assay were 96.83% and 47.80%, respectively. A cutoff of 10,000 copies/ml of whole blood with the Alere Q NAT POC assay appears to be a better predictor of ART failure threshold (1,000 copies/ml of plasma), with a sensitivity of 84.0% and specificity of 90.3%. The precision of the whole-blood Alere Q NAT POC assay was comparable to that observed with the laboratory technology (5.4% versus 7.5%) between detectable paired samples. HIV POC viral load testing is feasible at the primary health care level. Further research on the value of whole-blood viral load to monitor antiretroviral therapy is warranted.

Jani IV, Meggi B, Vubil A, Sitoe NE, Bhatt N, Tobaiwa O, Quevedo JI, Loquiha O, Lehe JD, Vojnov L, Peter TF. 2016. Evaluation of the whole-blood Alere Q NAT point-of-care RNA assay for HIV-1 viral load monitoring in a primary health care setting in Mozambique. J Clin Microbiol 54:2104 –2108.

METHOD Q POC HIV VL CAPILLARY PERFORMANCE



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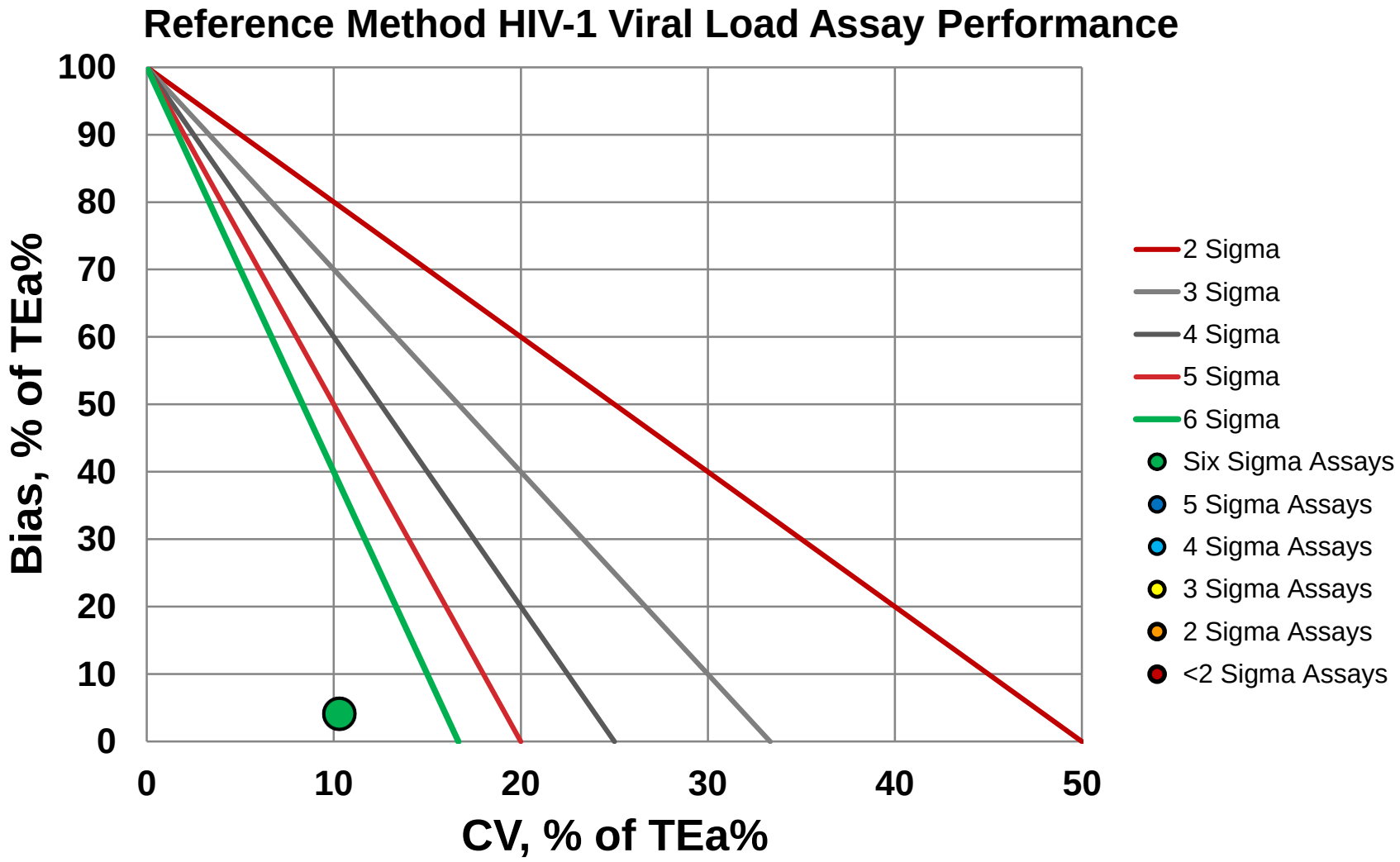
FROM THE DIAGNOSTICS PREQUALIFICATION DOCS



A SECOND LOOK AT BRAND X POC HIV VL

GeneXpert HIV-1 quant assay, a new tool for scale up of viral load monitoring in the success of ART programme in India

Smita Kulkarni, Sushama Jadhav, Priyanka Khopkar, Suvarna Sane, Rajkumar Londhe, Vaishali Chimanpure, Veronica Dhilpe, Manisha Ghate, Rajendra Yelagate, Narayan Panchal, Girish Rahane, Dilip Kadam, Nitin Gaikwad, Bharat Rewari and Raman Gangakhedkar

BMC Infectious Diseases BMC series – open, inclusive and trusted 2017 **17**:506
https://doi.org/10.1186/s12879-017-2604-5 | © The Author(s). 2017
Received: 12 March 2017 | **Accepted:** 17 July 2017 | **Published:** 21 July 2017

GeneXpert HIV-1 quant assay, a new tool for scale up of viral load monitoring in the success of ART programme in India
Smita Kulkarni, Sushama Jadhav, Priyanka Khopkar, Suvarna Sane, Rajkumar Londhe, Vaishali Chimanpure, Veronica Dhilpe, Manisha Ghate, Rajendra Yelagate, Narayan Panchal, Girish Rahane, Dilip Kadam, Nitin Gaikwad, Bharat Rewari and Raman Gangakhedkar
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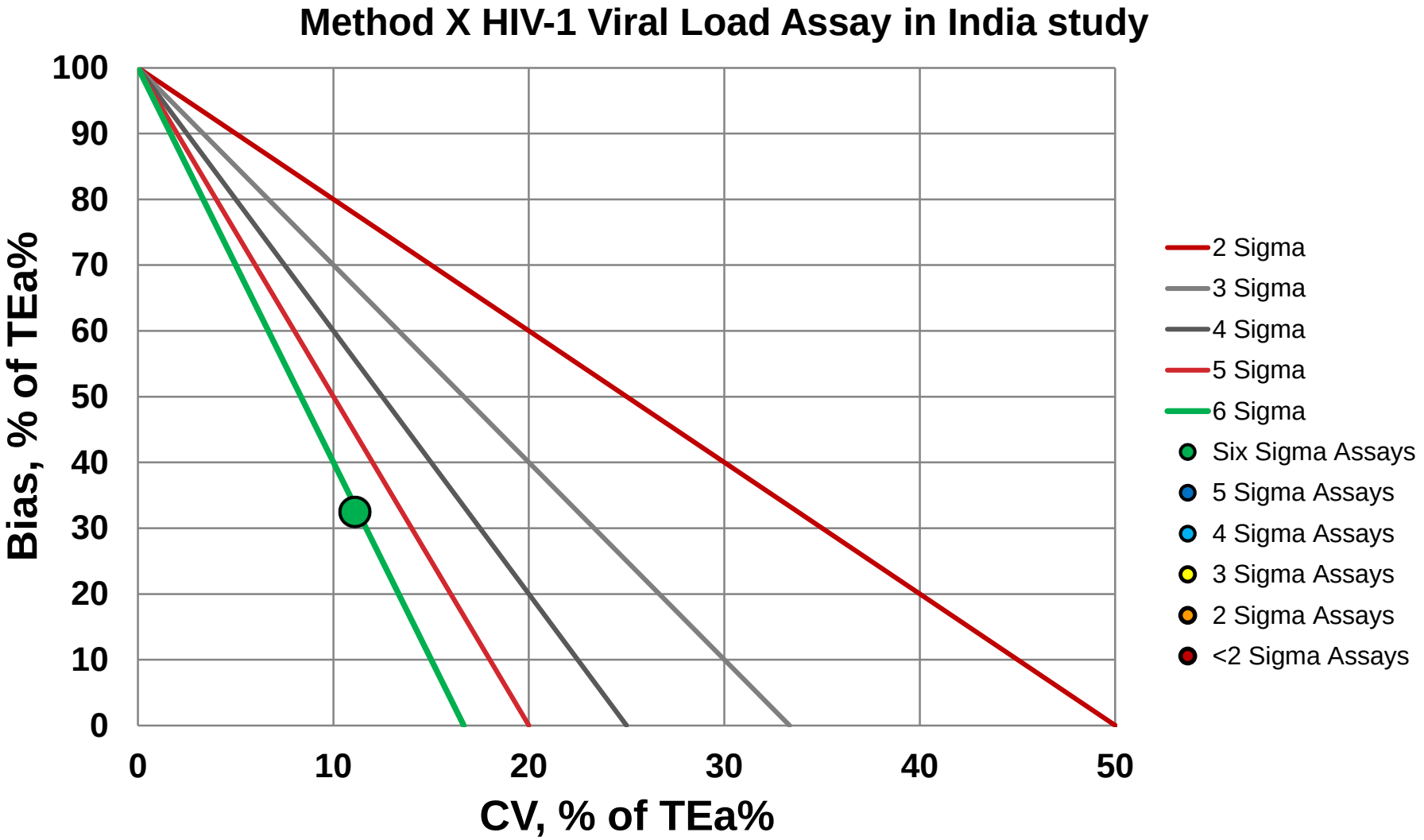
https://doi.org/10.1186/s12879-017-2604-5

A SECOND LOOK AT BRAND X POC HIV VL



QUICK REVIEW OF HIV VL QUALITY: WHAT DOES IT MEAN?

Method	Sigma-metric	Control Rules	N	QC Frequency	Controls per 1000
A	**5**				
N	**<2**				
X	**>6**				
L	**<2**				
Q	**<2**				
Reference	**3**				
X take 2	**>6**				
Ref take 2	**>6**				

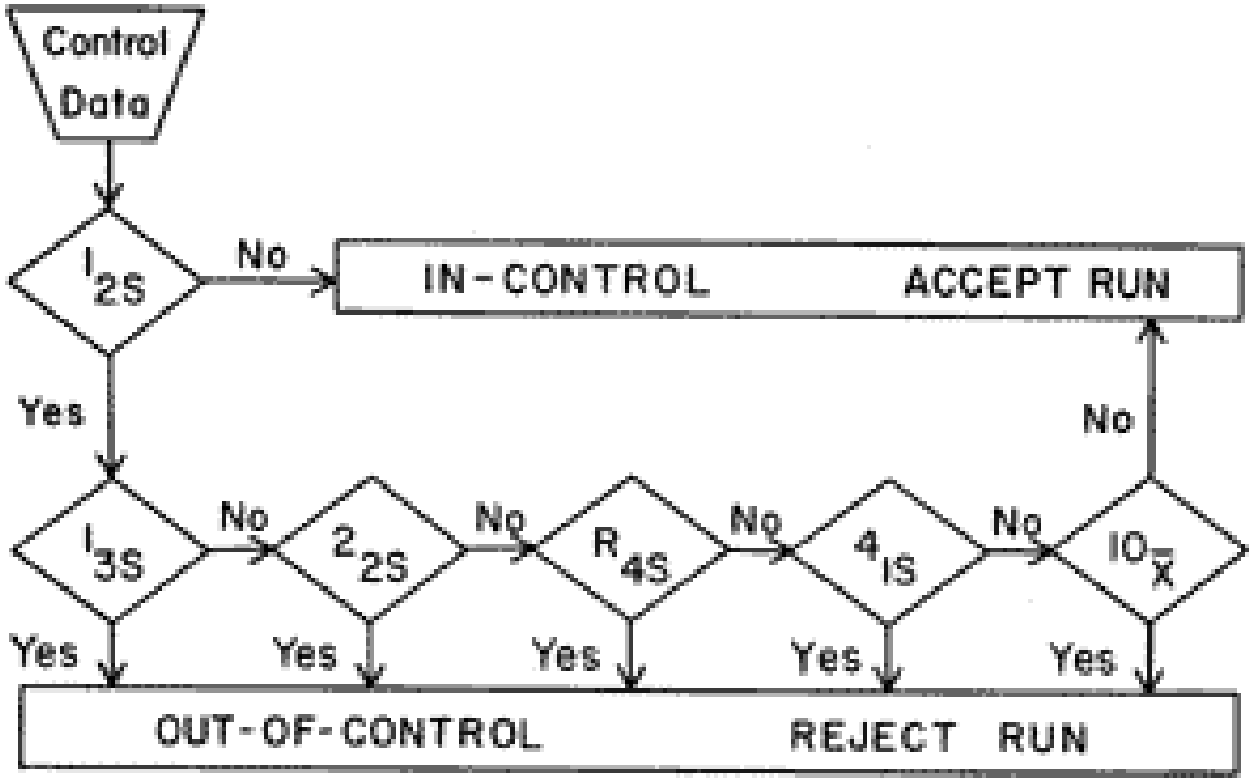
NOTHING BUT THE TRUTH FOR 90-90-90

- *To provide **Nothing but the Truth**, a test result should not be confounded by unknown or undisclosed factors, such as changes in the subject due to biological variation or changes in the method due to lack of stability and quality control.*

- So far, we've only looked at analytical errors – there are many other kinds
- High Sigma-metric methods allow room in the error budget for pre-analytical and post-analytical errors
- Low Sigma-metric methods leave no room for error – or just make errors no matter how well the sample is handled

- ***Now, How do we assure Quality Control for POC VL?***

QC VIA THE ORIGINAL "WESTGARD RULES"

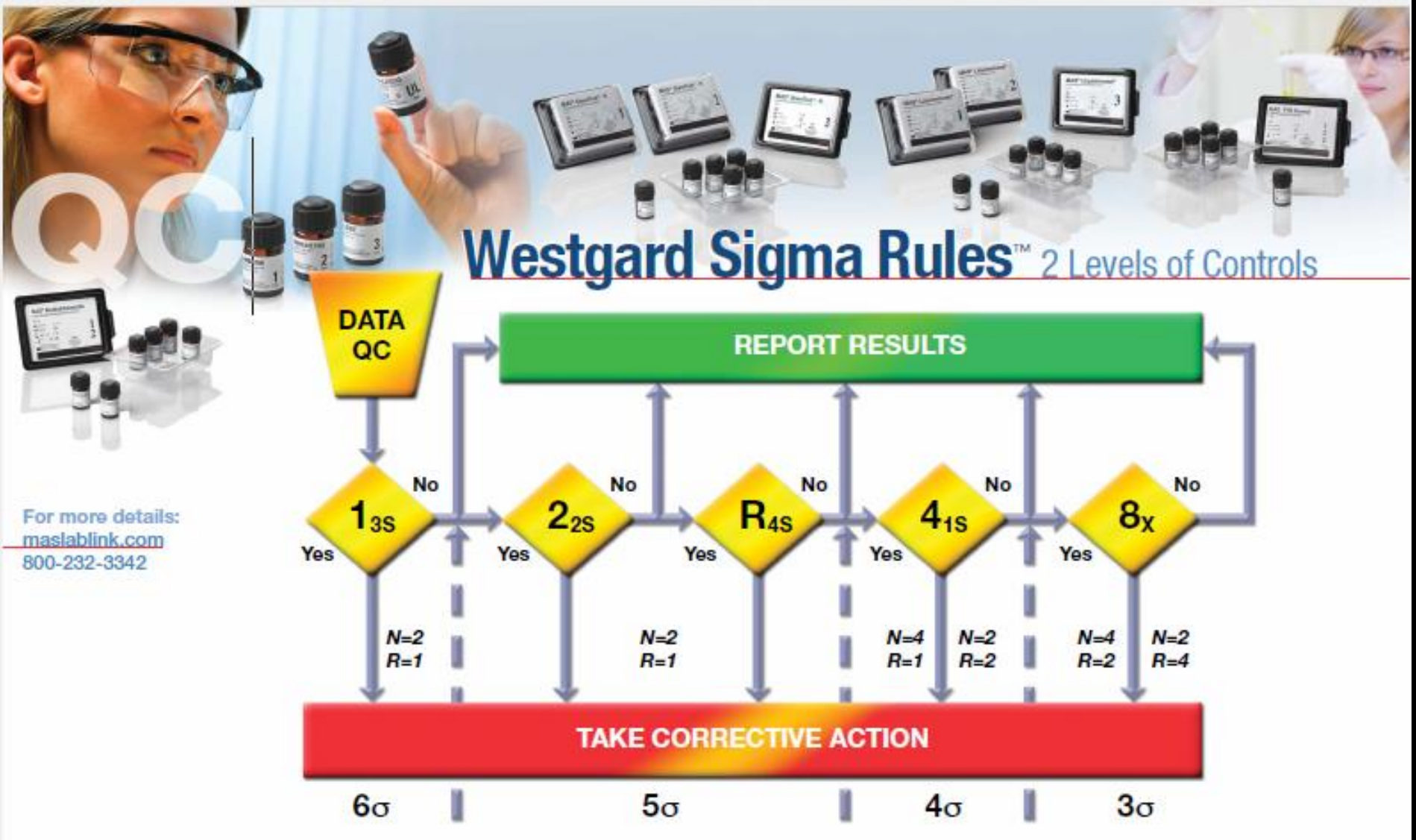


Westgard JO, Barry PL, Hunt MR, Groth T. A multi-rule Shewhart chart for quality control in clinical chemistry. Clin Chem 1981;27:493-501.

https://www.westgard.com/mltirule.htm
https://www.westgard.com/westgard-rules.htm

WESTGARD QC

THE LATEST EVOLUTION: WESTGARD SIGMA RULES



QC FREQUENCY

RUN LENGTH

CAN WE DEVELOP A DATA-DRIVEN WAY TO DETERMINE QC FREQUENCY?

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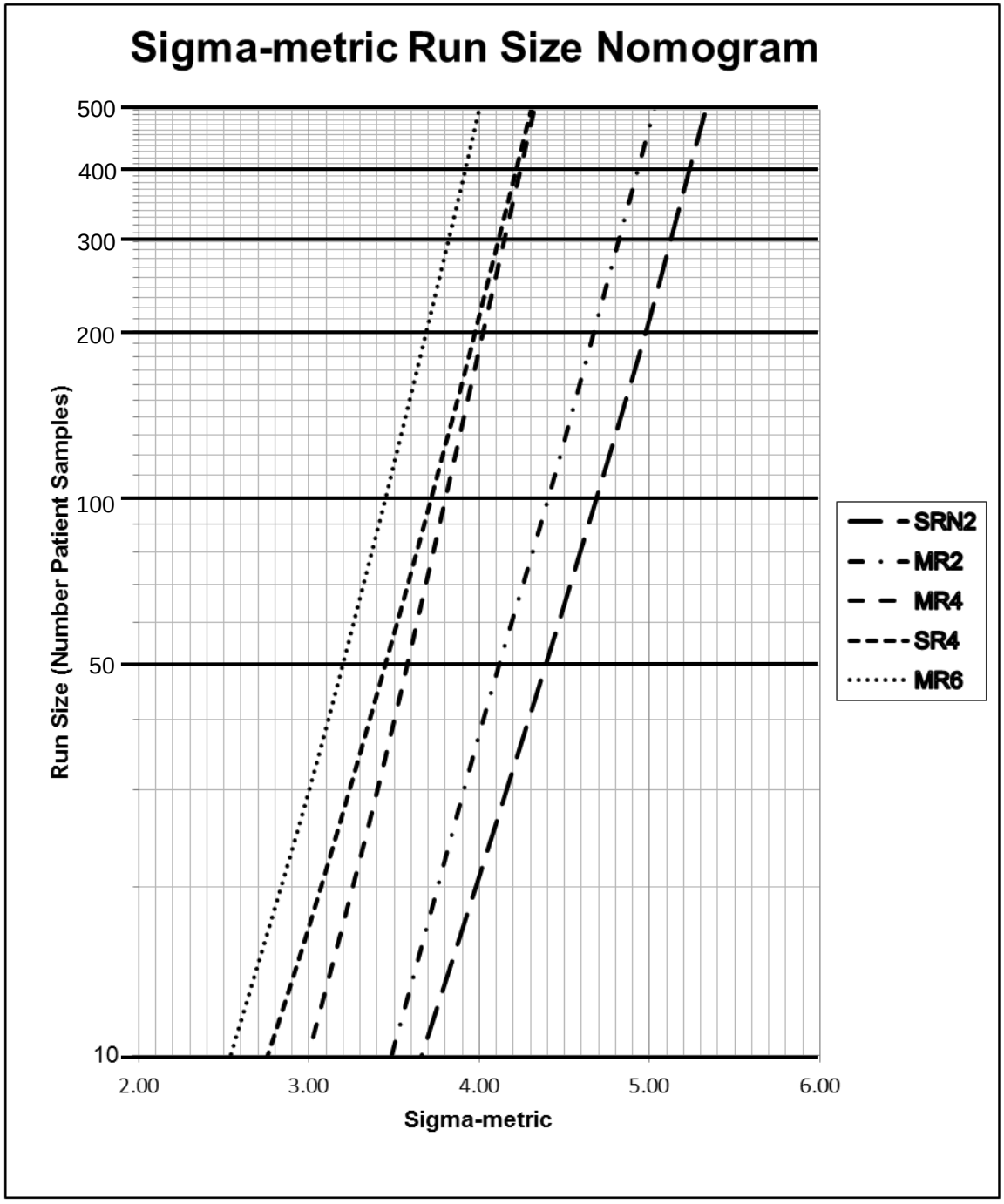
NEWEST WESTGARD TOOL: QUANTITATIVE RISK ASSESSMENT OF TESTING?

SIGMA QC FREQUENCY NOMOGRAM



SIX SIGMA TOOLS FOR QC DESIGN AND FREQUENCY

Sigma-metric	Control Rule	N	QC Frequency	Controls per 1000
Six Sigma	1:3s	2	1 per **1000** patients	2
Five Sigma	1:3s/2:2s/R:4s	2	1 per **400** patients	10
Four Sigma	1:3s/2:2s/R:4s/4:1s	4	1 per **200** patients	20
Three Sigma	1:3s/2:2s/R:4s/4:1s/10:x	8	1 per **50** patients	120
≤ Two Sigma	1:3s/2:2s/R:4s/4:1s/10:x	8,12,??	1 per **10** patients	600

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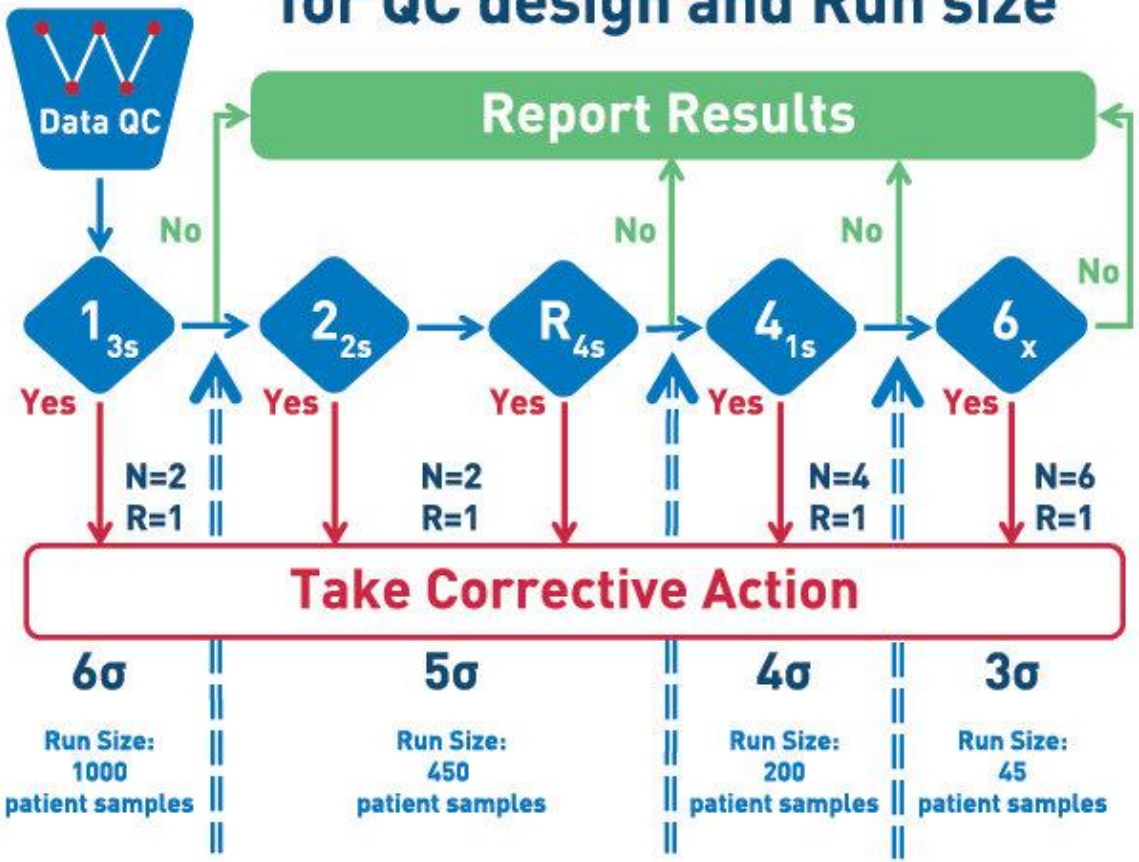
TECHNOPATH CLINICAL DIAGNOSTICS

Westgard Sigma Rules® for QC design and Run size



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Sigma Scale = (%TEa-%Bias)/%CV

Ref. Clin Chem 2018; 64:289-296

THE QUALITY CONTROL COMPANY

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QUICK REVIEW OF HIV VL QUALITY: WHAT DOES IT MEAN?

Method	Sigma-metric	Control Rules	N	QC Frequency	QC events per 1000
A	**5**	**1:3s/2:2s/R:4s**	**2**	**1 per 450**	**2**
N	**<2**	1:3s/2:2s/R:4s/4:1s/10:x	8	1 per 10	100
X	**>6**	**1:3s**	**2**	**1 per 1000**	**1**
L	**<2**	1:3s/2:2s/R:4s/4:1s/10:x	8	1 per 10	100
Q	**<2**	1:3s/2:2s/R:4s/4:1s/10:x	8	1 per 10	100
Reference	**3**	1:3s/2:2s/R:4s/4:1s/10:x	8	1 per 10	100
X take 2	**>6**	**1:3s**	**2**	**1 per 1000**	**1**
Ref take 2	**>6**	**1:3s**	**2**	**1 per 1000**	**1**

GOALS

1. Know your Sigma – There are Great methods and Poor methods out there.

2. Adjust your QC rules, controls, and frequency to the Sigma of your method – you can save a lot of effort if you have 6 Sigma, but 3 Sigma means a lot of QC

3. If you can't afford the QC, you can't afford the method - demand better from your vendor

THE TRUTH, THE WHOLE TRUTH, AND NOTHING BUT THE TRUTH FOR UNAIDS 90-90-90

- We are not seeking perfection, nor will we be able to achieve it in the current program structure with the currently available diagnostics devices
- We can do better, in practice, in performance, and eventually in program goal-setting
- POC VL methods are mostly poor in quality, which will significantly impede progress in the 90-90-90 initiative
- Careful selection of VL methods will be essential to supporting the success of 90-90-90

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Thank you for your time. Questions?