March 23, 2017

MEDICAL DEVICE INNOVATION CONSORTIUM (MDIC)
CLINICAL DIAGNOSTICS PROJECT REPORT

CONTRIVED / SURROGATE SAMPLE USE SURVEY RESULTS

- A SURVEY OF THE MEDICAL DEVICE INDUSTRY / FDA / LABORATORIES

Introduction to the MDIC Contrived/Surrogate Sample Use Survey Results

The Medical Device Innovation Consortium (MDIC), a 501(c)3 organization, is the first public-private partnership focused exclusively on advancing regulatory science of the medical device industry. MDIC is designed to create a collaborative environment where sponsors, nonprofit organizations, and government can work together to advance pre-competitive medical device research so that the medical device community can keep pace with the needs of patients in the United States in a timely manner. For additional information visit www.mdic.org .

The speed at which innovative and improved diagnostics are developed is dependent upon clinical specimen acquisition. When clinical specimens are unavailable, the speed at which innovative and improved diagnostics are developed suffers. The difficulty in obtaining clinical specimens may be due to a variety of reasons, such as rare markers, lack of specimens with markers at the high or low end of the assay range, specimen stability, the difficulty in obtaining certain specimens due to clinical setting (e.g., emergency room), or patient care taking precedence over the ability to collect specimens under defined conditions. When clinical specimens are difficult to obtain the use of contrived/surrogate samples fosters innovation. MDIC's Contrived/Surrogate Sample (CSS) working group has been tasked to deliver a foundational framework under which the use of contrived/surrogate samples can support product innovation, with an initial focus on studies to support product submissions.

Stakeholders in the *In Vitro Diagnostics* "ecosystem" were invited to complete a survey regarding the use of Contrived / Surrogate Samples (CSS). The survey was constructed by the MDIC CSS working group in order to obtain information about stakeholder experiences with the use of contrived or surrogate samples in a variety of settings to advance regulatory science for clinical diagnostics. Respondents were queried regarding a number of technical and regulatory areas to understand barriers and challenges of using surrogate samples, as well as successful use in diagnostics by study type.

For purposes of the survey and this report, *a contrived or surrogate sample means material used as a substitute for unmodified body fluid or tissue taken directly from one patient*. The terms contrived sample and surrogate sample are used interchangeably throughout this report.

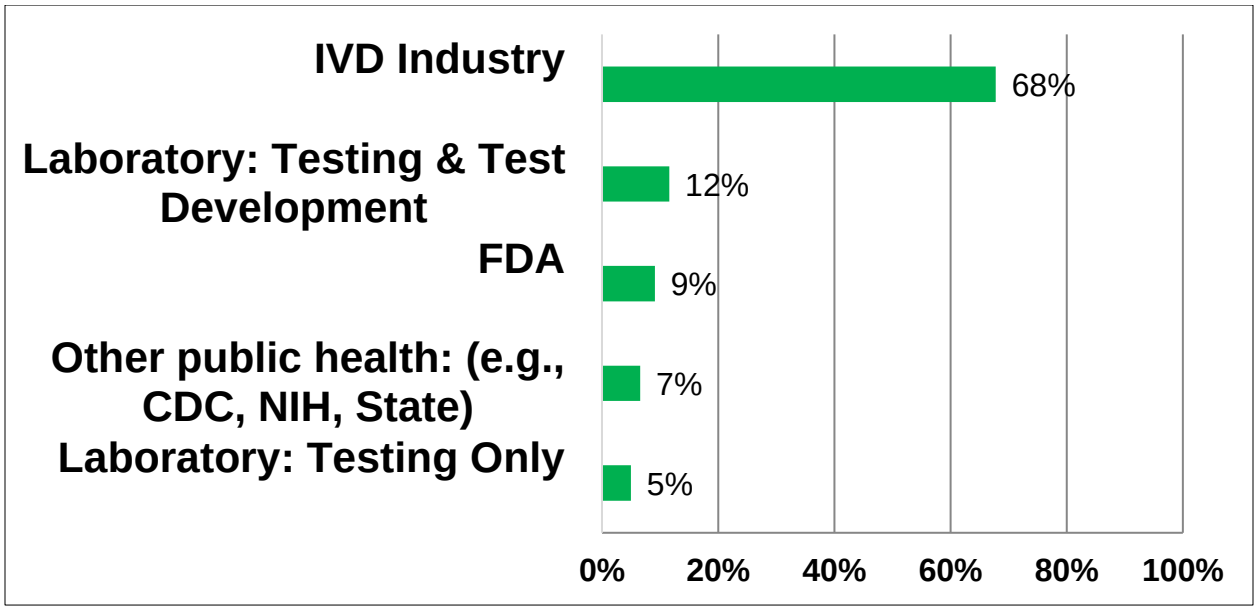
A total of 121 individuals responded to the survey. Of this total, 110 individuals were experienced with the use of surrogate samples and were invited to complete the remainder of the survey.

A few notable observations, respondents reported a variety of different experiences regarding their use of contrived/surrogate samples. When queried as to study types in which use of contrived/surrogate samples were more frequently accepted, the following ranked higher: detection limit, interference, linearity/reproducibility, method comparison, matrix comparison, and precision/reproducibility.

The goal of the MDIC CSS working group is to provide a foundational framework for the use of contrived/surrogate samples in the study types used to support in vitro diagnostic device submissions, which will provide common terminology and scientific support to foster in vitro diagnostic device innovation and improvements. We anticipate this Framework will be available during the second half of 2017 at www.mdic.org/clinicaldx/.

1. PLEASE TELL US YOUR ORGANIZATION TYPE

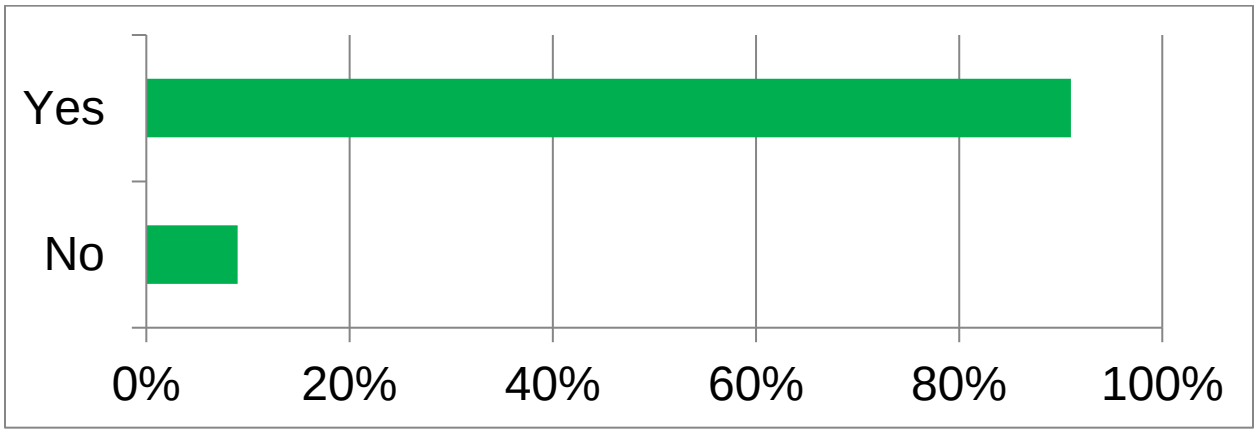
A. Laboratory: Testing Only
B. Laboratory: Testing and Test Development
C. IVD industry
D. FDA
E. Other public health (e.g., CDC, NIH, State)



N = 121

2 DO YOU HAVE EXPERIENCE WITH THE USE OF CONTRIVED/SURROGATE SAMPLES?

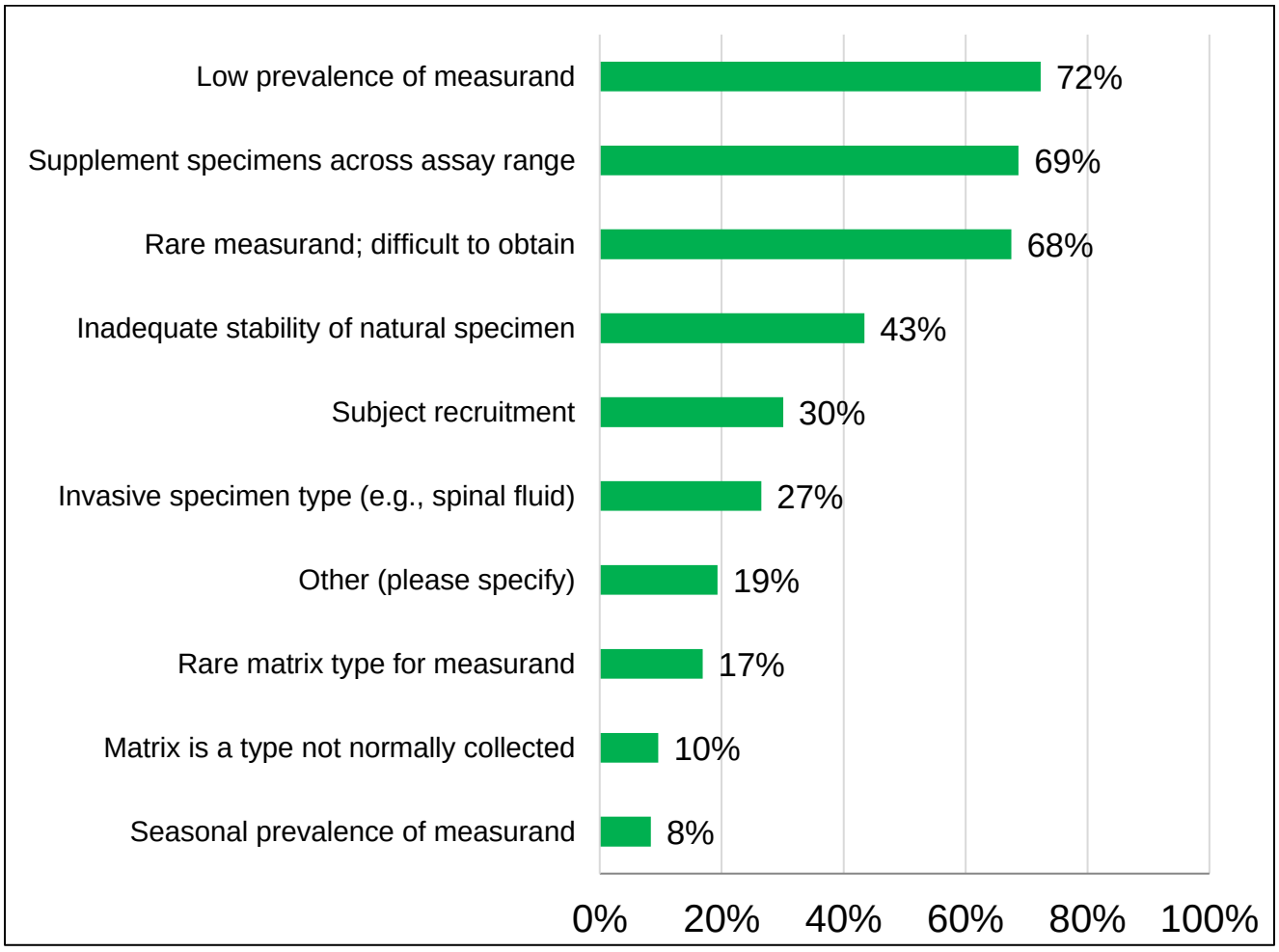
A. Yes
B. No



N = 121

3. WHY DID YOU USE CONTRIVED/SURROGATE SAMPLES? (MAY SELECT MORE THAN ONE ANSWER)

A. General low prevalence of measurand
B. Inadequate stability of naturally occurring specimen
C. Invasive specimen type (e.g., spinal fluid)
D. Matrix is a type not normally collected (e.g., sweat or skin specimen)
E. Rare matrix type for a particular measurand
F. Rare measurand, naturally occurring specimen difficult to obtain
G. Seasonal prevalence of measurand
H. Subject recruitment
I. Supplement specimens across the range for testing accuracy
J. Other



N = 83

Question 3 "Other" Responses:

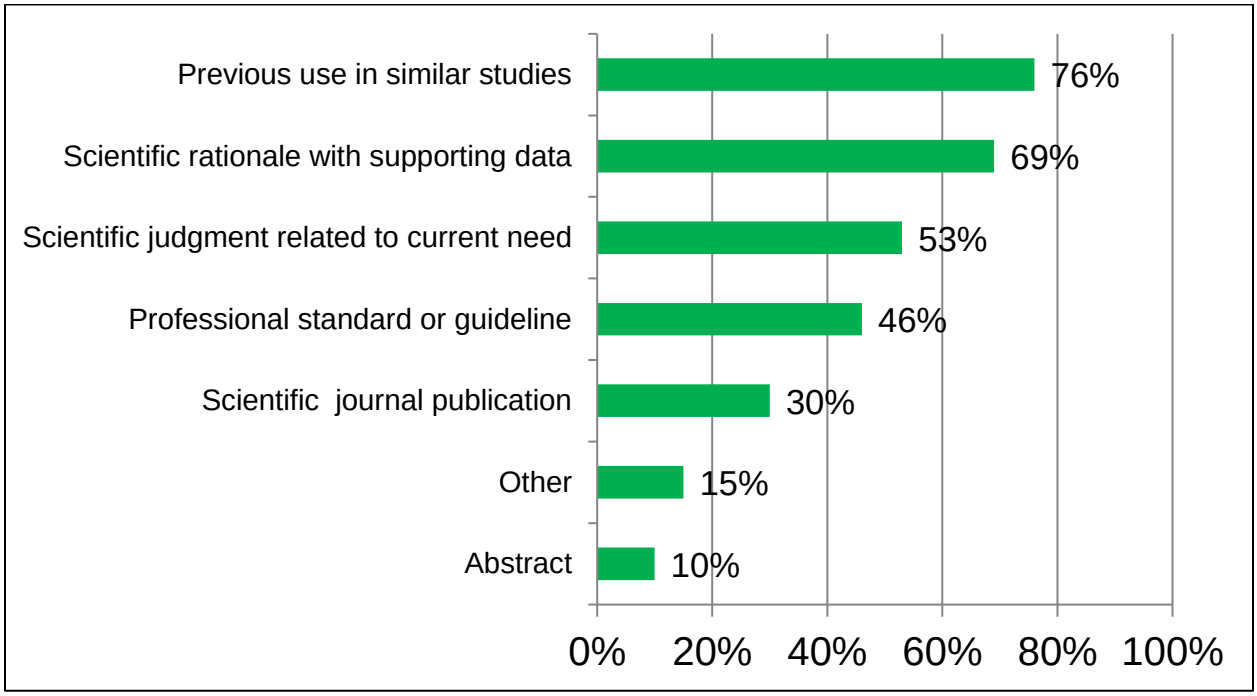
Why did you use contrive/surrogate samples?

1. Need for identical biological specimens for precision studies (remove biological variable)
2. To supplement specimens at low assay cutoffs. Insufficient volume of sample available from single subject/patient. Need samples with measurand concentration greater than what is found in clinical samples
3. Analyte being measured does not naturally occur at concentrations near limit of detection; contrived samples required to assess assay sensitivity.
4. Sometimes we need samples with > 2mL volume for multiple testing and we need to pool samples rather than individual samples.
5. Finding analyte negative native specimens not possible
6. Samples needed at extreme ranges of dynamic range to verify measuring interval. Also to supplement samples for method comparison outside reference range where clinical samples are rare or nonexistent.
7. Difficulty obtaining samples at very high or very low measurand concentrations. Difficulty obtaining fresh whole blood samples. Contrived measurand (for example recombinant material) may not fully represent natural measurand in patient samples.
8. QC, reproducibility studies
9. Lack of adequate reference method to characterize and quantify measurand in natural specimens. In ability to obtain naturally low enough levels to prepare a blank matrix
10. Measurand present at medium to high level in every natural specimen
11. Need large quantities for a PT program with up to 6,000 customers
12. Research
13. I work in a diagnostics manufacturing and R&D setting. We often use contrived samples for the purposes of 1) improved stability of measurand, 2) lack of availability of measurand, 3) lack of standardization of biological measurands, including measurands which represent groups of related proteins or metabolites.
14. To expand AMR, most subjects fall in a certain range, but FDA won't approve full linearity without proving accuracy at ends of the measurement range.
15. To have a larger volume of samples for repeatability studies

N = 15 "Other" responses

4. WHAT SCIENTIFIC RATIONALE DO YOU RELY UPON TO SUPPORT YOUR USE OF CONTRIVED/SURROGATE SAMPLES? (MAY SELECT MORE THAN ONE ANSWER)

A. Abstracts
B. Previous use of the contrived/surrogate sample in similar studies
C. Professional standard or guideline
D. Scientific journal publication
E. Scientific judgment related to current need
F. Scientific rationale with supporting data
G. Other



N = 83

Question 4: "Other" Responses

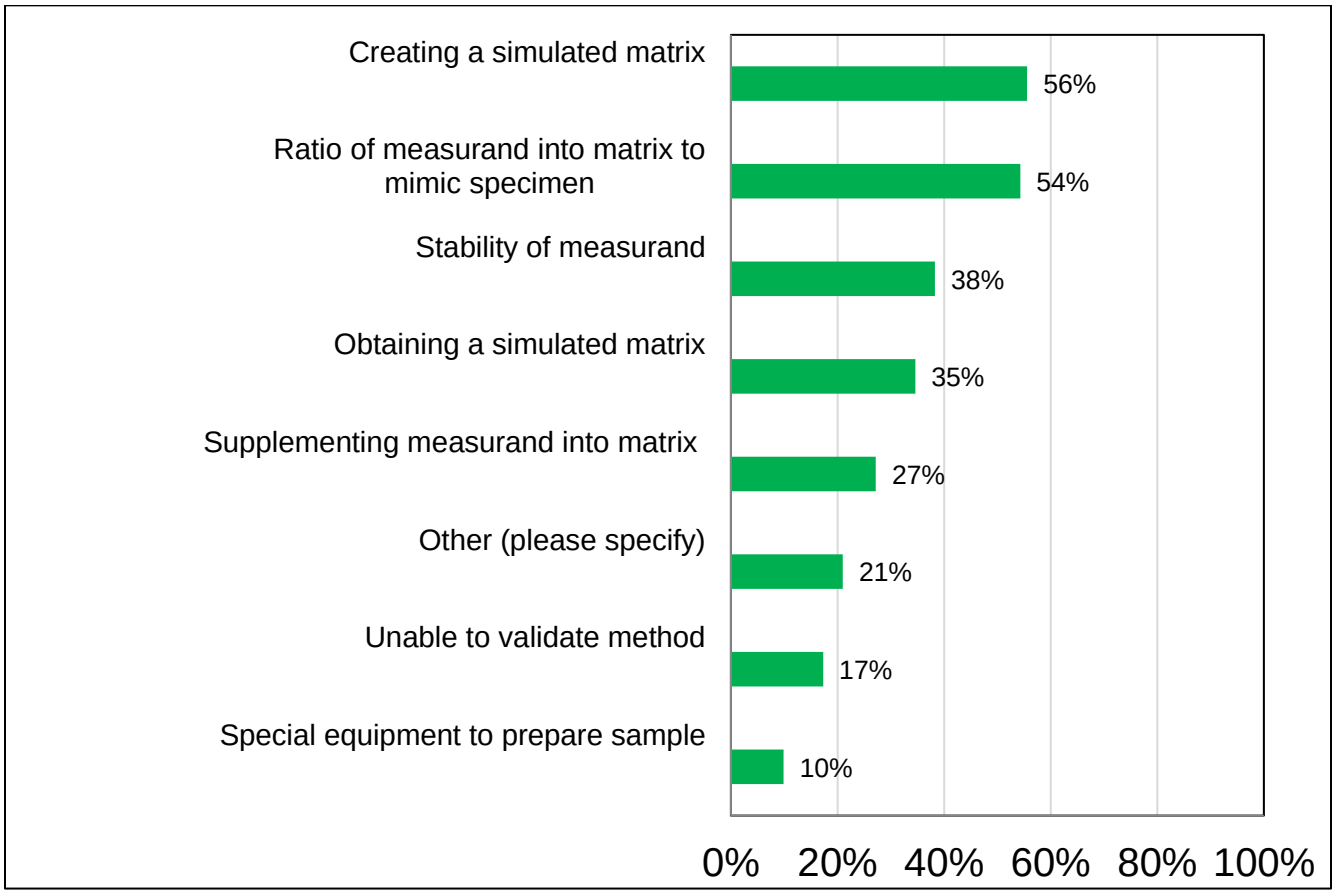
What scientific rationale do you rely upon to support your use of contrived/surrogate samples?

1. Data confirming equivalent assay performance (data requirement depends on how contrived samples will be used)-FDA guidance
2. Commutability study
3. Data generated demonstrating comparability between natural and contrived samples. Data may be generated in house or from scientific literature.
4. Pre-sub discussion with regulatory agency
5. Comparison of performance between clinical samples and contrived samples gives high concordance.
6. Precedent with other recently FDA cleared tests
7. Assay analytical and clinical validation
8. CMS allows for contrived specimens that are peer group graded
9. research use
10. We must verify and validate the use of contrived samples (including commutability). This is done through formal protocols, often based upon CLSI or regulatory body guidelines.
11. Limitations of obtaining samples at the extremes of the measuring ranges that are clinically relevant

N = 11 "Other" responses

5. WHAT TECHNICAL CHALLENGES HAVE YOU ENCOUNTERED WHEN USING CONTRIVED/SURROGATE SAMPLES? (MAY SELECT MORE THAN ONE)

A. Assessing the right ratio of measurand to supplement into matrix, so it can adequately represent clinical sample
B. Creating a simulated matrix
C. Obtaining a simulated matrix
D. Special equipment to prepare sample
E. Stability of measurand
F. Supplementing measurand into matrix (e.g., precision pipetting)
G. Unable to validate method
H. Other



N = 81

Question 5: "Other" Responses:

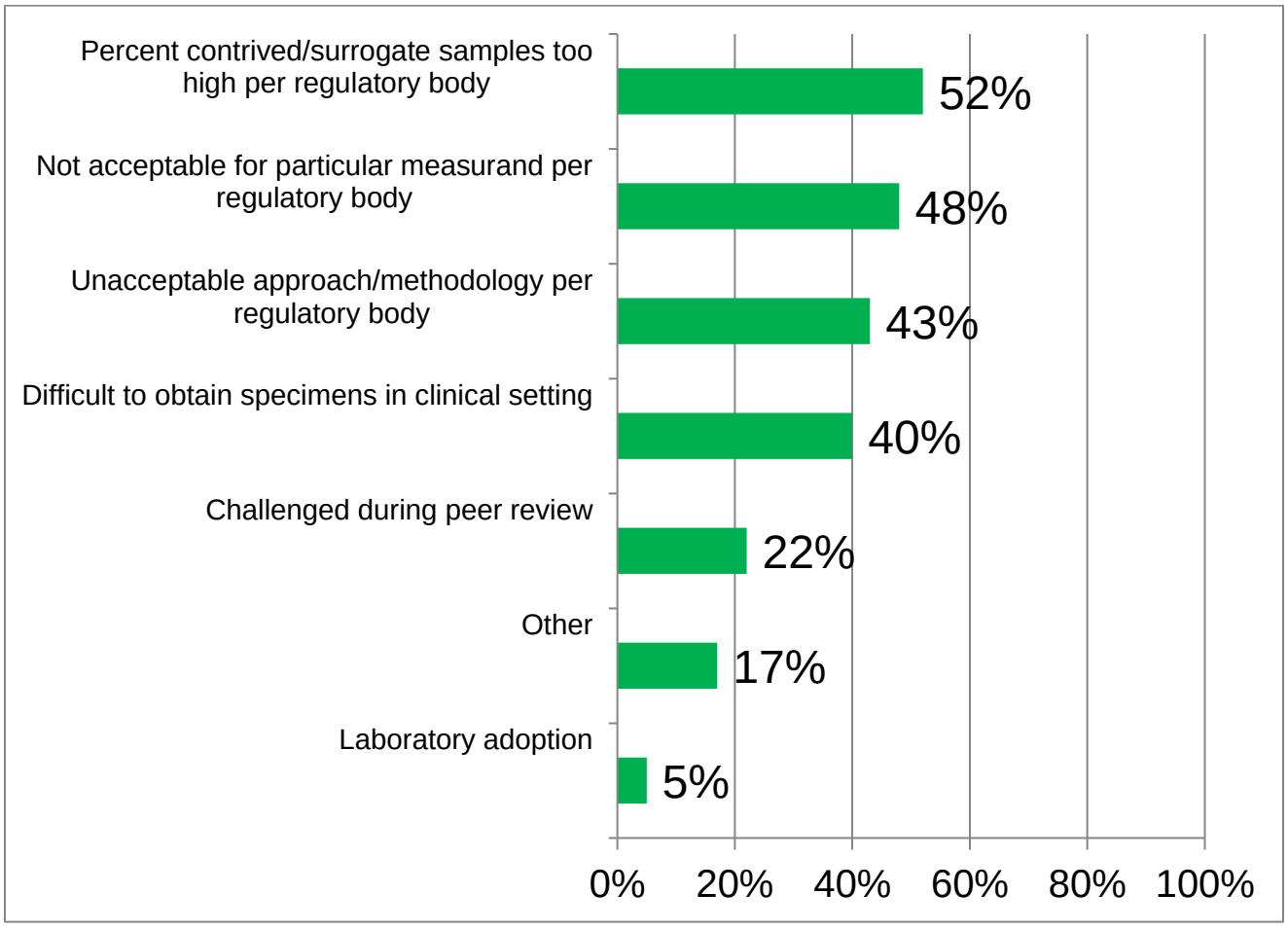
What technical challenges have you encountered when using contrived/surrogate samples?

1. Interaction of measurand with incompatibility in the natural occurring matrix; i.e. NHS
2. Demonstrating that data from contrived samples are equivalent to unmodified clinical samples -Variable results with various contrived sample lots
3. Surrogate shows expression but not at level in number of fluorescence intensity
4. obtaining critical specimens (genotypes)
5. Unexpected interactions between measurand and matrix.
6. Interference due to the components in in the matrix that would not occur in natural specimens.
7. Obtaining the physiological molecular form of the measurand from a commercially available source. Determining the appropriate physiological molecular form of the measurand for use in surrogate matrix studies. There may be multiple molecular forms of the measurand in-vivo, and all forms may not be known or available. Alternate molecular forms could potentially affect assay performance.
8. Challenges demonstrating commutability between contrived samples and actual patient samples.
9. Creating homogeneous pools
10. Lack of adequate independent method to quantify natural measurand. Lack of naturally low enough level specimens
11. Matrix sensitivity of the analytical procedure
12. Spiked purified material does not behave exactly as native measurand
13. Artifacts by preparing contrived material, unavailability of drug metabolites, solubility issues
14. Reagent lot matrix effects.
15. Determining the measurand concentration with an orthogonal method to confirm.

N = 15 "Other" responses

6. WHAT NON-TECHNICAL CHALLENGES HAVE YOU ENCOUNTERED WHEN USING CONTRIVED/SURROGATE SAMPLES? (MAY SELECT MORE THAN ONE)

A. Challenged during peer review
B. Difficult to obtain specimens in clinical setting (e.g., timed draws from patients in emergency setting)
C. Laboratory adoption
D. Not acceptable for particular measurand per regulatory body
E. Percent contrived/surrogate samples too high per regulatory body
F. Unacceptable approach/methodology per regulatory body
G. Other



N = 77

Question 6 "Other" Responses:

What non-technical challenges have you encountered when using contrived/surrogate samples?

1. My response is a hybrid of two of those above. Approach was challenged by the regulatory body, but with supporting data, good rationale, and several communications we were allowed to use contrived samples for specific studies to support our submission.
2. Biggest challenge: regulatory body agrees to approach and study design using contrived samples, then later in review process regulatory body reverses decision and/or significantly increases scope of work.
3. Contrived results compared to perspecitively collected samples
4. The practice of contrived samples has not been historically used. The use of contrived positives in microbiology actually allows us to cover many more species that would be encountered in a clinical trial.
5. Have not had non-technical challenges of note
6. Cost can be high although timing is shorter than obtain patient samples
7. Still required by FDA to have some clinical specimens. The CSS were required to fill in the assay range.
8. No Certified Reference Materials
9. Cannot measure actual concentrations due to matrix effect
10. Bioethical issues
11. Challenges when procedures call to use few contrived samples, but also say to have samples spread evenly across a particular interval.
12. Usually regulatory body doesn't want to allow or severely limits the ability to use contrived samples

N = 12 "Other" responses

7. When working with a regulatory body (or as a regulatory body) what has been the acceptance of using contrived/surrogate samples for the following study types?

Survey respondents were asked to rate acceptability using the following scale

1 = routinely acceptable to use contrived/surrogate samples
2 = partially acceptable (i.e. methodology questioned, % contrived samples/total questioned)
3 = not acceptable to use contrived samples

	Routinely Acceptable	Partially Acceptable	Not Acceptable	Response Count
Assay Cut-off	18	33	22	73
Clinical Sensitivity	5	27	44	76
Clinical Specificity	3	24	47	74
Detection Limit	30	37	8	75
Interference	33	35	6	74
Linearity/Reportable Range	34	34	4	72
Matrix Comparison	23	38	13	74
Method Comparison (with another dx test)	11	54	13	78
Precision / Reproducibility	32	39	4	75
Reference Range	7	25	42	74
Specimen Stability	7	32	34	73

Rank Order created by assigning to raw data a multiplier of 3 for each routinely acceptable response, 2 for each partially acceptable response, and 1 for each not acceptable response.

Rank Order Assays	Routinely Acceptable	Partially Acceptable	Not Acceptable	Weighted Totals
Linearity/Reportable Range	102	68	4	174
Interference	99	70	6	175
Precision / Reproducibility	96	78	4	178
Detection Limit	90	74	8	172
Matrix Comparison	69	76	13	158
Assay Cut-off	54	66	22	142
Method Comparison (with another dx test)	33	108	13	154
Specimen Stability	21	64	34	119
Reference Range	21	50	42	113
Clinical Sensitivity	15	54	44	113
Clinical Specificity	9	48	47	104

N = 82

8. Each of the following contrived/surrogate sample type is used most frequently in which study type? (may select more than one)

Survey respondents were presented with ten different types of contrived/surrogate samples and asked to identify when they were most frequently used in a list of ten common diagnostic development study types.

Contrived/Surrogate Sample Types (in alphabetical order)

- Cell line supplemented with measurand
- Diluent supplemented with measurand to obtain positive value
- Negative patient sample pool supplemented with measurand to obtain positive value
- Negative patient specimen supplemented with measurand to obtain positive value
- Patient sample pool that has been treated and supplemented with measurand to obtain positive value
- Plasmid supplemented with measurand
- Positive patient sample pool diluted with diluent to obtain low positive value
- Positive patient sample pool diluted with negative patient sample pool to obtain low positive value
- Positive patient sample pool supplemented with measurand to obtain higher value
- Positive patient specimen supplemented with measurand to obtain higher value

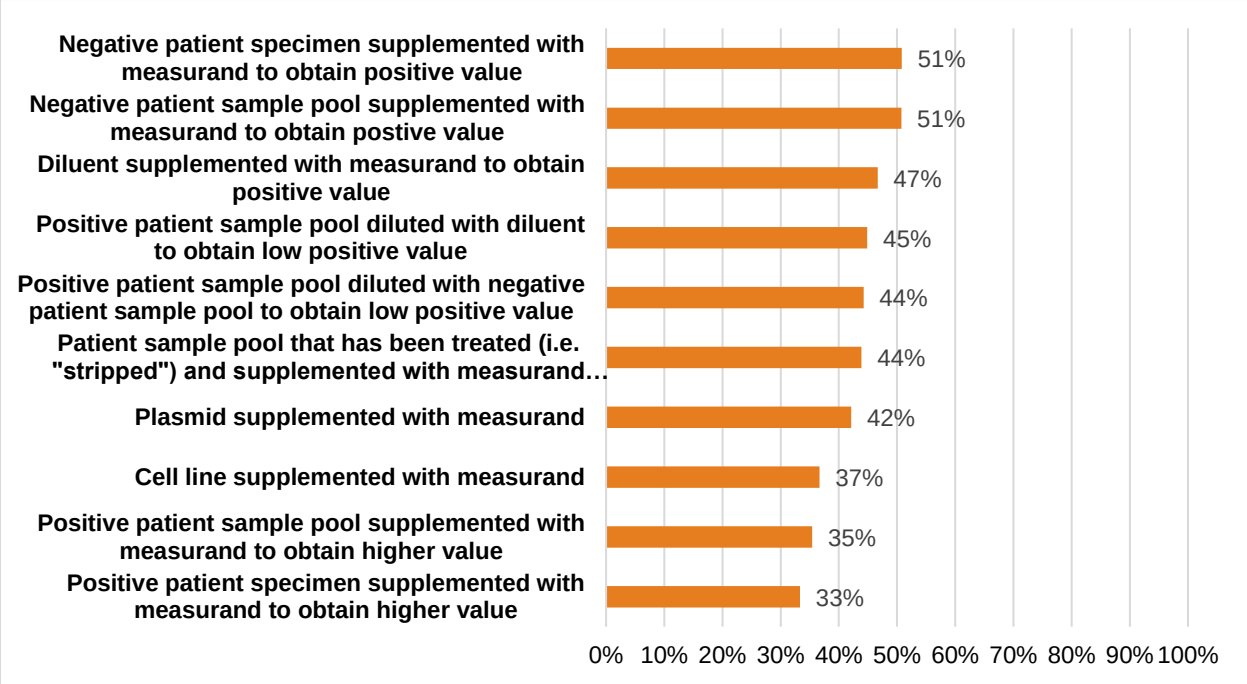
Study Types (in alphabetical order)

- Assay Cut-off
- Clinical Sensitivity
- Clinical Specificity
- Detection Limit
- Interference
- Linearity/Reportable Range
- Matrix Comparison
- Method Comparison
- Precision/Reproducibility
- Reference Range

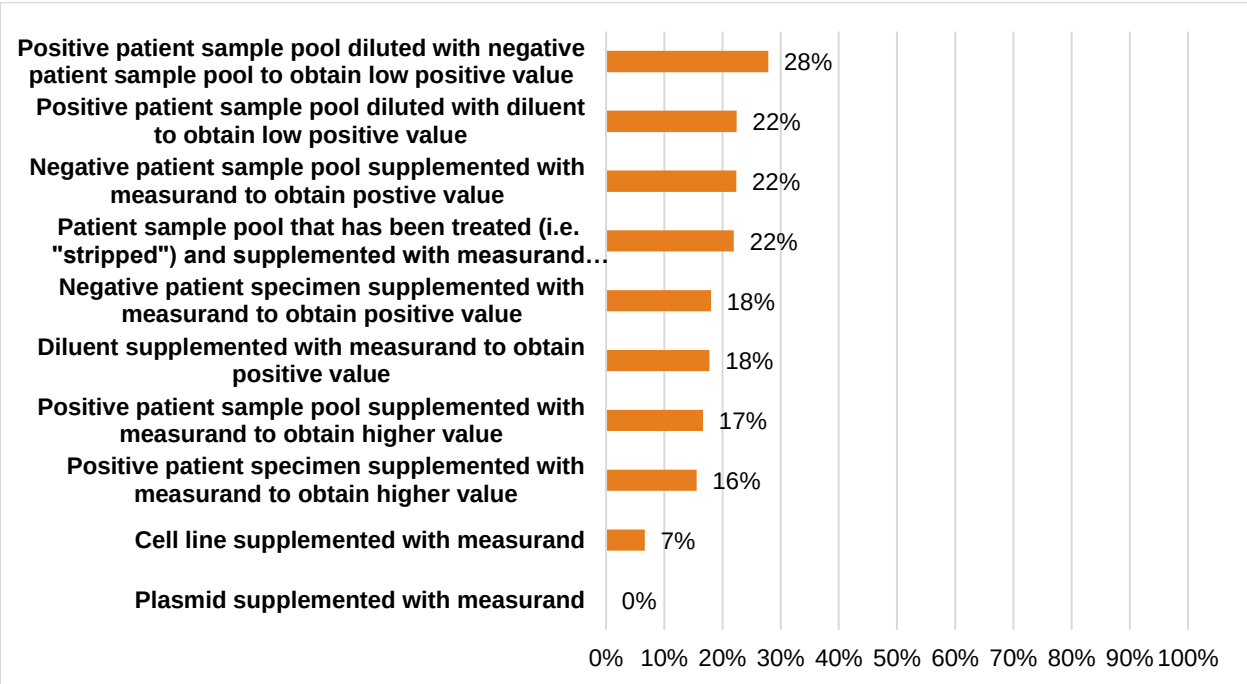
Survey Results Presented by Study Type (N = 74)

8. Each of the following contrived/surrogate sample type is used most frequently in which study type? (may select more than one)

Assay Cut-off

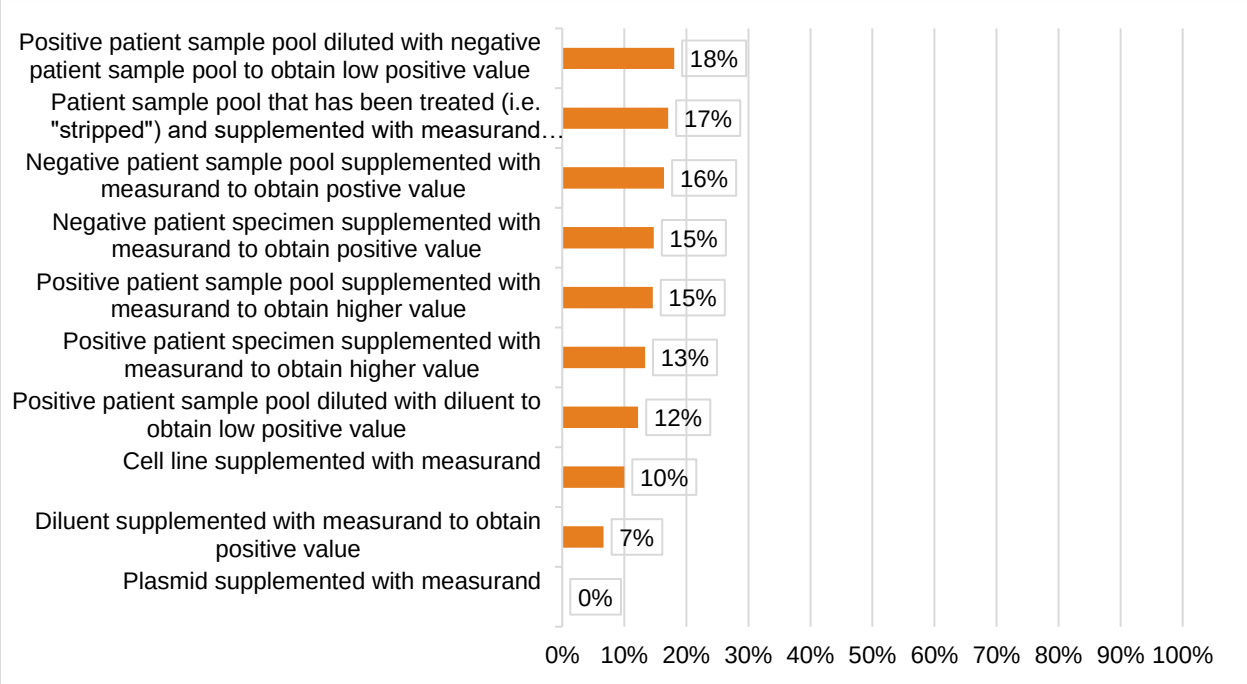


Clinical Sensitivity

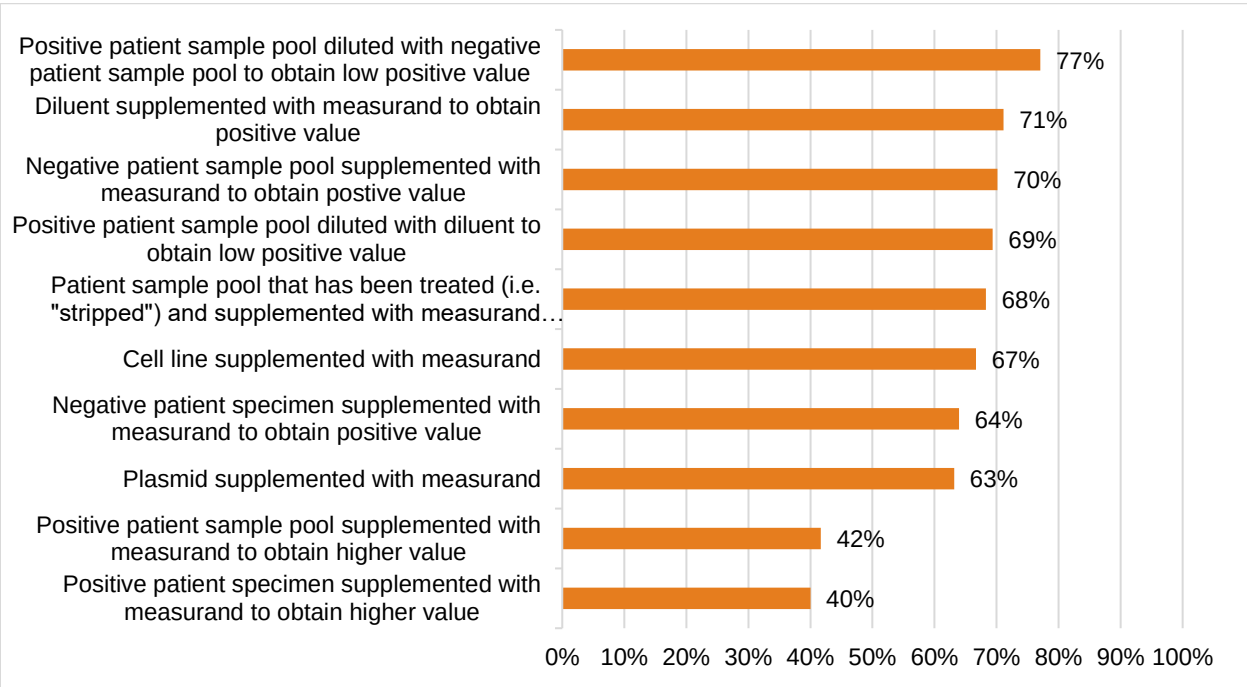


8. Each of the following contrived/surrogate sample type is used most frequently in which study type? (may select more than one)

Clinical Specificity

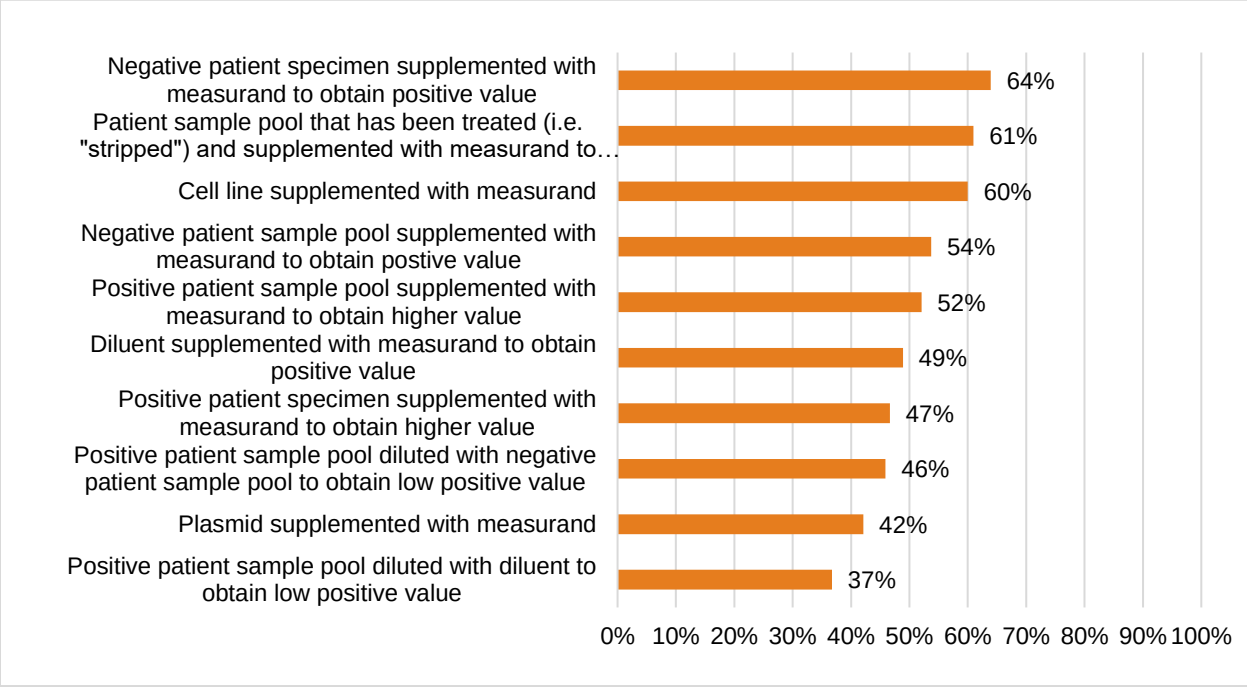


Detection Limit

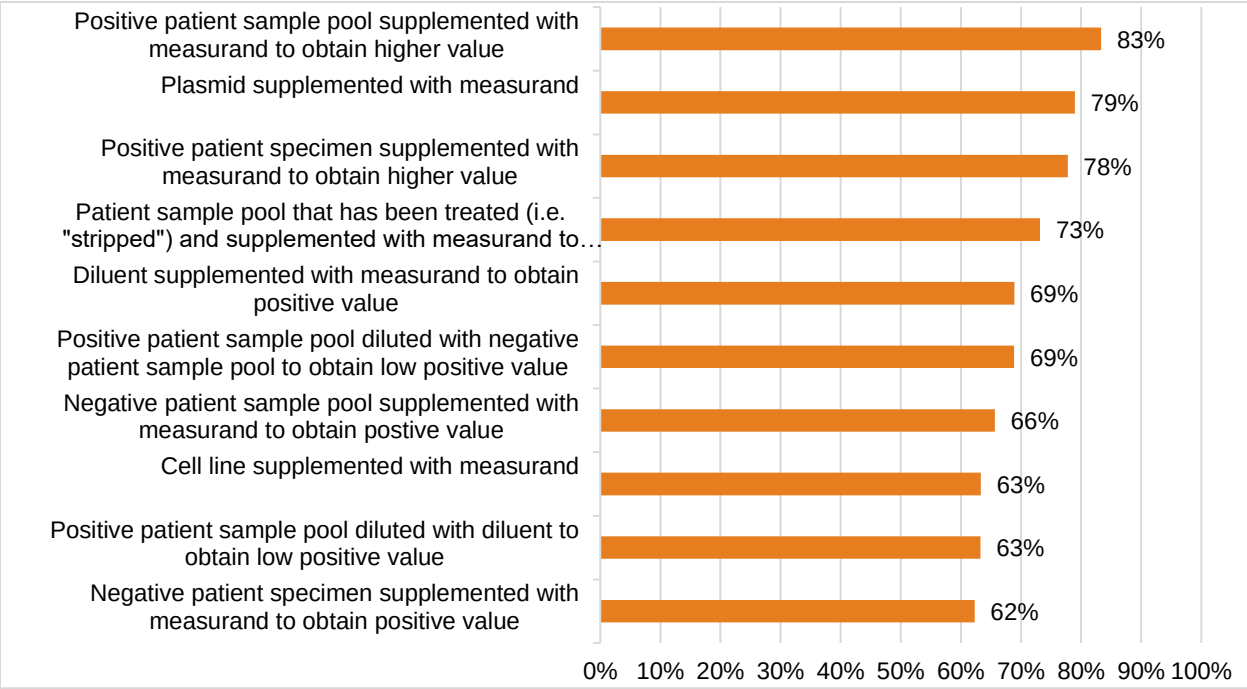


8. Each of the following contrived/surrogate sample type is used most frequently in which study type? (may select more than one)

Interference

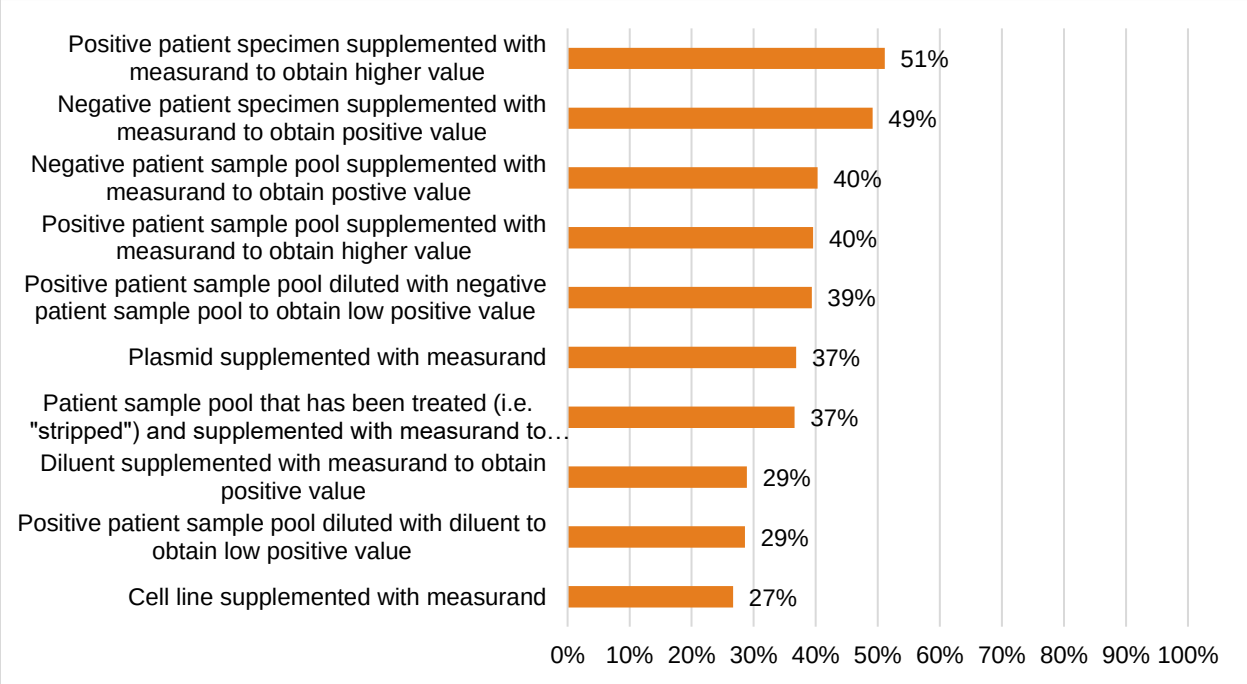


Linearity/Reportable Range

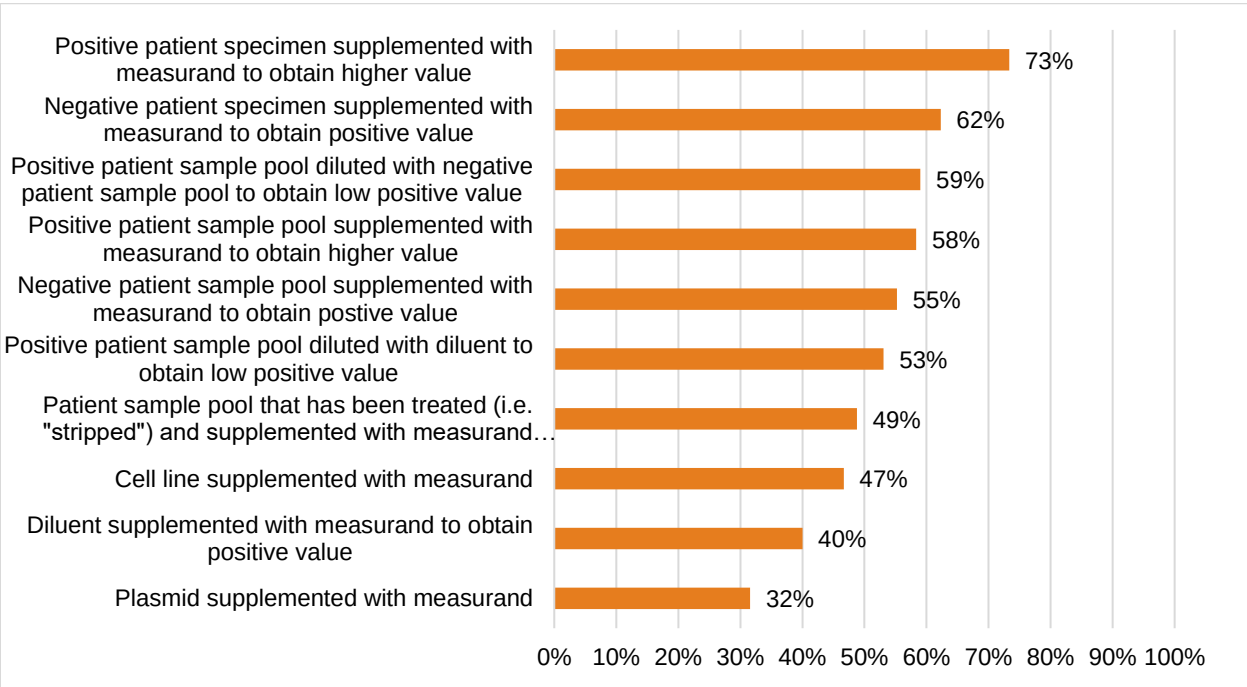


8. Each of the following contrived/surrogate sample type is used most frequently in which study type? (may select more than one)

Matrix Comparison

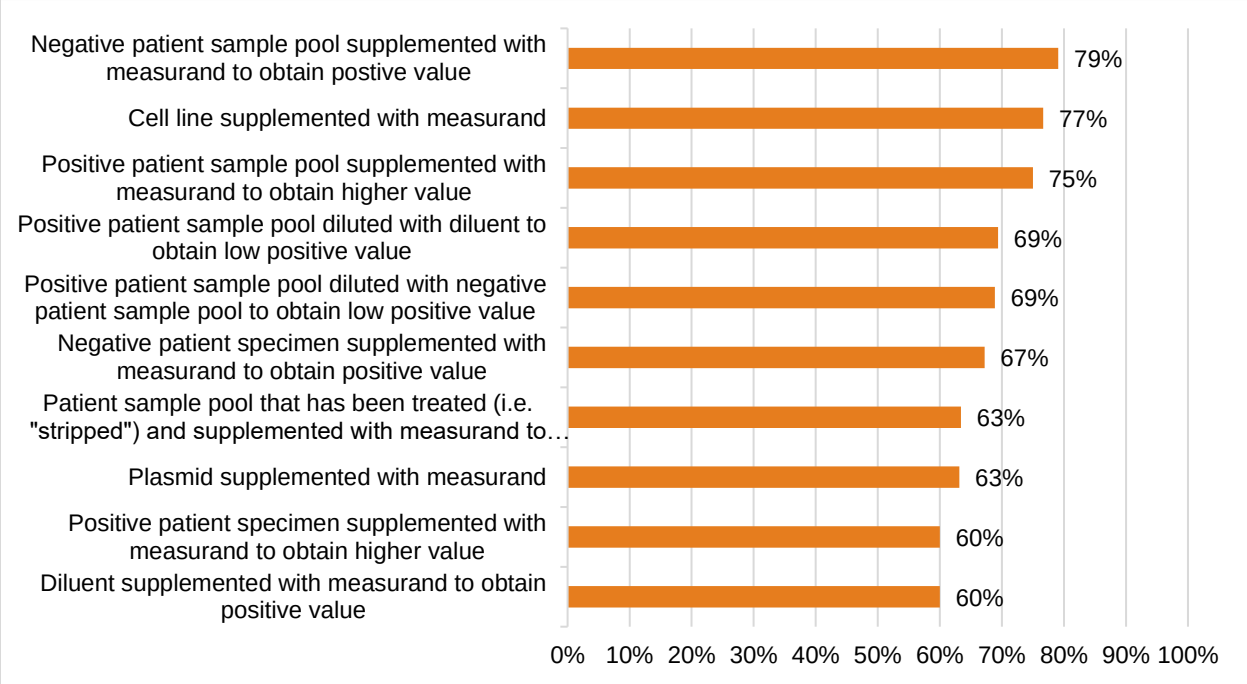


Method Comparison (with another diagnostic test)

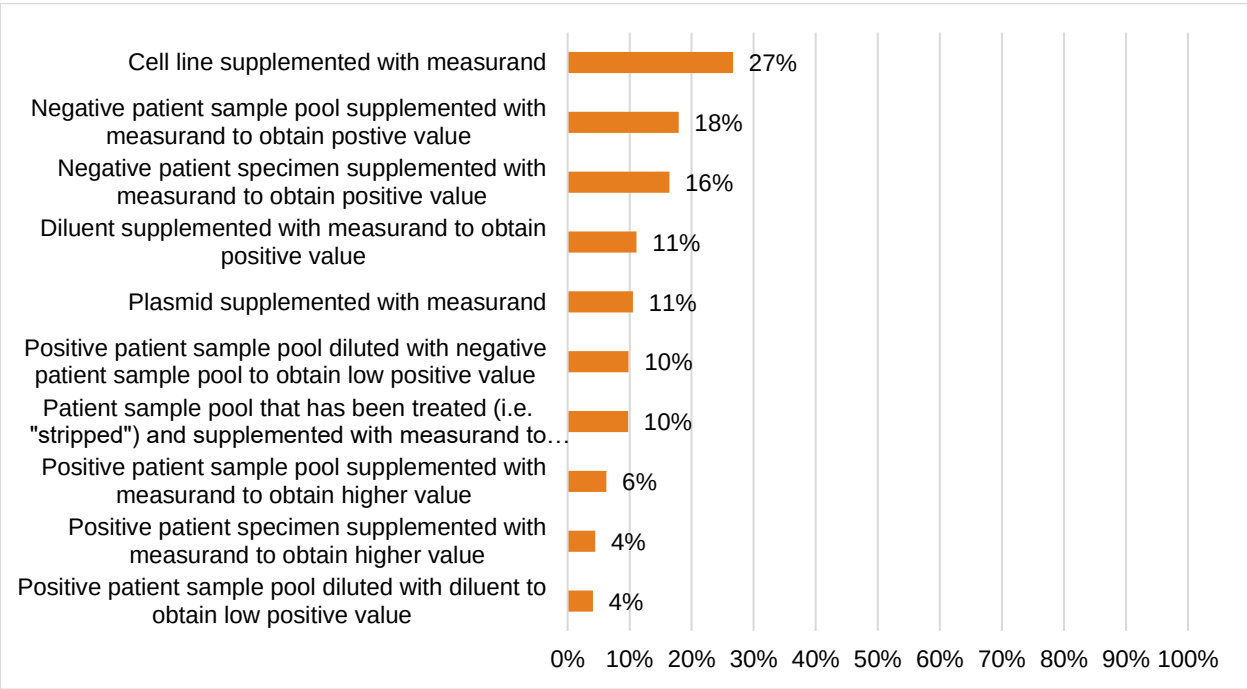


8. Each of the following contrived/surrogate sample type is used most frequently in which study type? (may select more than one)

Precision/Reproducibility



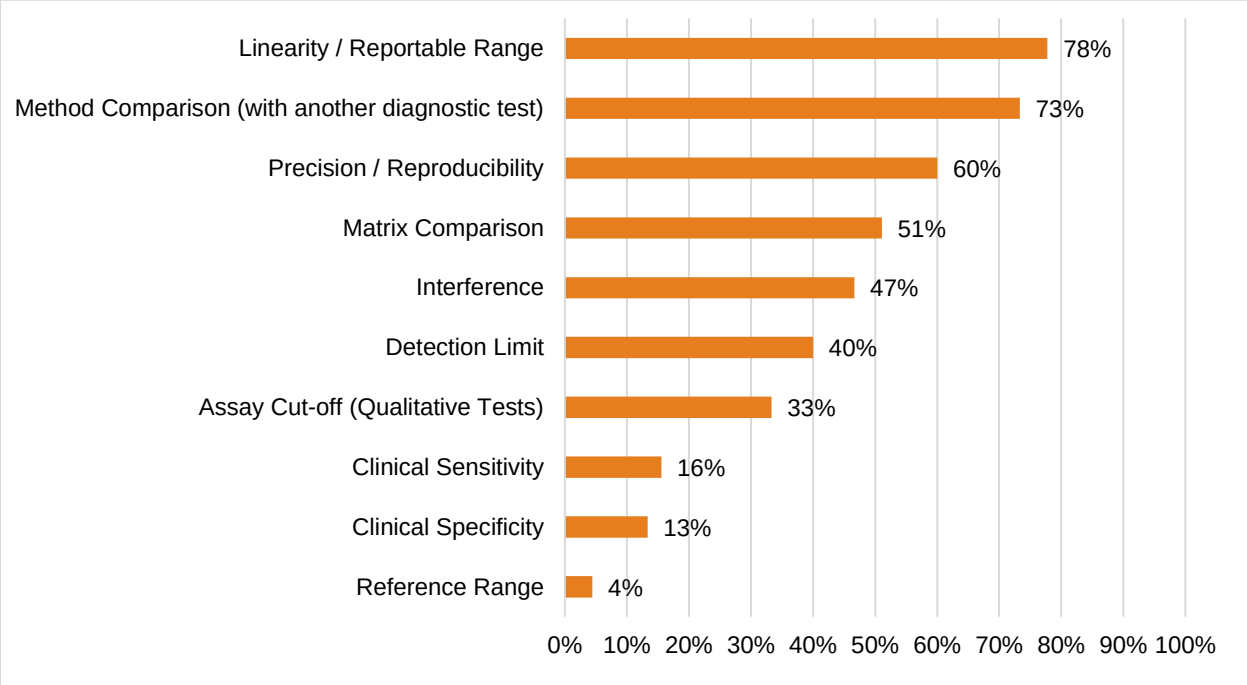
Reference Range



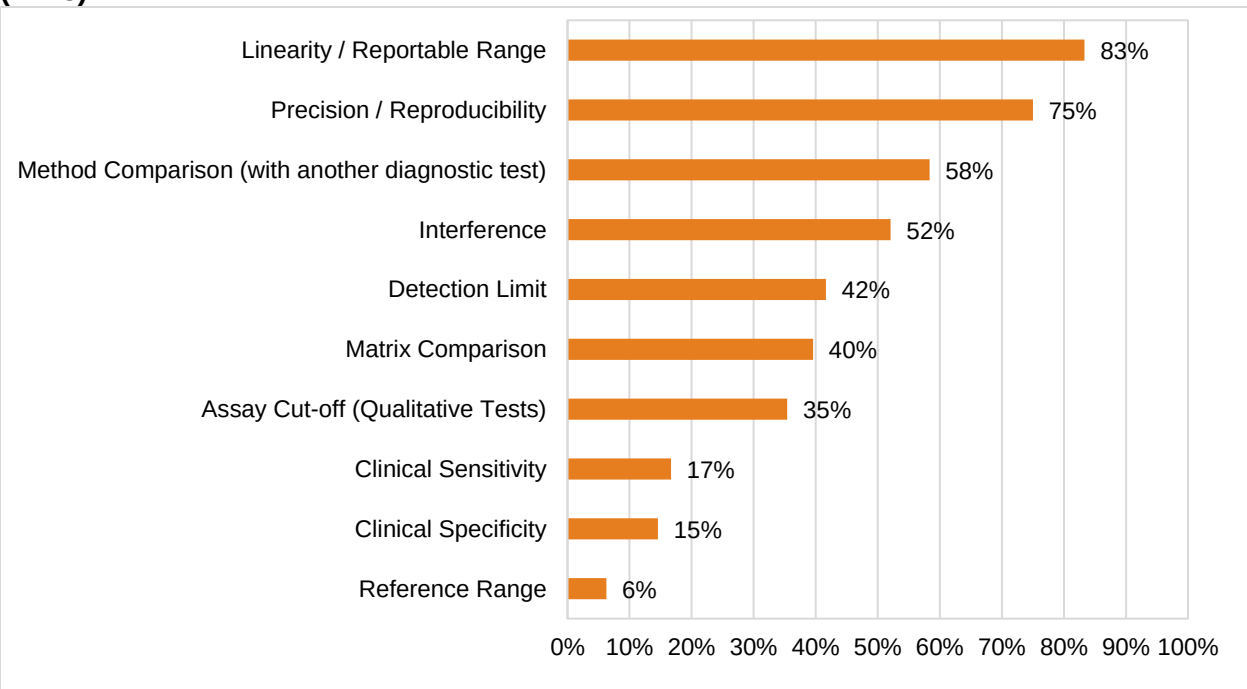
8. Each of the following contrived/surrogate sample type is used most frequently in which study type? (may select more than one)

Survey Results Presented by Contrived/Surrogate Sample Type

Positive Patient Specimen Supplemented with measurand to obtain higher value (n=45)



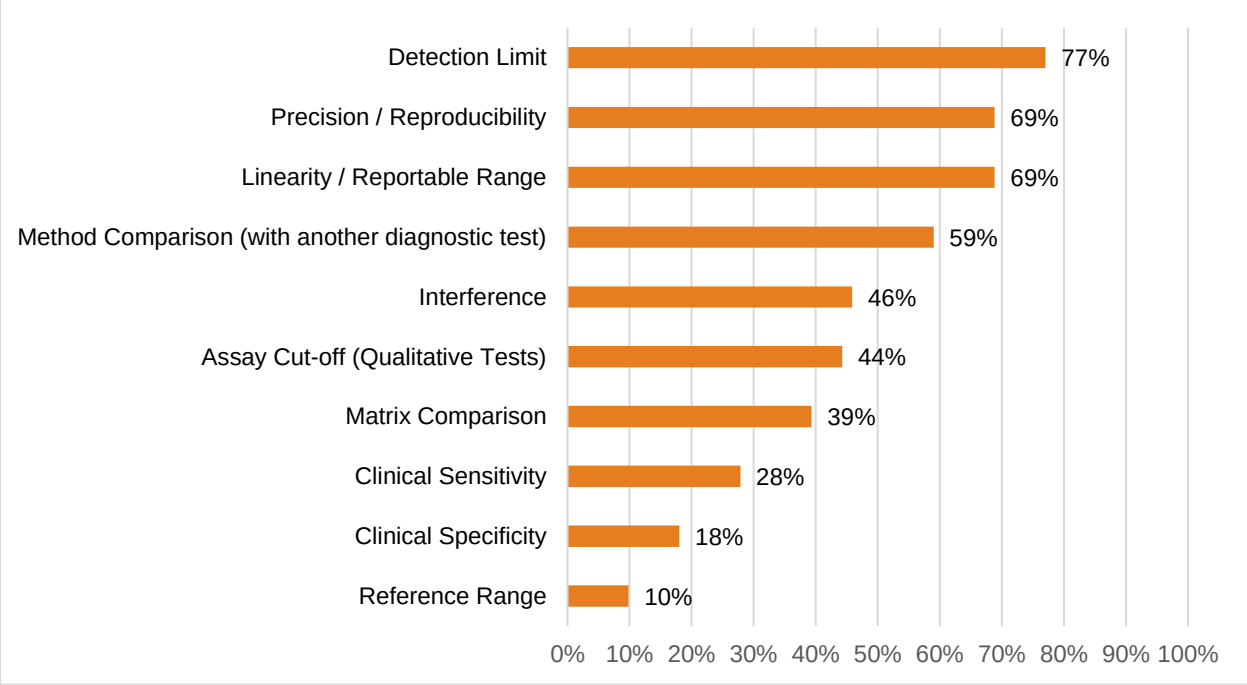
Positive Patient Sample Pool Supplemented with Measurand to Obtain Higher Value (n=48)



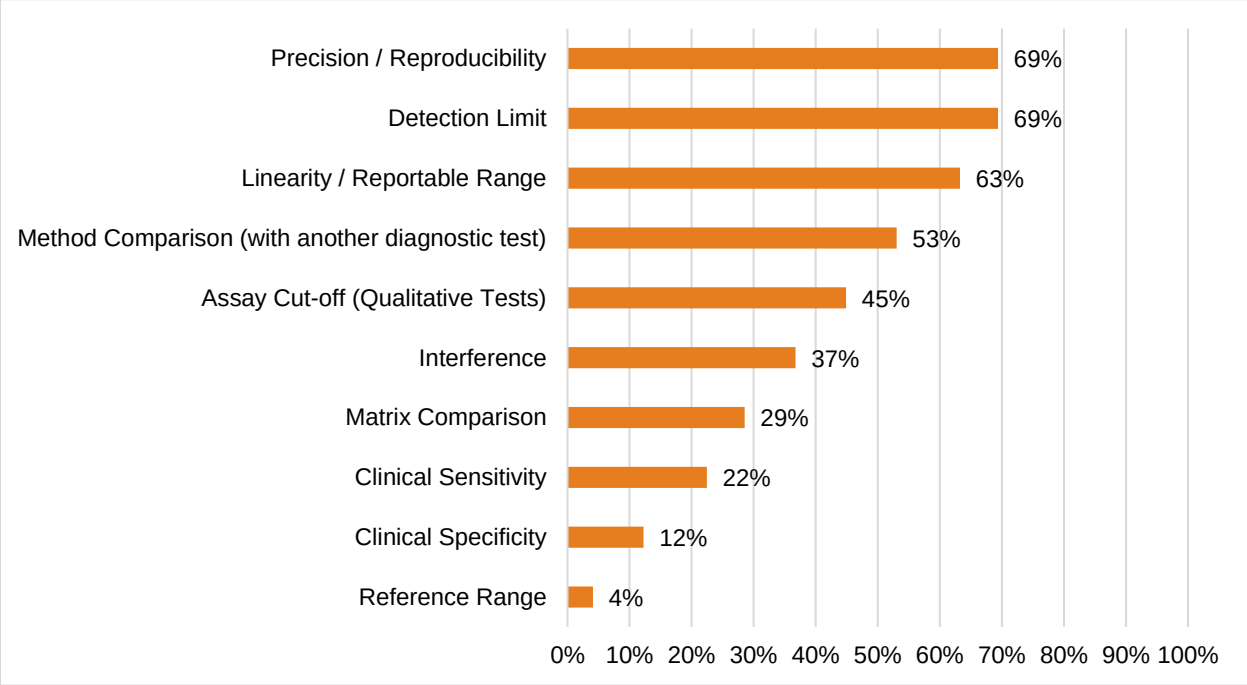
8. Each of the following contrived/surrogate sample type is used most frequently in which study type? (may select more than one)

Survey Results Presented by Contrived/Surrogate Sample Type

Positive Patient Sample Pool Diluted With Negative Patient Sample Pool To Obtain Low Positive Value (n=61)



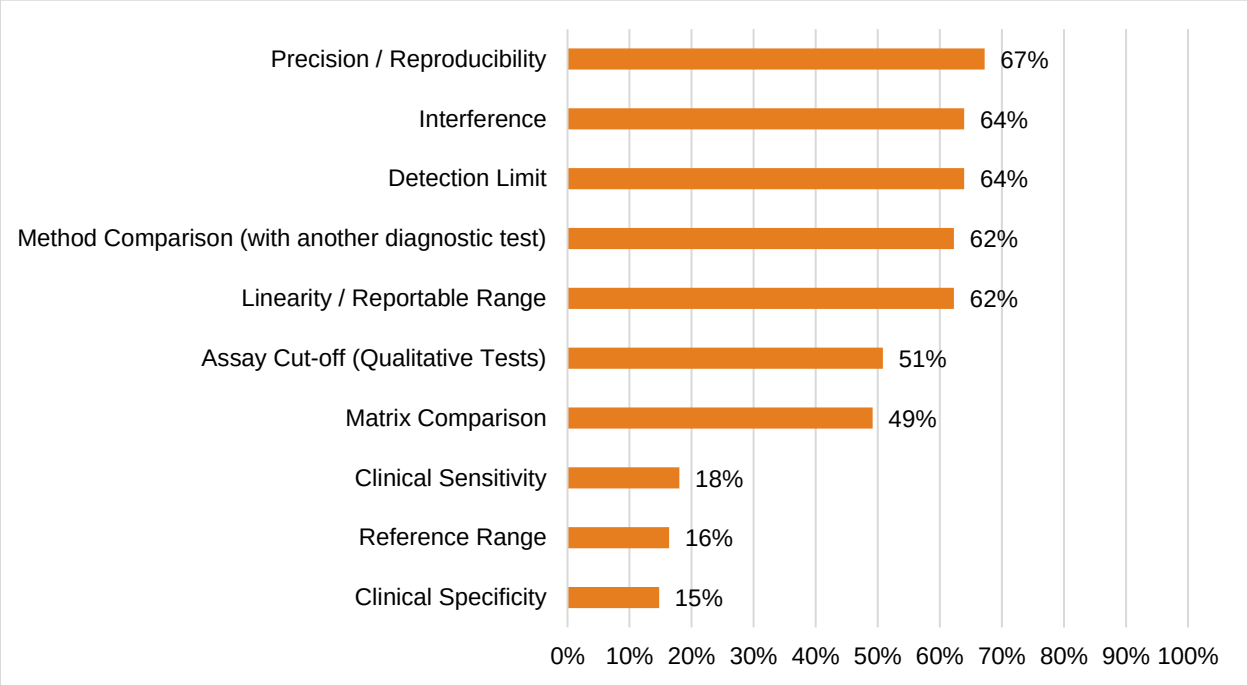
Positive Patient Sample Pool Diluted With Diluent To Obtain Low Positive Value (n=49)



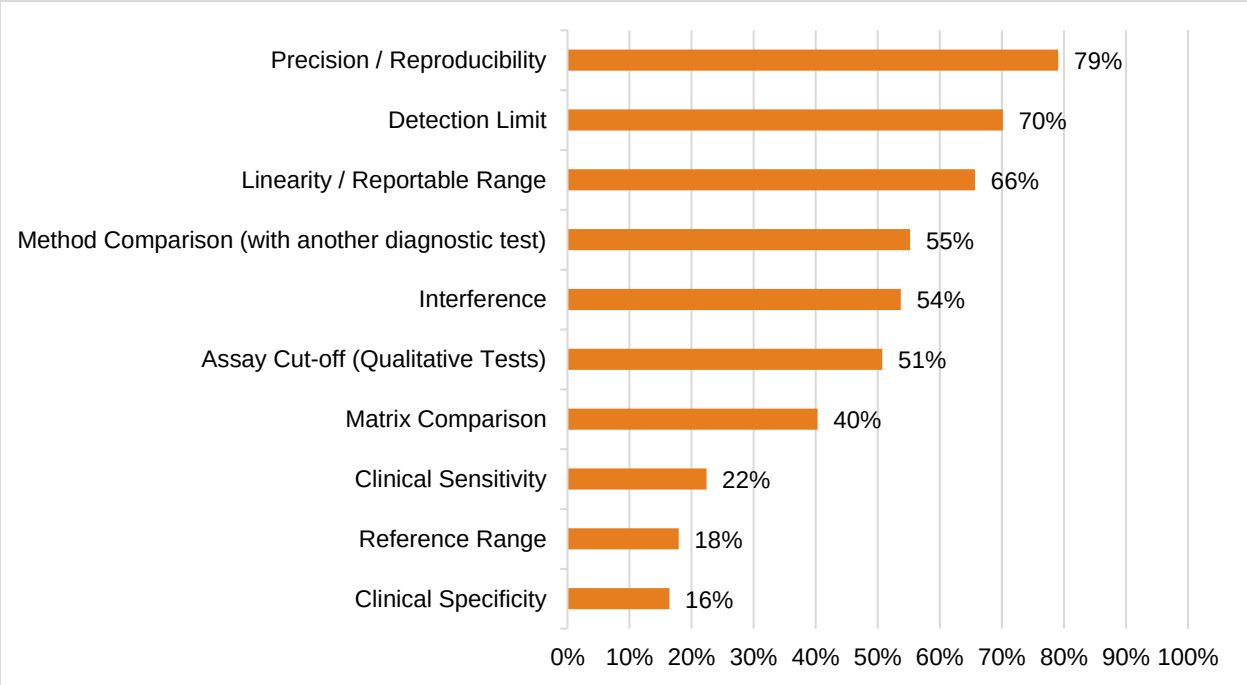
8. Each of the following contrived/surrogate sample type is used most frequently in which study type? (may select more than one)

Survey Results Presented by Contrived/Surrogate Sample Type

Negative Patient Specimen Supplemented with Measurand to Obtain Pos Value (n=61)



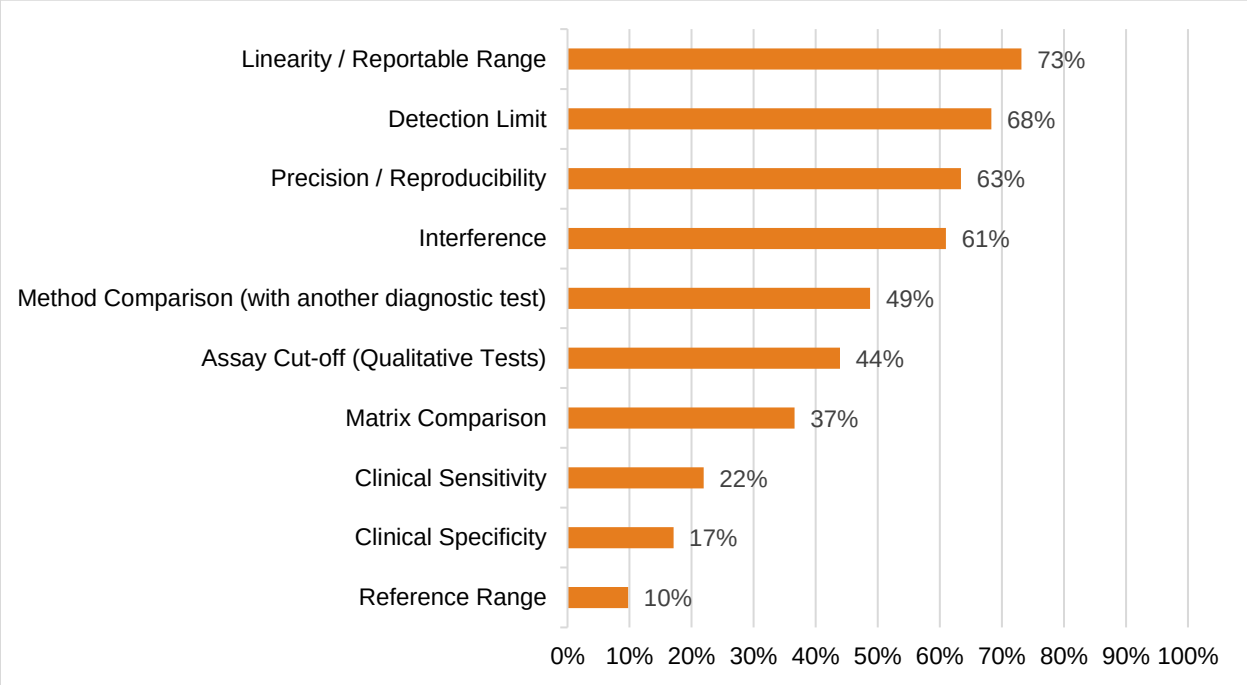
Negative Patient Sample Pool Supplemented with Measurand to Obtain Pos Value (n=67)



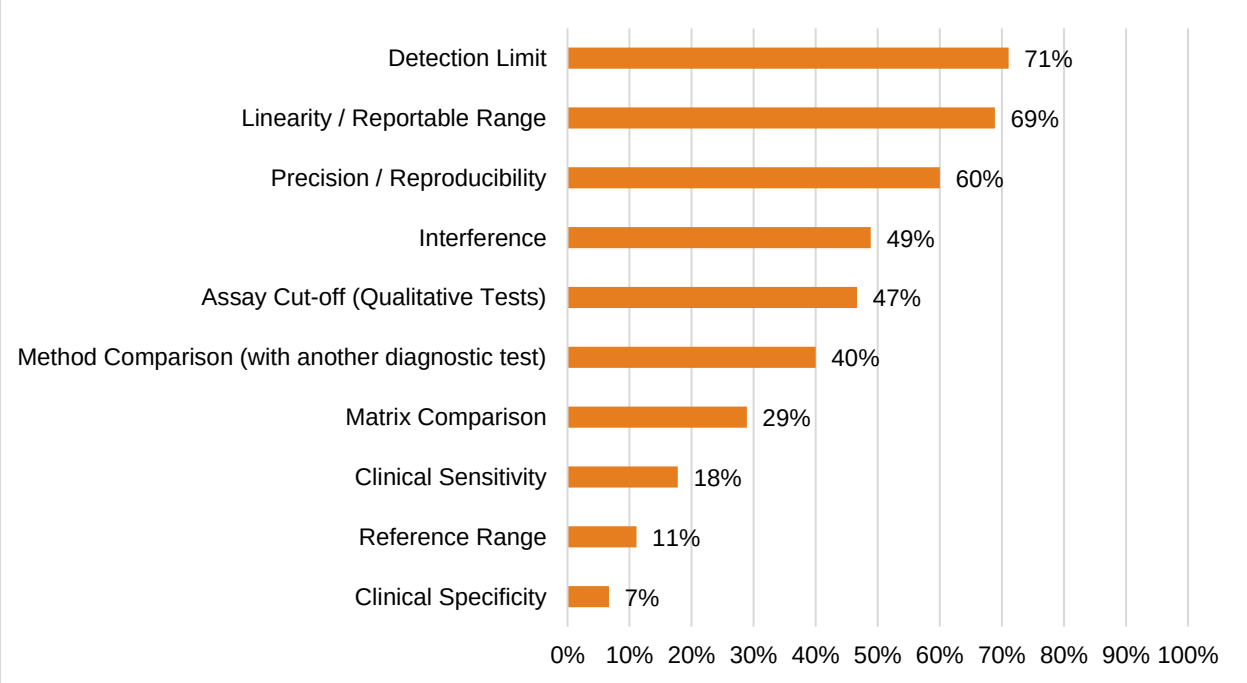
8. Each of the following contrived/surrogate sample type is used most frequently in which study type? (may select more than one)

Survey Results Presented by Contrived/Surrogate Sample Type

Patient Sample Pool That Has Been Treated (i.e. "stripped") And Supplemented With Measurand To Obtain Positive Value (n=41)



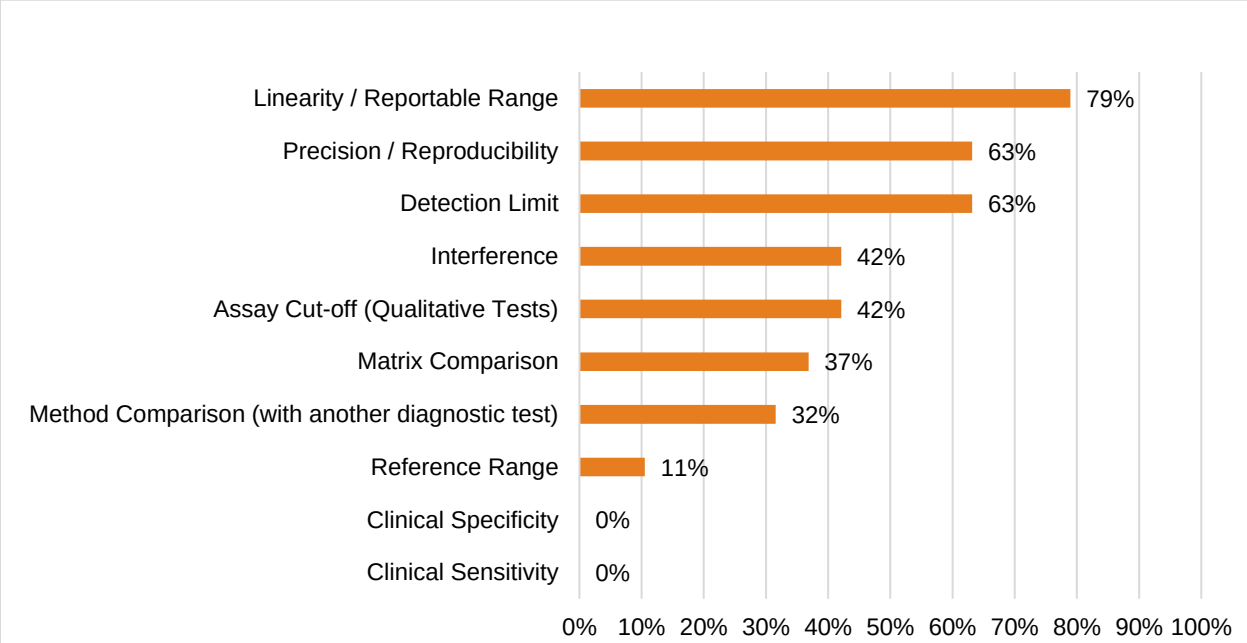
Diluent Supplemented With Measurand To Obtain Positive Value (n=45)



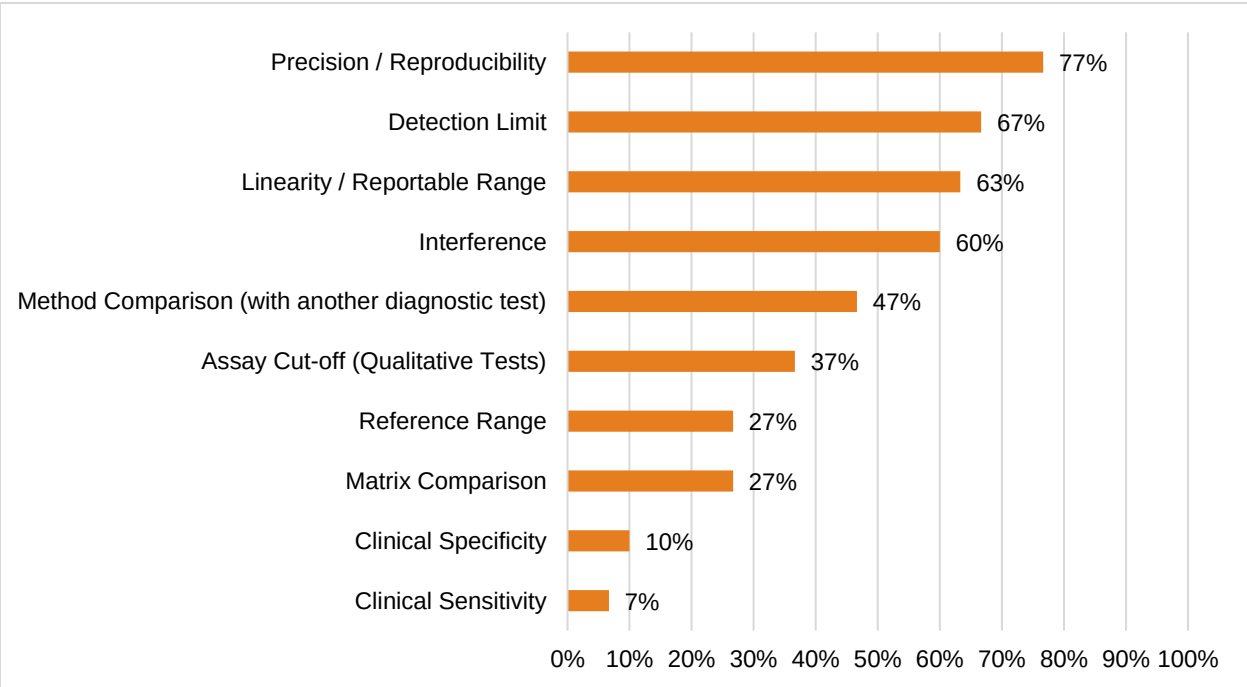
8. Each of the following contrived/surrogate sample type is used most frequently in which study type? (may select more than one)

Survey Results Presented by Contrived/Surrogate Sample Type

Plasmid Supplemented with Measurand (n=19)



Cell Line Supplemented With Measurand (n=30)



Question 8 "Other Responses":

The following table lists IVD study types. For each study type, when would you most frequently us the specified contrived/surrogate sample type to complete the study?

1. In microbiology we use/detect live organism and several of these do not apply.
2. Healthy-donor sample pool with measurand added at specified levels for interference, reagent stability, matrix comparison and similar non-clinical studies

N = 2 "Other" responses

9. Describe instances where additional studies were necessary to supplement use of contrived samples.

1. Demonstrate commutability
2. Interfering substance testing (pooled samples spiked to varying levels); Precision/Reproducibility to attain levels near clinical cut-off; Limits of Detection (using purified plasmid DNA in sample matrix).
3. Question is not clear to me. Additional studies to provide supporting data for use of specific contrived samples. For example, use of synthetic DNA representative of converted methylated DNA in background matrix, use of plasmid DNA. Also supplemental studies using patient samples to confirm linearity and LoD was performed when contrived samples were used to establish their performance levels.
4. # samples needed at the low end of the range not available
5. Generally, FDA requires a rationale about why the contrived matrix is acceptable. The extent of the justification greatly depends on the branch of the FDA, the assay type and the matrix being replaced by the contrived sample. The studies usually require a comparison of the contrived matrix to the clinical specimens spiked at similar concentration levels.
6. Stability, reproducibility, process validation
7. Surrogate samples provided high samples for method comparison but middle gap needed filling with more native specimens.
8. Process controls were used as markers needing to be identified not present on normal donor blood

9. Describe instances where additional studies were necessary to supplement use of contrived samples. (continued)

9. We have used contrived/surrogate samples throughout all Development/Feasibility/Characterization testing phases as well as System Verification testing for all our products, as patient specimens are logistically impossible to obtain within the required time frames, and are too rare to complete all the necessary testing in acceptable time frames from a product development (program time lines) and business competitiveness perspective.
10. Clinical Study
11. Blood analyse
12. When working with FFPE samples we have always had to demonstrate comparability between contrived and real samples.
13. The main use is to cover range. FDA has been adamant on many of the recent submissions of this requirement for both method comparison and matrix comparison. Regardless of the measurand and were is typically reported in patient specimens
14. Detection of HSV-2 in oral/facial swabs
15. For analytes that are not difficult to find natural specimens, fewer samples may be contrived.
16. The use of clinical samples to measure false positive rate is necessary since many times the causes of false positives is not thoroughly understood.
17. Addition of matrix equivalency studies: contrived/surrogate versus true negative and true positive specimens.
18. Spiking of endogenous interferents into an assay sample pool
19. Precision study using patient sample was requested by FDA
20. Precision, LoBDQ, Linearity, Recovery, Correlation, Interferences, Analytical Specificity
21. In linearity studies FDA has required the overlap of two concentration levels to validate use of contrived samples for verification of the upper range of the assay

9. Describe instances where additional studies were necessary to supplement use of contrived samples. (continued)

22. For several clinical assays, the drug concentrations are in a small reference region but overdose can lead to higher values than can be obtained clinically, thus contrived samples are necessary.
23. When it is unclear if the contrived sample will appropriately mimic the performance of a clinical sample
24. To validate the analytical measurement range, to validate the limit of detection and limit of quantification, to increase concentration range of specimens used for method comparison studies, for recovery studies, for precision studies (ex: native matrix based commercial QC material supplemented with measurand) and interference studies (spike a native matrix to create high and low measurand concentration materials for interference studies).
25. In our lab, all clinical studies must depend on clinical samples to support the validation done with contrived samples
26. To populate low and high ends of measurement range. To prepare negative and positive samples close to cutoff for qualitative tests. To evaluate performance of whole blood samples
27. Study demonstrating commutability between sheared and intact cell-line DNA (in plasma); study demonstrating commutability between healthy-donor and patient plasma samples
28. Clinical specimen stability study to demonstrate the need for CSS for reproducibility study. Accepted by FDA.
29. When using contrived samples in studies to support linearity, spike and recovery, and dilution, FDA required additional commutability studies to support these original studies.
30. Autoantibody assays for which naturally blank specimens do not exist
31. Generally necessary to do commutability validation for contrived samples.
32. If contrived samples are used so that the whole measuring range in e.g. precision studies can be covered, additional contrived samples at concentration levels that have natural samples available are needed to prove the commutability of the contrived samples.
33. Defer to suppliers to meet targets
34. Neonatal bilirubin. hemolysis index
35. In order to obtain lower/high test results - example to mimic low blood glucose or high

9. Describe instances where additional studies were necessary to supplement use of contrived samples. (continued)

36. Procedurally required to show data supporting the use of contrived samples
37. Linearity or reportable range to extend the range beyond native samples that can easily be found
38. We must verify/validate the commutability of contrived/surrogate samples before we can use them for precision studies, accuracy studies, product release, etc.
39. High positive samples are rare, no samples at LoQ,
40. Spike positive sample to obtain very high result. Sample used for carryover studies.
41. Additional studies are used when using contrived samples as release samples for test assays.
42. Shifts in recovery of patient specimens with reagent lot changes may not be observed when shifts of contrived samples occur
43. AMRs, interferences
44. Verification of FDA-approved meningitis and gastrointestinal panels. Interference studies for Chlamydia/Neisseria gonorrhoeae in urine (not an FDA-approved specimen type at the time).
45. The use of contrived samples has been accepted to demonstrate analytical performance parameters such as linearity, recovery, LoQ, interferences. These bench studies needed to be supplemented with real parent data for method comparison and precision.
46. Insufficient positive samples available
47. Registration of Class III IVD in the US

N= 47

10. Describe instances when contrived samples were unsuccessful, include reason.

1. Samples need to be diluted with appropriate matrix, not diluent, for any study
2. Use of cell line DNA for methylation assays did not work well because of unstable DNA copy number.
3. Interference with one patient serum containing the measured reacted with component in the NHS matrix
4. source was not regulated in quantity of expression, just that it was positive
5. Creation of selected secondary reference calibrators were shown to be non-commutable.
6. Contrived samples (Process control) did not display required marker and the marker is shed quickly from patient cells so using patient sample not possible.
7. For some of the markers that are targeted with our products, there are no surrogates available that express the exact epitopes or at the desired levels.
8. FDA told us no more than 15% can be spiked for matrix comparison studies. Regardless of the measurand
9. For analytes that are not difficult to find natural specimens, fewer samples may be contrived.
10. In some cases, the patient response plays a significant role in recovery of the infectious agent and this is very difficult to simulate.
11. lack of homogeneity/stability of contrived samples (spiking of viruses or bacteria in negative stool samples)
12. Number of contrived samples exceeding 15% of total sample size in a particular bin
13. Matrix effect, especially if contrived samples used together with real specimens
14. Plasmids for rare genotypes in companion diagnostic studies. FDA flat out rejected the proposal.
15. Use of non-human plasma as a source of vitamin D free negative samples.
16. Sometimes the only way to get a low enough value with a contrived sample is to dilute the analyte or patient sample in an artificial matrix ex. saline as the endogenous level is too high to get a sample with zero analyte to do low end studies.
17. When the contrived sample performed significantly better than the clinical sample (plasmid DNA sensitivity much better than clinical sample sensitivity)

10. Describe instances when contrived samples were unsuccessful, include reason. (continued)

18. Contrived samples cannot be used for method comparison studies if the surrogate matrix response does not match the native matrix.
19. Highly polyploidy cell lines can give unexpected measurements
20. Some recombinant antigens have different reactivities than native antigen in immunoassays.
21. Health authority would not allow the use of intact cell-line DNA as a surrogate sample for a test measuring tumor DNA in plasma
22. Attempted measurand stability with contrived samples. The study did not mimic the (in)stability of true clinical specimens.
23. Some interference is observed when using spiked samples. may due to matrix effect
24. Recombinant cytokines showed different activities than naturally occurring material
25. Excessive matrix manipulation alters measurand form or reactivity with reagents.
26. Sometimes the measurand will bind some receptor (or something like that) when spiked into a sample, which sometimes disturbs the natural equilibrium in the sample. In such cases contrived samples may behave differently as compared to natural samples.
27. Due to difference in methodologies, suppliers may spec PT material on method but recoveries on other methods do not meet specified targets
28. Method comparison studies to predicate device as the predicate may have a matrix issue with the sample
29. Interference studies where parent drug is present but metabolite is not - can't assess for natural metabolism
30. For matrix sensitive measurement procedures, contrived samples used for method comparison, proficiency testing, reportable range verification often are complicated by the alter response of the measurement procedure to the contrived matrix
31. Tried to use purified TnI spiked into patient samples in method comparison and matrix comparison but the purified material reacted differently than native measurand
32. Lack of commutability makes such samples inappropriate for use.
33. Spiking samples with drugs that have strong first pass effect, spiking samples w protein: albumin vs IgG to obtain high protein levels, contrived samples for analytes that are protein bound, e.g. Testosterone, Vitamin-D

10. Describe instances when contrived samples were unsuccessful, include reason. (continued)

34. Different stability from native sample. Different 3-dimensional conformation of measurand and hence different assay performance
35. Tried making linearity samples for viral DNA test. Did not respond as expected.
36. Contrived survey samples provided by external sources do not align with native samples due to matrix effects. Peer grouping is required.
37. Immunoaffinity extraction for LC-MSMS assay. Unable to find native protein to create surrogate samples and available peptides or partial proteins did not react with antibodies sufficiently.
38. Certain contrived samples may lack components that tend to stabilize variation in reagent lot measurand recovery. A contrived sample require modification to minimize the variation.
39. Allows for neonatal AMRs, not for adult AMRs for glucose
40. Once with CMV using pooled patients' plasma as matrix
41. Method comparison against a predicate device. Only a small number of contrived samples was acceptable.
42. Use of 100% contrived samples has been rejected occasionally by FDA and we were required to use as many clinical specimens as possible and supplement with contrived.

N = 42

11. Free text field to provide any additional information about contrived/surrogate samples.

1. Consider and propose alternate matrices from different species rather than buffer or diluent
2. There are issues specific to the type of specimen and design of the assay. These need to be taken into consideration. Another key issue is that some contrived samples and input target cannot be quantified by an alternative method besides the test they are designed for (possibly because of very low copy number). This can be a challenge.
3. Important to qualify the samples on the god standard method before assigning a known value
4. Challenges but absolutely feel they are necessary, regulatory bodies need to adapt
5. Especially when the prevalence is low, FDA encourages discussions about contrived/surrogate samples.
6. GOST 30538. FOOD-STUFFS. Analysis of toxic elements by atomic-emission method
7. The acceptance of contrived samples by regulatory bodies will be critically important to accelerate innovation in the field of genomics; genetic diseases are rare and real samples hard to come by.
8. In one FDA submission, we had to show commutability for spiking material (even though it was a naturally occurring source of the measurand).
9. The use of both contrived sample and clinical samples can be more effective in evaluating the effectiveness of a diagnostic test. However, when using a contrived sample that challenges the system the usual expectations need to be adjusted in some cases. We can test worst cases testing where the error rates on the surface appear to be high, while in reality the reference method could do no better.
10. Challenges include Regulatory requirements in regards to the allow % of contrived samples in a study or interference observed in a test due to a component in the contrived matrix (which is not present in natural samples)
11. We usually discus with FDA upfront by means of the Pre-submission process. For Method comparison FDA does not allow to use more than 10% contrived samples
12. When using an artificial matrix for the low pool, regulatory agencies typically challenge not using the sample matrix. Technical arguments do not succeed all the time and there is a request to use real samples.
13. Contrived samples may be used to assess analytical assay performance parameters. However, contrived samples should not be used to establish clinical sensitivity or clinical specificity, and should not be used to establish reference intervals.

11. Free text field to provide any additional information about contrived/surrogate samples. (continued)

14. Contrived samples are essential in developing assays and evaluating performance at extremes of assay ranges.
15. Go talk to the FDA, go early, go often. They will work with you.
16. I've always obtained FDA agreement with use and % of surrogate samples for IVDs, and provided scientific rationale for CLIA/CAP LDTs
17. The important aspect of using contrived samples is their characterization and correlation to the clinical condition. A well characterized and reproducible contrived/surrogate is more accurate and useful than an unstable, biologically complex and variable material.
18. there are very significant ethical, regulatory and legal issues with the use of contrived/surrogate samples. These can include consent, privacy, ability to determine what research the source supports or doesn't want to support, return of research results, return of incidental findings, etc. These issues must be resolved before wide spread use of contrived/surrogate samples continues.

N = 18