

Figure 3. Examples of appropriate kinetic curve shapes

Kinetic curves should have a shape with an upward increasing curve as in the examples above. The sample examples shown here are from across the index range of the Fungitell STAT® assay. Use these examples to review the quality criteria.

Note:

- Each user of the test should establish a quality control program to assure proficiency in the performance of the test in accordance with the regulations applicable to their location.
- It is recommended to test serum control samples (negative, close to the limit value or strongly positive) in the context of further laboratory checks and good laboratory practice. These are not included in the Fungitell STAT® kit.

11. Interpretation of Results

- Negative Result**
Index values ≤ 0.74 are interpreted as negative results.
The laboratory performing the test should inform the ordering physician that not all fungal infections result in elevated levels of serum (1→3)-β-D-glucan. Some fungi, such as the genus *Cryptococcus*^{16,17} produce very low levels of (1→3)-β-D-glucan. *Mucorales*, such as *Absidia*, *Mucor* and *Rhizopus*¹⁻¹⁷ are not known to produce (1→3)-β-D-glucan. Similarly, *Blastomyces dermatitidis*, in its yeast phase, produces little (1→3)-β-D-glucan, and blastomycosis patients usually have undetectable levels of (1→3)-β-D-glucan in the Fungitell STAT® assay¹⁸.
- Indeterminate Result**
Index values from 0.75 to 1.1 are considered inconclusive (equivocal). Additional sampling and testing of sera is recommended. Frequent sampling and testing improves the utility for diagnosis.
- Positive Result**
Index values ≥ 1.2 are interpreted as a positive result. A positive result means that (1→3)-β-D-glucan was detected. A positive result does not define the presence of disease and should be used in conjunction with other clinical findings to establish a diagnosis.

12. Limitations of the Test

- The tissue locations of fungal infection⁷, encapsulation, and the amount of (1→3)-β-D-glucan produced by certain fungi may affect the serum concentration of this analyte. Reduced ability to contribute (1→3)-β-D-glucan to the bloodstream can reduce the ability to detect certain fungal infections.
- Some individuals have (1→3)-β-D-glucan index values that fall into the indeterminate zone. In such cases, additional surveillance testing is recommended.
- The frequency of patient testing will depend upon the relative risk of fungal infection. Sampling rates of at least two to three times per week are recommended for at risk patients.
- Positive results have been found in hemodialysis patients^{19,20,39}, subjects treated with certain fractionated blood products such as serum albumin and immunoglobulins^{23,24} and in specimens or subjects exposed to glucan-containing gauze and surgical sponges. Patients require 3 – 4 days for the restoration of baseline levels of serum (1→3)-β-D-glucan, after surgical exposure to (1→3)-β-D-glucan containing sponges and gauze^{21,22}. Accordingly, the timing of sampling of surgical patients should take this into account.

- Samples obtained by heel or finger stick methods are unacceptable as the alcohol-soaked gauze used to prepare the site (and, potentially, the skin surface-pooling of blood) has been shown to contaminate the specimens. In studies to date, no differences have been observed between samples obtained by line draws or venipuncture^{25,26}.
- Test levels were established in adult subjects. Infant and pediatric normal and cut-off levels are under investigation^{27,28}.

13. Performance Characteristics

13.1 Expected Values

- Diagnostic sensitivity and diagnostic specificity of the reference method, Fungitell® assay**
A multi-center, prospective study conducted to determine the diagnostic sensitivity and diagnostic specificity of the Fungitell® assay (USA predicate and 2008 CE-marked) has shown that the (1→3) β-D-glucan values are increased in various fungal infections. When signs and symptoms are present at the 80 pg/mL level or greater, the predictive value that the subject is positive for a fungal infection ranges from 74.4 to 91.7%. In the absence of signs and symptoms at less than 60 pg/mL, the negative predictive values ranged from 65.1% to 85.1%²⁹.
- Determination of the Fungitell STAT® cut-off values**
De-identified, frozen patient serum samples collected for routine clinical care of the intended population and received at Beacon Diagnostics Laboratory, Inc for Fungitell® testing were used for the purpose of this study. Beacon Diagnostics Laboratory, Inc is a licensed Clinical Laboratory Improvement Amendments (CLIA) laboratory part of Associates of Cape Cod (ACC). A population of 93 de-identified patient serum samples was included in the study with (1→3)-β-D-Glucan concentrations distributed over the full range of the Fungitell® standard curve of 31 – 500 pg/mL. The Fungitell STAT® cut-off assessment followed the ROC curve analysis (Receiver Operating Characteristic Curves)³⁰. The results indicated that Fungitell STAT β-glucan index values ≥ 1.2 are to be interpreted as a positive result in alignment with the Fungitell® product’s 80 pg/mL cutoff while index values ≤ 0.74 are to be interpreted as negative results in alignment with the Fungitell® product’s 60 pg/mL cutoff. These cut-off values were validated as part of the Method Comparison study and calculation of the Negative Percent Agreement and Positive Percent Agreement presented below.

13.2. Method Comparison

Similarly to the Cut-off value study but using a different set of samples, 488 de-identified, frozen patient serum samples also with (1→3)-β-D-Glucan concentrations distributed over the full range of the Fungitell® standard curve of 31 – 500 pg/mL were used for the purpose of the method comparison study³⁰. These included 309 samples that fell within the Negative zone of the Fungitell® test results, 143 samples that fell within the Positive zone of the Fungitell® and 36 samples that fell within the Indeterminate zone of the Fungitell® (Table 2). All samples were tested with both the Fungitell STAT® and Fungitell® assays during this study. When samples falling within the Indeterminate zone of the Fungitell STAT® were excluded from analysis, there were 290 samples remaining for the negative percent agreement analysis and 119 samples remaining for positive percent agreement analysis.

Table 2. Fungitell STAT® Performance Compared to Fungitell®					
		Fungitell®			
		Negative	Indeterminate	Positive	Total
Fungitell STAT®	Negative	283	17	1	301 (61.7%)
	Indeterminate	19	17	24	60 (12.3%)
	Positive	7	2	118	127 (26.0%)
Total		309 (63.3%)	36 (7.4%)	143 (29.3%)	488 (100%)
		NPA: 97.6%* (283/290) 95% CI: (95.4, 99.9)		PPA: 99.2%* (118/119) 95% CI: (95.4, 99.9)	

*Indeterminate (i.e., equivocal) results not included in analysis; if all indeterminate results are considered discordant results (e.g., false positive or false negative), performance is as follows: PPA - 73.8% (118/160), 95% CI: (66.4%, 80.0%); NPA - 91.0% (283/311), 95% CI: (87.3%, 93.7%)

- Negative Percent Agreement**
Two hundred eighty-three (283) of the 290 samples that were negative when tested with the Fungitell® device were also negative with the Fungitell STAT® assay. The calculated negative percent agreement (NPA) with the Fungitell® method was 97.6% (95% Confidence Interval: 95.4%, 99.9%) (Table 2)
- Positive Percent Agreement**
One-hundred eighteen (118) of the 119 samples that were positive when tested with the Fungitell® device were also positive with the Fungitell STAT® assay. The calculated positive percent agreement (PPA) with the Fungitell® method was 99.2% (95% Confidence interval: 95.4%, 99.9%) (Table 2).
- Measuring Range, Linearity and Accuracy**
The index results ranged from approximately 0.4 to 3.5, covering the full Standard curve (31 – 500 pg/mL) of the Fungitell®. The linear correlation between the Fungitell® concentration and Fungitell STAT® index results was 0.92 (95% Confidence interval: 89.9% and 93.6%).

13.3 Analytical Inter-laboratory Study

The Fungitell STAT® was evaluated for precision (i.e., repeatability and reproducibility), analytical sensitivity and analytical specificity by spiking human serum with *Saccharomyces cerevisiae* (1→3)-β-D-Glucan to produce a five-member panel consisting of a low negative sample, high negative sample (just below the lower cut-off of 0.74), indeterminate (equivocal) sample, low positive sample (just above the upper cut-off of 1.2) and high positive sample (~2x above the upper cut-off of 1.2). The panel was distributed to three CLIA laboratories for testing with the Fungitell STAT® assay. Each laboratory provided 150 data points (i.e., 5 samples x triplicate per run x two operators performing a run per day x 5 days) for a total of 450 data points and including 30 runs (i.e., assays) and 90 datapoints per sample (i.e., panel member). The mean study Index values presented in Table 3 below are derived from the data provided by the three laboratories. The Percent Positive column represents the percentage of samples for a given panel member that fell within the Positive zone. Among all three laboratories, the Percent Positive results were 1.1% for the Low Negative sample, 0% for the High Negative sample, 3.3% for the Indeterminate sample, 96.7% for the Low Positive sample and 100% for the High Positive samples.

Table 3. Analytical Inter-laboratory Study					
Panel Member	Mean Index	Standard Deviation	% CV	Percent Positive (Number pos./ Number tested)	Analytical Specificity (True Negative) and Analytical Sensitivity (True Positive)
Low Negative	0.55	0.10	20.4%	1.1% (1/90)	89/90 True Negative
High Negative	0.75	0.08	11.1%	0% (0/90)	90/90 True Negative
Indeterminate	0.94	0.10	11.1%	3.3% (3/90)	87/90 Not Positive
Low Positive	1.6	0.30	18.7%	96.7% (87/90)	87/90 True Positive
High Positive	2.6	0.40	15.4%	100% (90/90)	90/90 True Positive

As indicated in the Table 3, the Inter-assay variation (i.e., %CV) ranged from 11 to 20.4% and served as a measure of reproducibility. The intra-assay variation ranged from 0.4% to 26.8% and served as a measure of repeatability. The distribution of the intra-assay % CV range is presented below in Figure 4. Overall, 94% of

CV values were 10% or less and 75% of CV values were 6% or less.

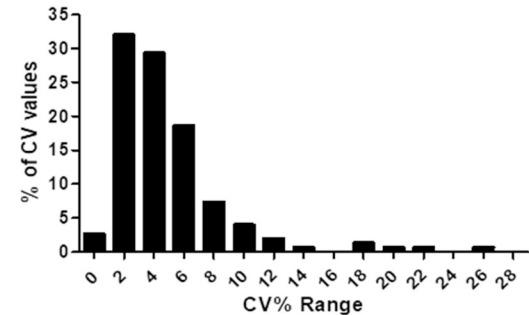


Figure 4. Distribution of intra-assay % CV values

13.4 Trueness

For each lot of the Fungitell STAT® product, the Fungitell STAT® Standard (1→3)-β-D-glucan concentration is calibrated to 80 +/- 8 pg/mL using the Fungitell® reference method and against an internal (1→3)-β-D-glucan reference standard.

13.5 Interfering Substances

- The following sample conditions can interfere with an accurate Fungitell STAT® assay result:
- Off-color or turbid samples such as those that are grossly hemolyzed, lipemic, or contain excessive bilirubin may cause optical interference with the assay. If such samples are tested, test results should be examined for evidence of optical interference and/or unusual kinetic patterns.
 - Elevated levels of Immunoglobulin G, such as may exist in the serum due to multiple melanomas, may result in precipitation in the reaction mixture upon the addition of Fungitell STAT® to the pre-treated serum³¹.
 - As of this writing, no activating Factor G ((1→3)-β-glucan detection element) of Fungitell® reagent have been described other than (1→3)-β-glucan. In some studies, where assertions of cross-reactivity have been made, treatment of the supposed activating material with purified (1→3)-β-glucanase have eliminated the signal, demonstrating that the observed activation had been due to contaminating (1→3)-β-glucan¹². Serine protease contamination may also result in para-nitroaniline release in Fungitell® reaction mixtures, but these are inactivated as part of the pre-treatment process.

14. Meta-Analyses

In addition, numerous peer-reviewed studies have been published on the subject of serum (1→3)-β-D-glucan-based support for invasive fungal disease diagnosis, including meta-analyses of diagnostic performance^{32,33,34,35}.

15. Symbols Legend

	“Use By”		“Temperature Limitation”
	“Contains Sufficient For ‘N’ Tests”		“Manufacturer”
	“Batch Code”		“Consult Instructions For Use”
	“In Vitro Diagnostic Medical Device”		“Authorised Representative”
	“Catalogue No.”		“CE Mark”
	“For Prescription Use Only”		“Keep Away From Sunlight”
	“Caution”		

16. Authorized representatives Emergo Europe
Prinsessegracht 20, 2514 AP, The Hague, The Netherlands

Note: serious incident that has occurred in relation to the device shall be reported to the manufacturer and the competent authority of the Member State in which the user and/or the patient is established.

17. Contact Information

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18. Revision History

- Rev 1-3: Added PKF08-PKG catalog # and related instructions; details about Fungitell STAT® Standard serving as Internal Control, contact information, clarifications and formatting. Clarified general QC criteria #3. Added Specimen stability data and determination of cut-off value, Measuring Range-Linearity-Accuracy and Trueness sections.
Rev 4: Changed EC representative, changed 0.03 value to 0.00 in Quality Control section and minor changes for clarification.

19. References

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