EUROPEAN FEDERATION OF STATISTICIANS IN THE PHARMACEUTICAL INDUSTRY
Representing Statistical Associations in Europe

Statistical methodology for biosimilars, comparison of process changes and comparison of dissolution profiles

A perspective from EFSPI

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on behalf of EFSPI WG

Three Fundamental Requirements

- Define what we mean by equivalence/comparability
- Provide a well-defined decision procedure
- Demonstrate the operating characteristics of the procedure
  - What is the probability of deciding in favour of equivalence/comparability?
  - What is the patient risk?
    - (Test product is deemed equivalent/comparable and a patient receives a bad lot from the Test product)
  - What is the producer risk?
    - (Test product is deemed not to be equivalent/comparable when it is)

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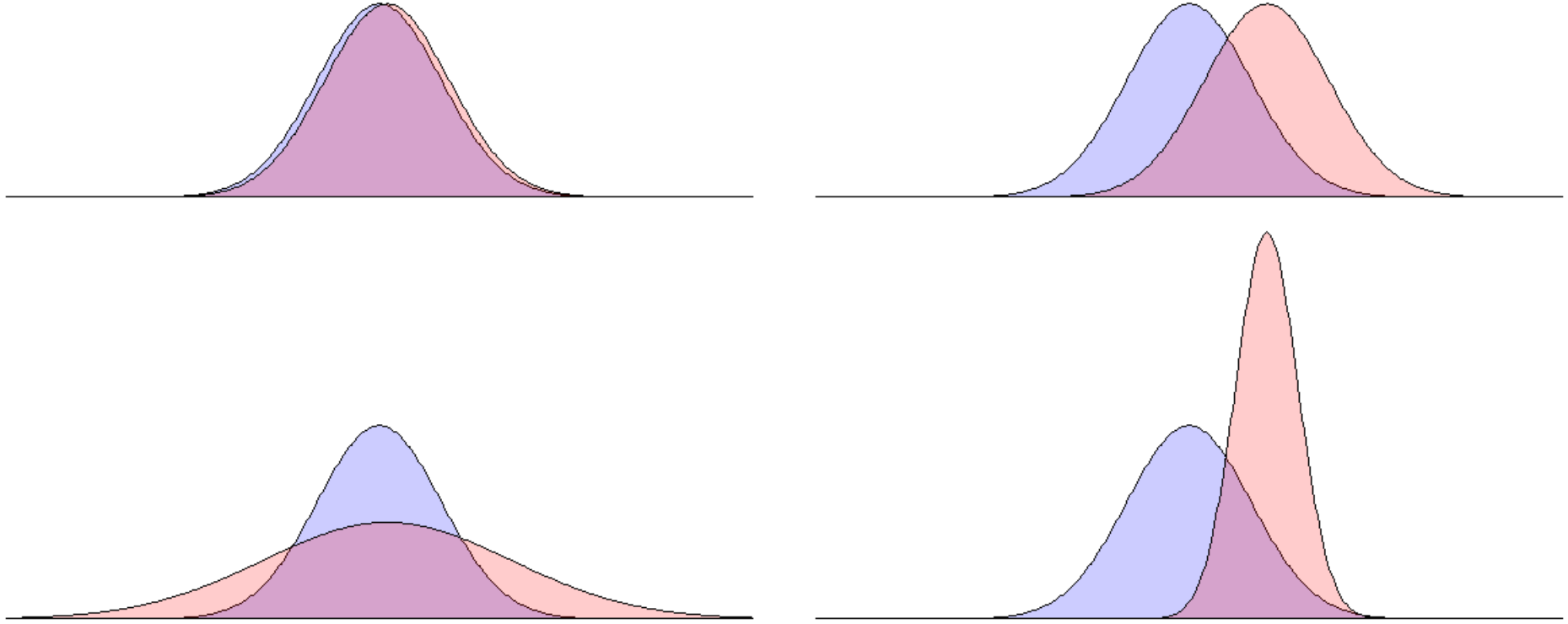
What do we mean by equivalent/comparable?

- Demonstrate that **proposed new process produces** lots of Test product that are (analytically) “equivalent/comparable” to those of the Reference product (both now and in the future).



When are the two distributions equivalent/comparable?

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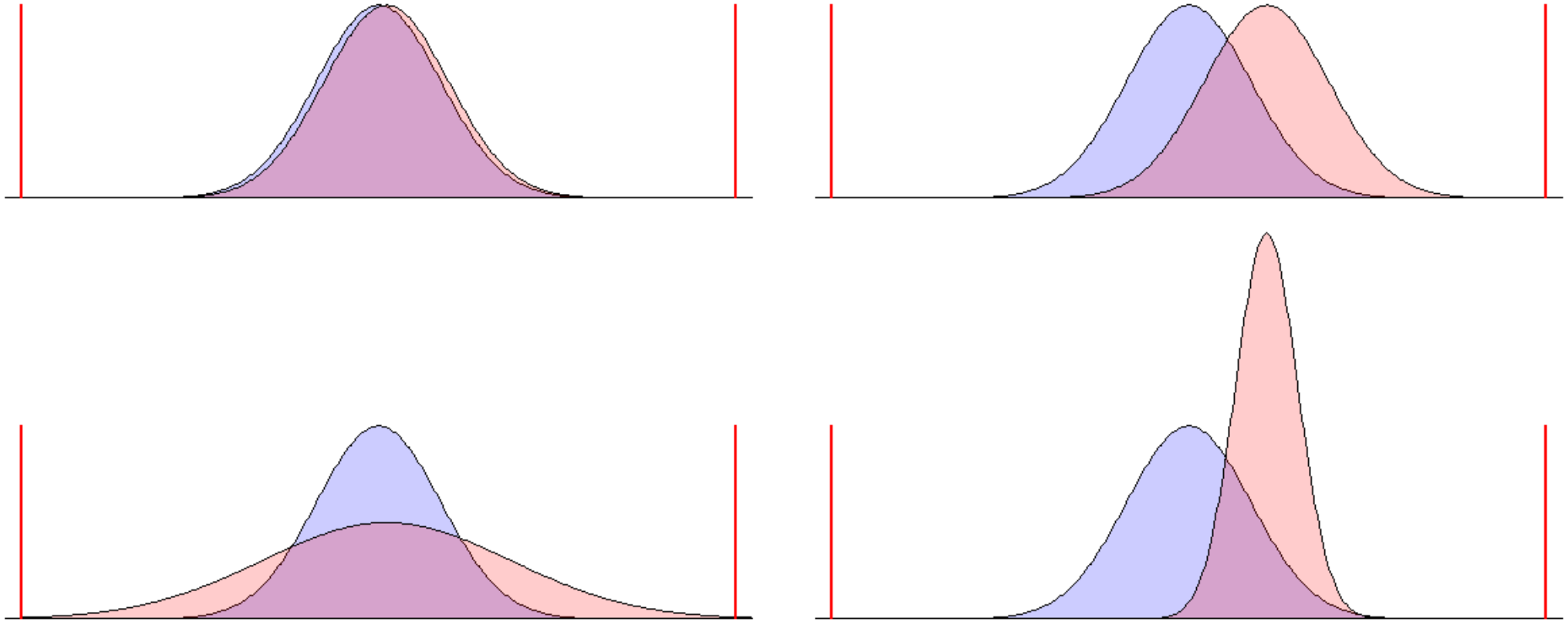

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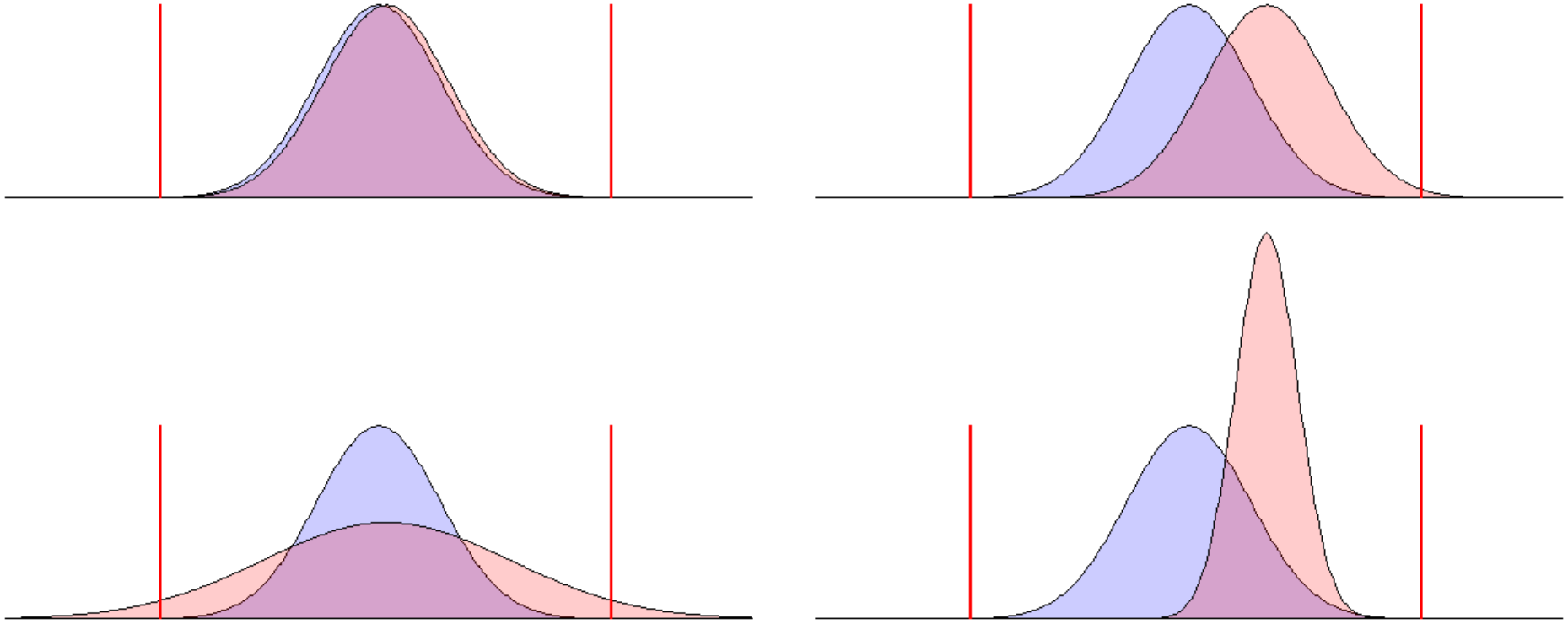
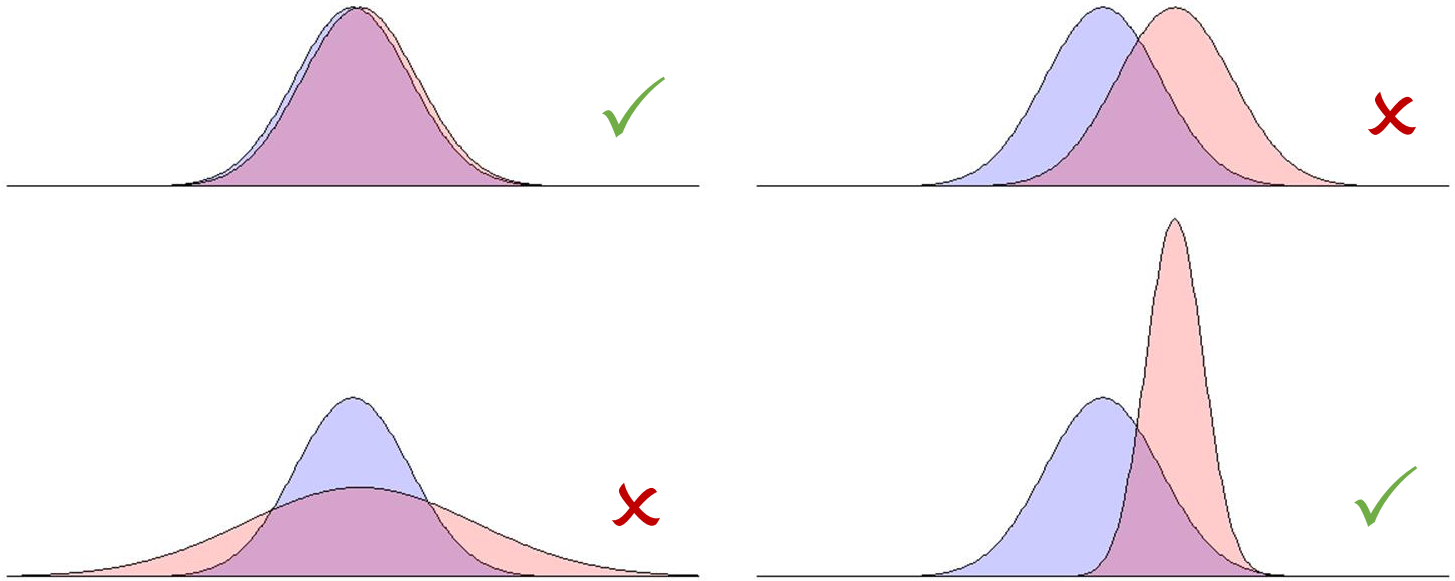


When are the two distributions equivalent/comparable?

A Definition of Biosimilarity

- The test product is analytically comparable (for a given attribute) to the Reference product if the middle P% of all lots produced by the Test product process lie within the middle P% of the lots produced by the Reference product process.
- In what follows we will use 99%.

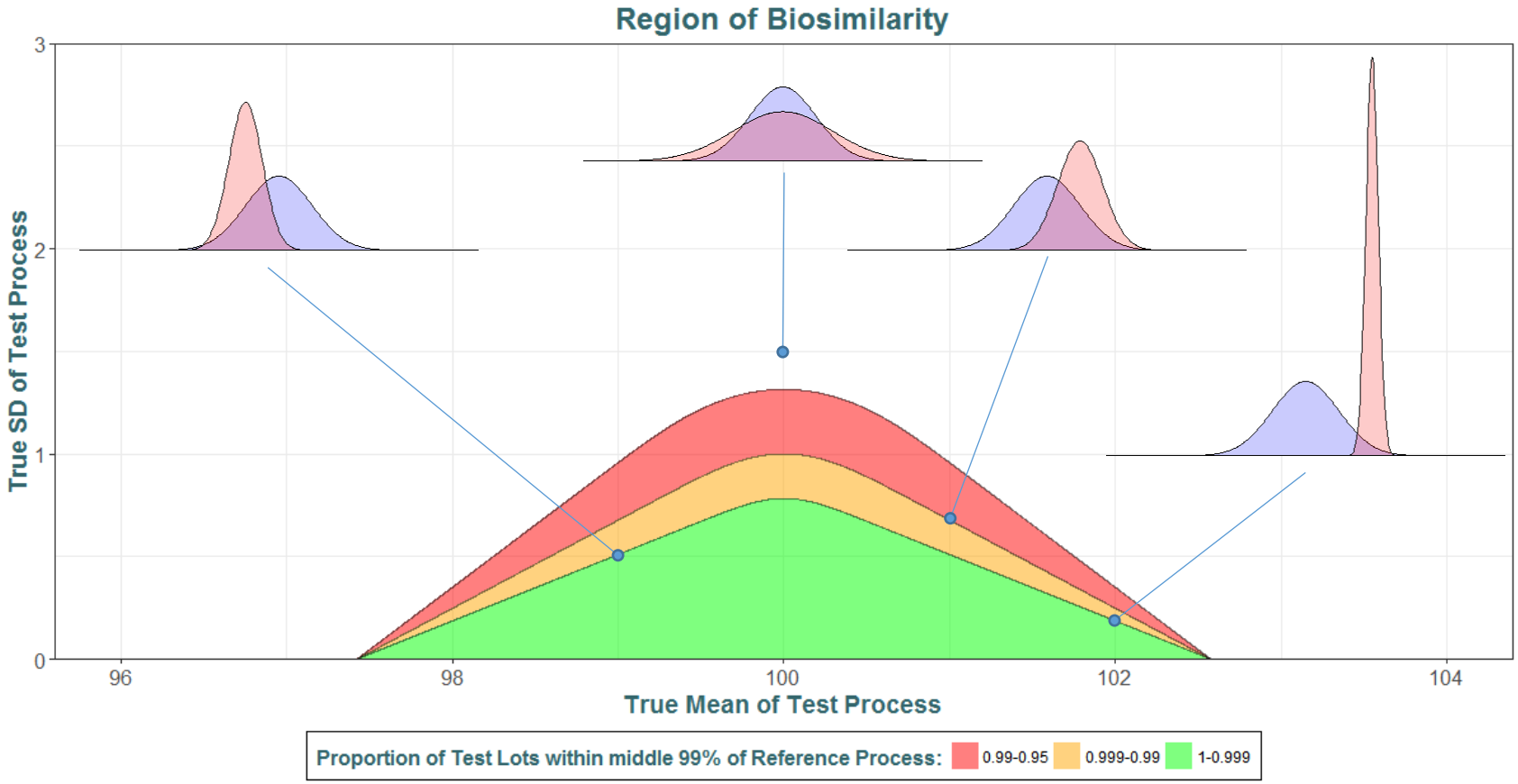
In the absence of specification limits



A Definition of Biosimilarity

- Combinations of Mean and SD that would be considered Biosimilar

Assumes
Ref Mean = 100
Ref Var = 1



A Decision Procedure for Biosimilarity (1)

- Interested in limits defined by central portion of distribution of Reference product lots
- Mean and variance of Reference estimated with uncertainty
- The β-content γ-Confidence Tolerance Interval (TI) on Reference is recommended

$$\bar{X}_{Ref} \pm k_c \times s_{Ref}$$

$$k_c : P_{\bar{X}_{Ref},\, s_{Ref}} \left\{ P_X \left(\bar{X}_{Ref} - k_c s_{Ref} < X < \bar{X}_{Ref} + k_c s_{Ref} \;\middle|\; \bar{X}_{Ref}, s_{Ref} \right) > \beta \right\} = \gamma$$

Tables and software for obtaining k_c are readily available

- Takes into account the uncertainty on the Mean and the Variance
- Better statistical properties than Min and Max
- Both Content and Confidence can be controlled

- A minimum sample size of Reference is recommended to make β-content γ-Confidence Tolerance Interval (TI) relevant for Similarity limits. (Here we will use 15)

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A Decision Procedure for Biosimilarity (2)

- Test if β-Prediction Interval (PI) of biosimilar is within β-γ-Tolerance Interval (TI) of reference

$$\bar{X}_{Test} \pm t_{(1+\beta)/2,(n_{Test}-1)} \times s_{Test} \sqrt{1+1/n_{Test}}$$

- Equivalent to a 100β% Credible Interval based on Posterior Predictive Distribution of X given the observed data using a Jeffreys Prior

- More relevant than using an arbitrary c factor (such as 3!)
- Takes into account the variability of the Test process (between-lots)
- Takes into account uncertainty on means and variability of new process
- Demonstrates that Test lots will be within the range of Reference lots with some level of confidence even in the future

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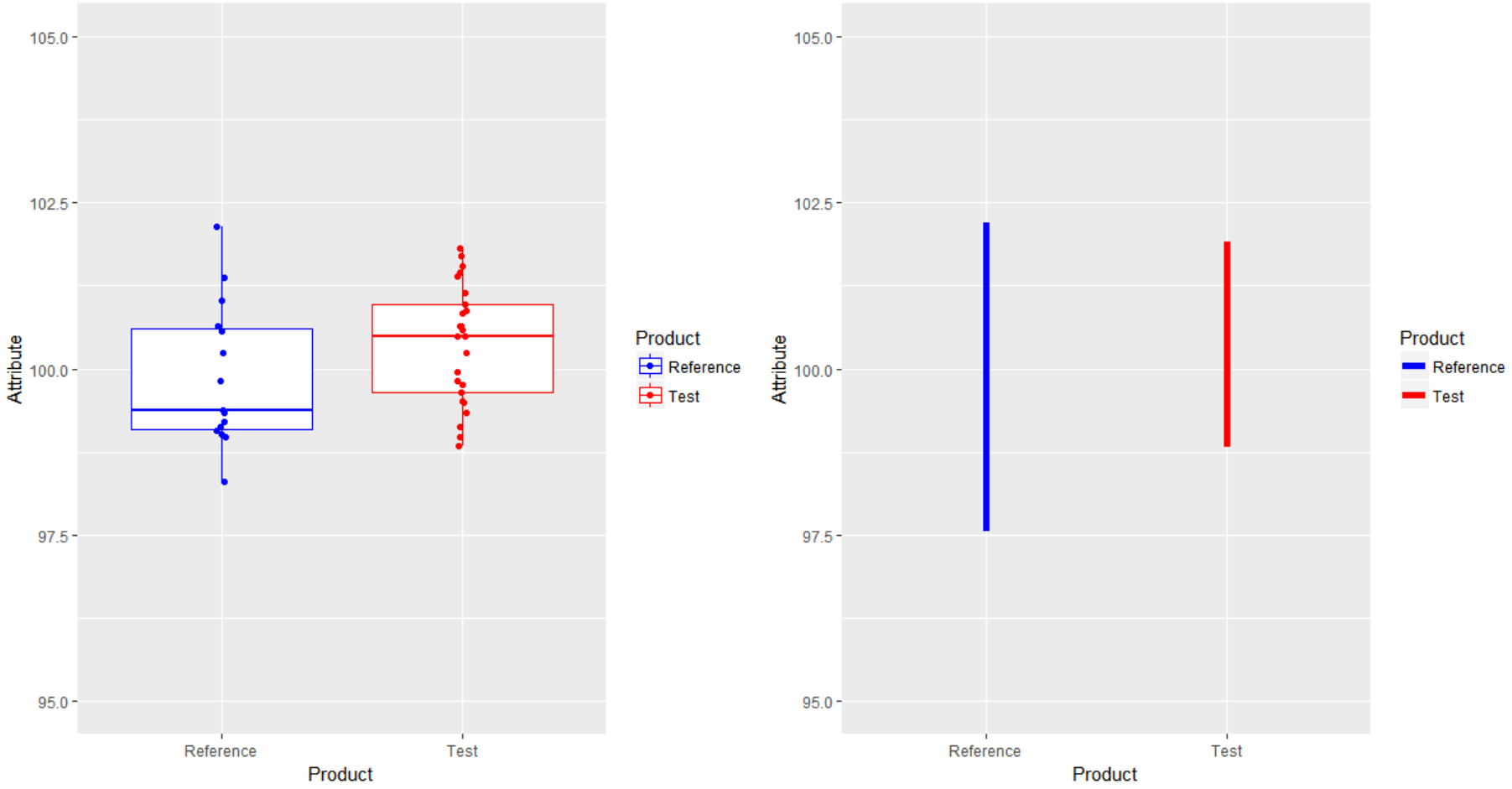
A Decision Procedure for Biosimilarity (3)

- Test if β-Prediction Interval is within β-γ-Tolerance Interval



Other Decision Procedures – FDA Tier Approach

Tier 1 – Most Critical
(1-2α)100% two-sided Confidence Interval for Difference in Means contained within +/-1.5s_{Ref}

Compares the means of the two distributions

Tier 2 – Moderate Critical
Quality Range Method: mean +/- k s_{Ref}

Compares the central portions of the two distributions

Tier 3 – Least Critical
Raw Data/Graphical Comparison

No 'formal' assessment of the two distributions

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Demonstrate the Operating Characteristics (1)

- Simulate or derive the performance of the decision rule for different combinations of the Mean and SD of the Test Product Process
- E.g.
  - Assume Reference Mean = 100, Reference SD = 1
  - # Reference Lots = 15
  - # Test Lots = 5, 10, 15, 20, 25

Decision methods:

- FDA Two-Sided 90% Confidence Interval of Mean Difference
- FDA 90% of Test Lots in Mean +/- 3 SD
- Proposal β PI within β/γ TI (80% and 98% chosen here)

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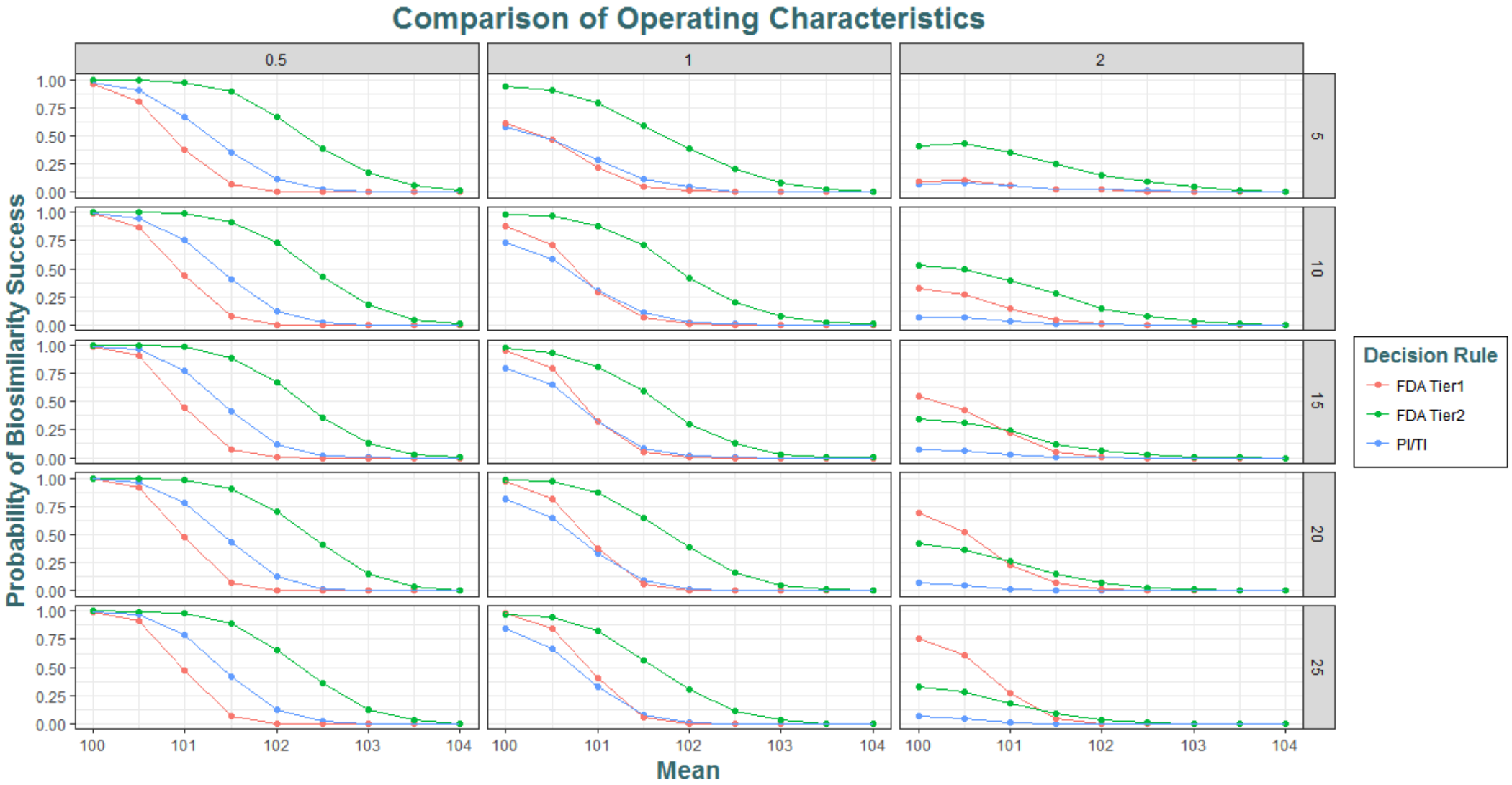
Demonstrate the Operating Characteristics (2)



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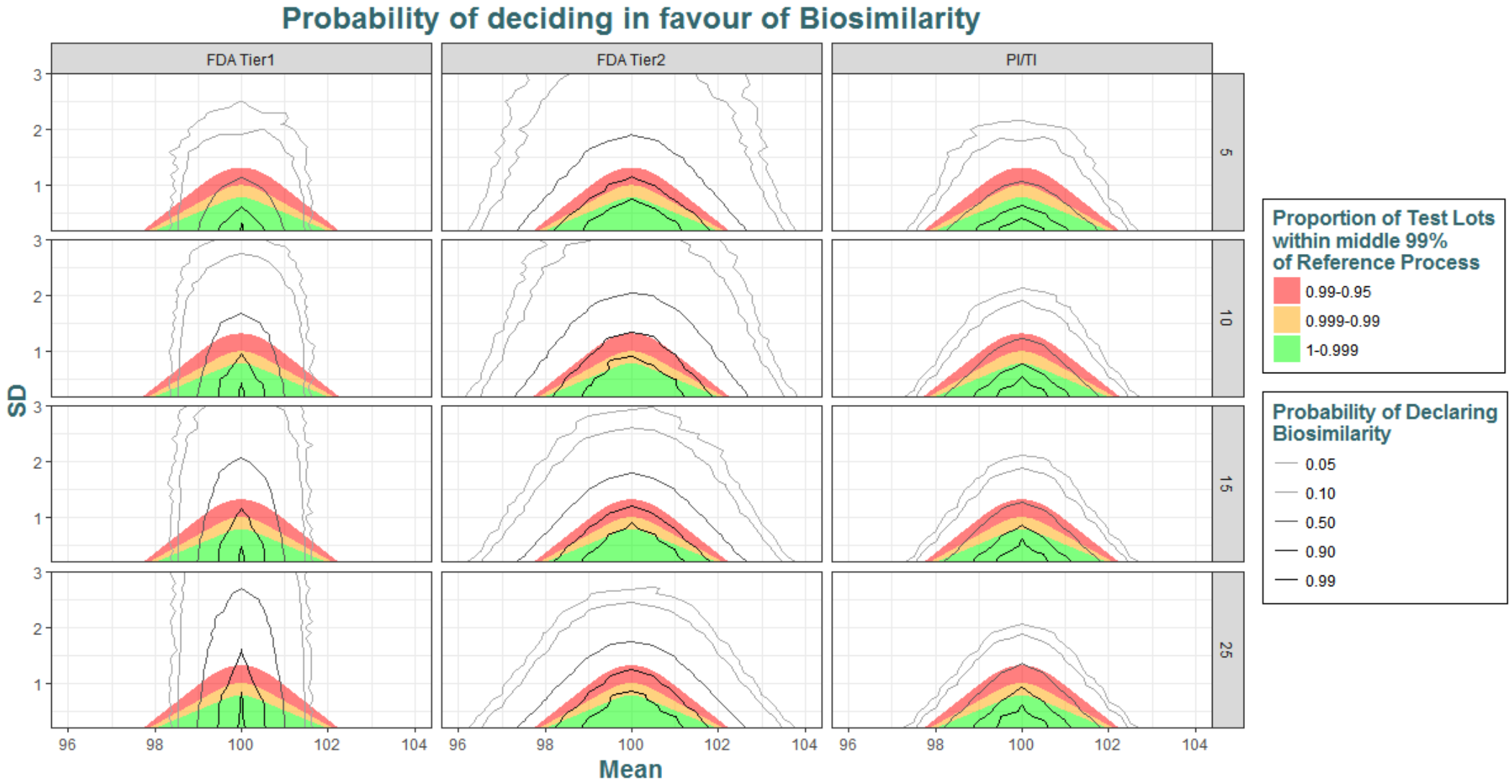
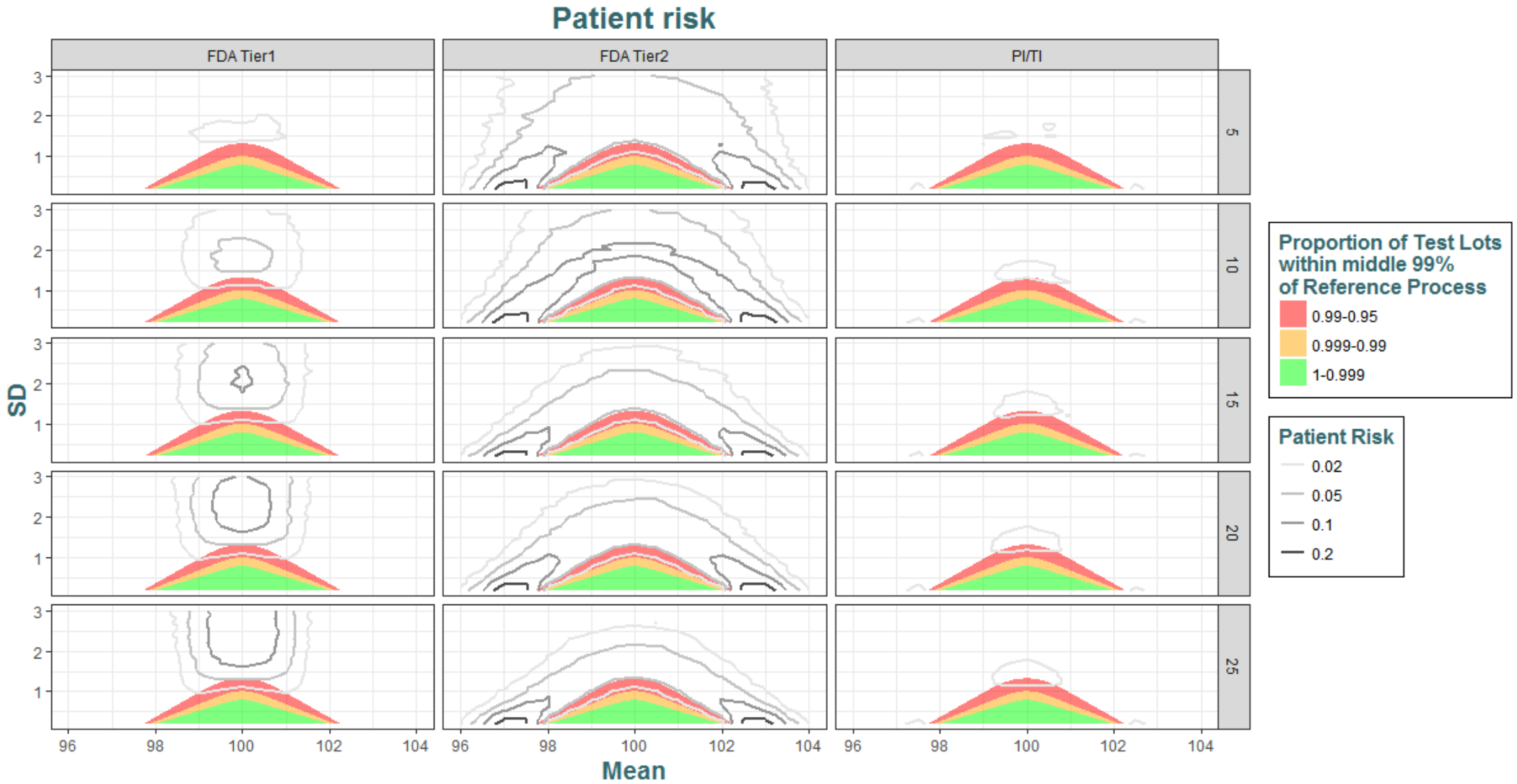
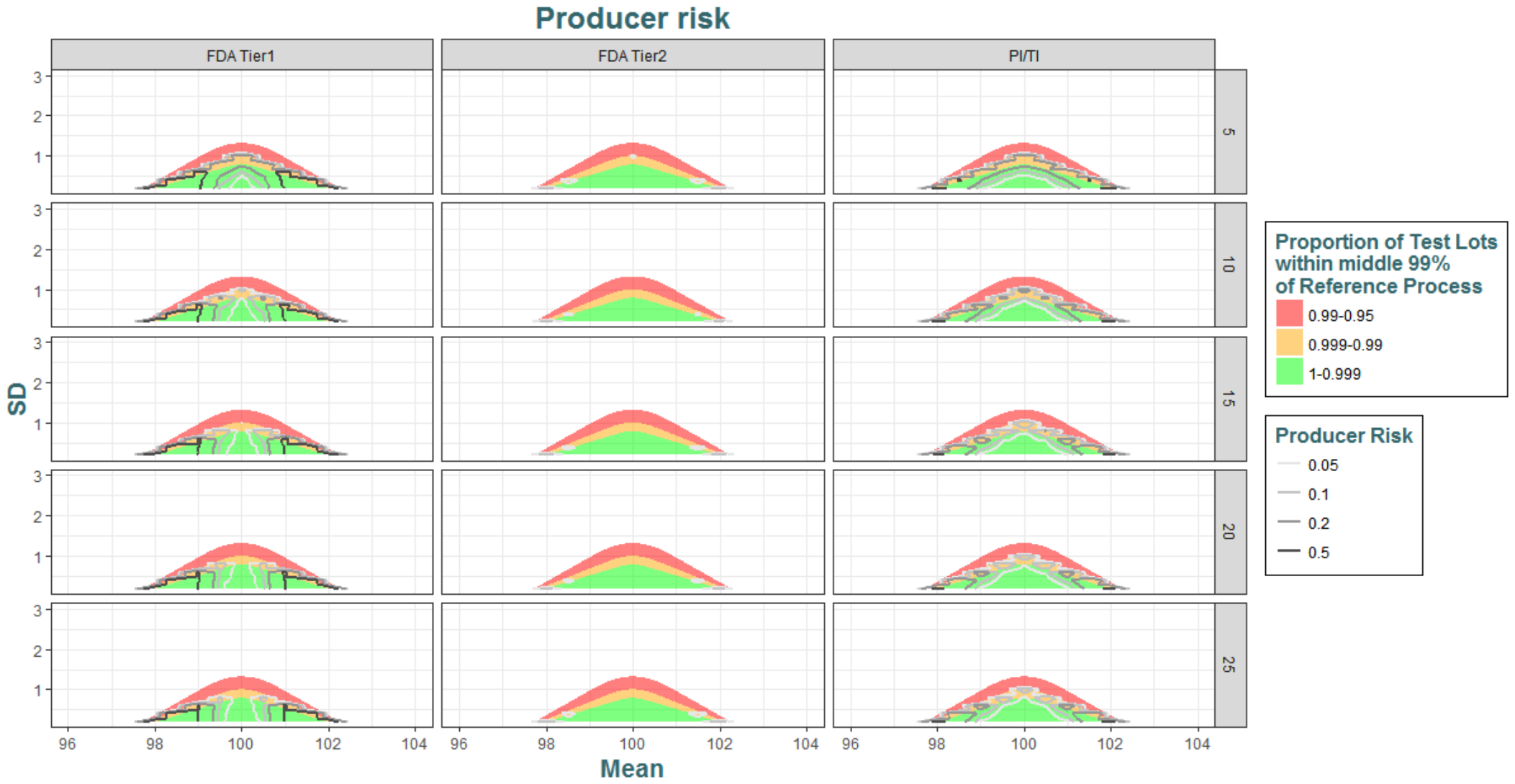


Patient Risk



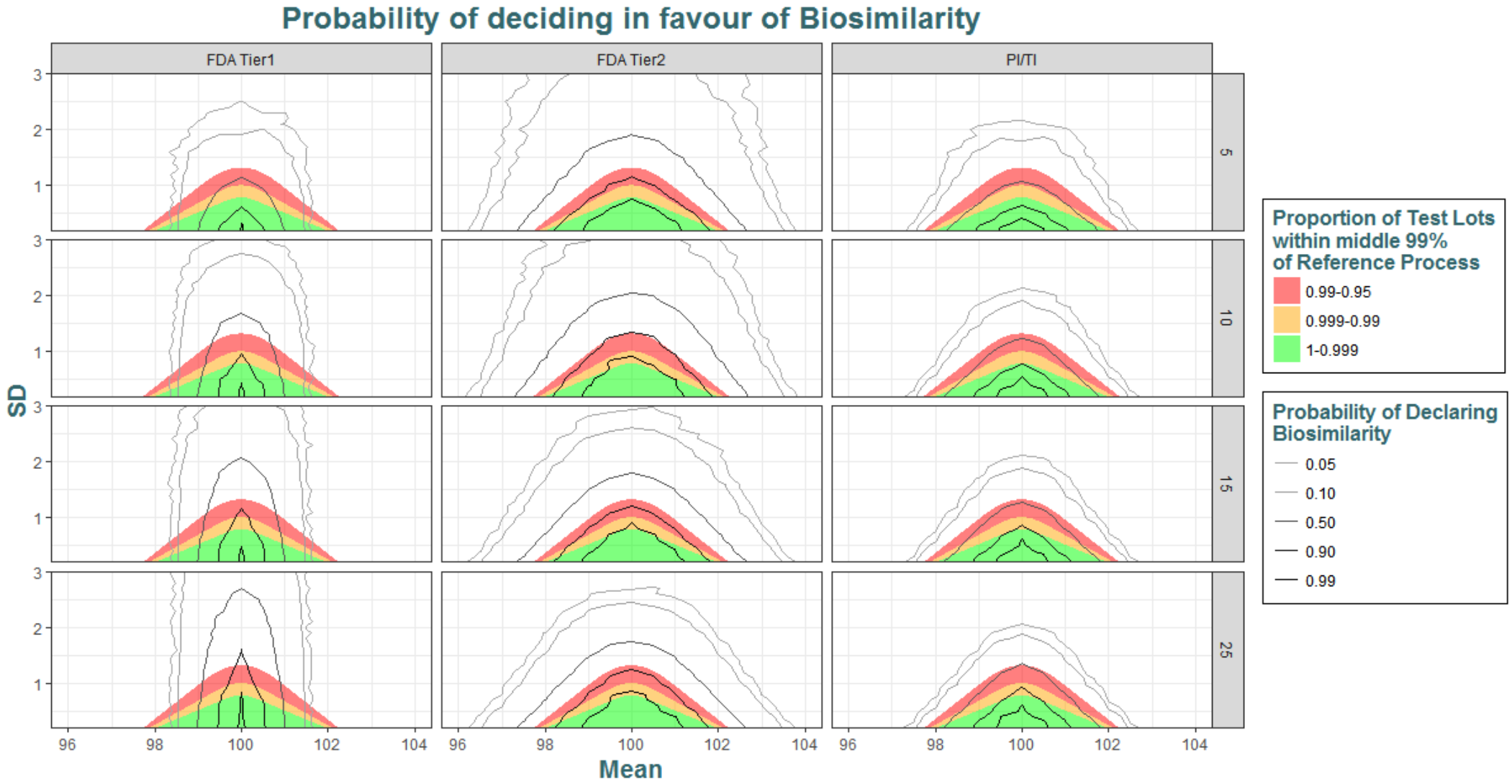
Producer Risk



Backup Slides

80% PI within 80/98% TI

Demonstrate the Operating Characteristics



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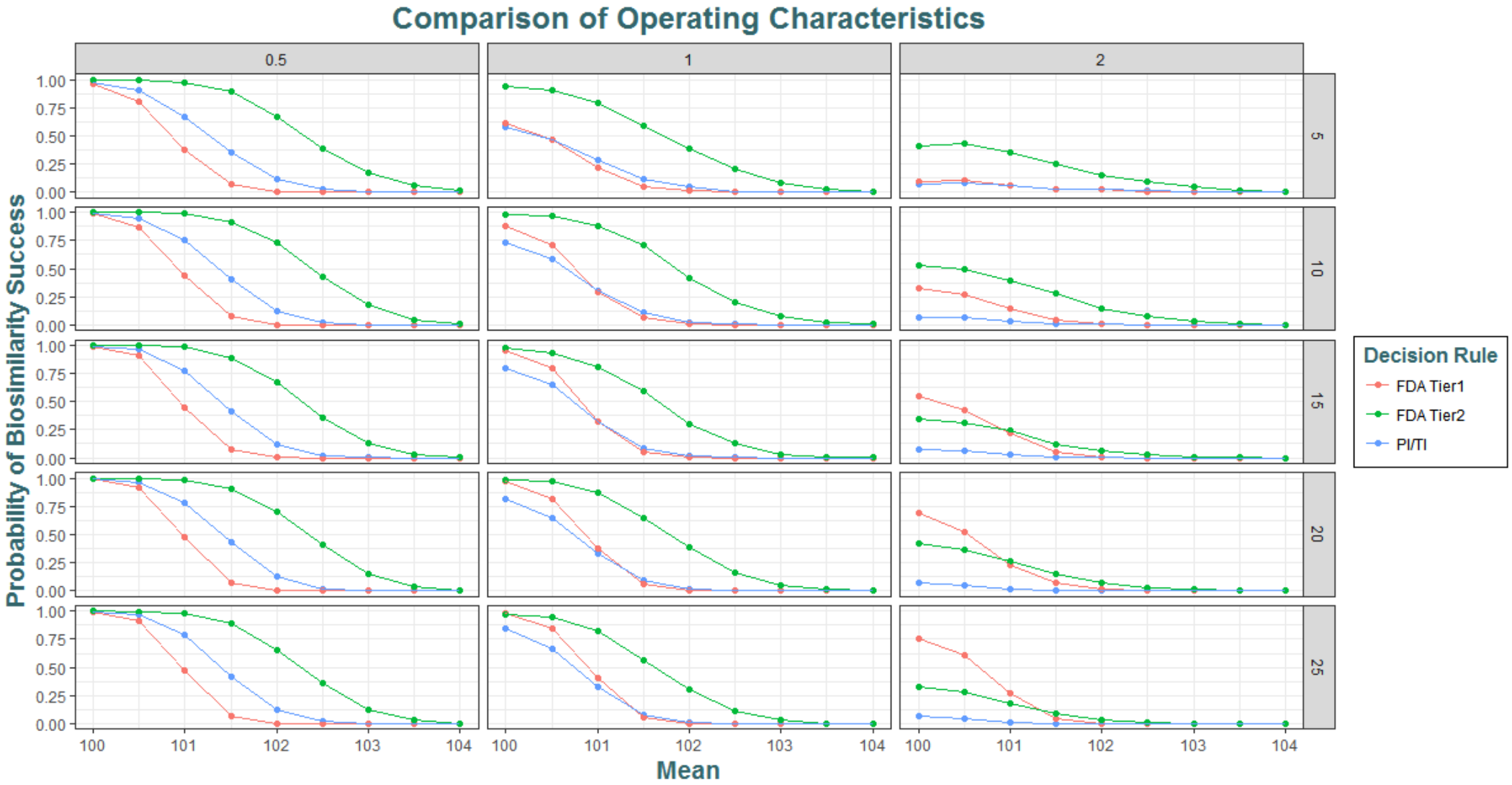

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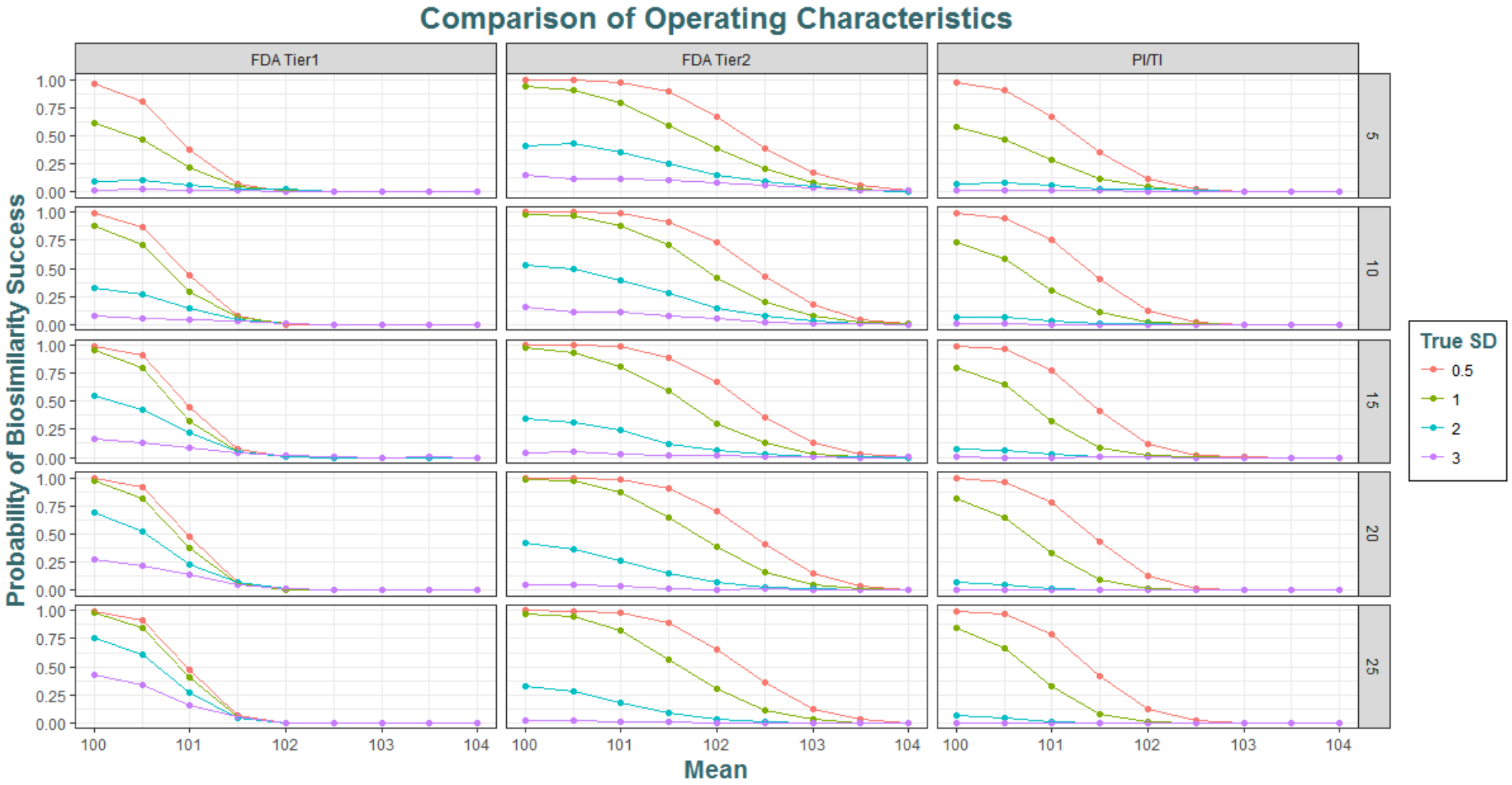

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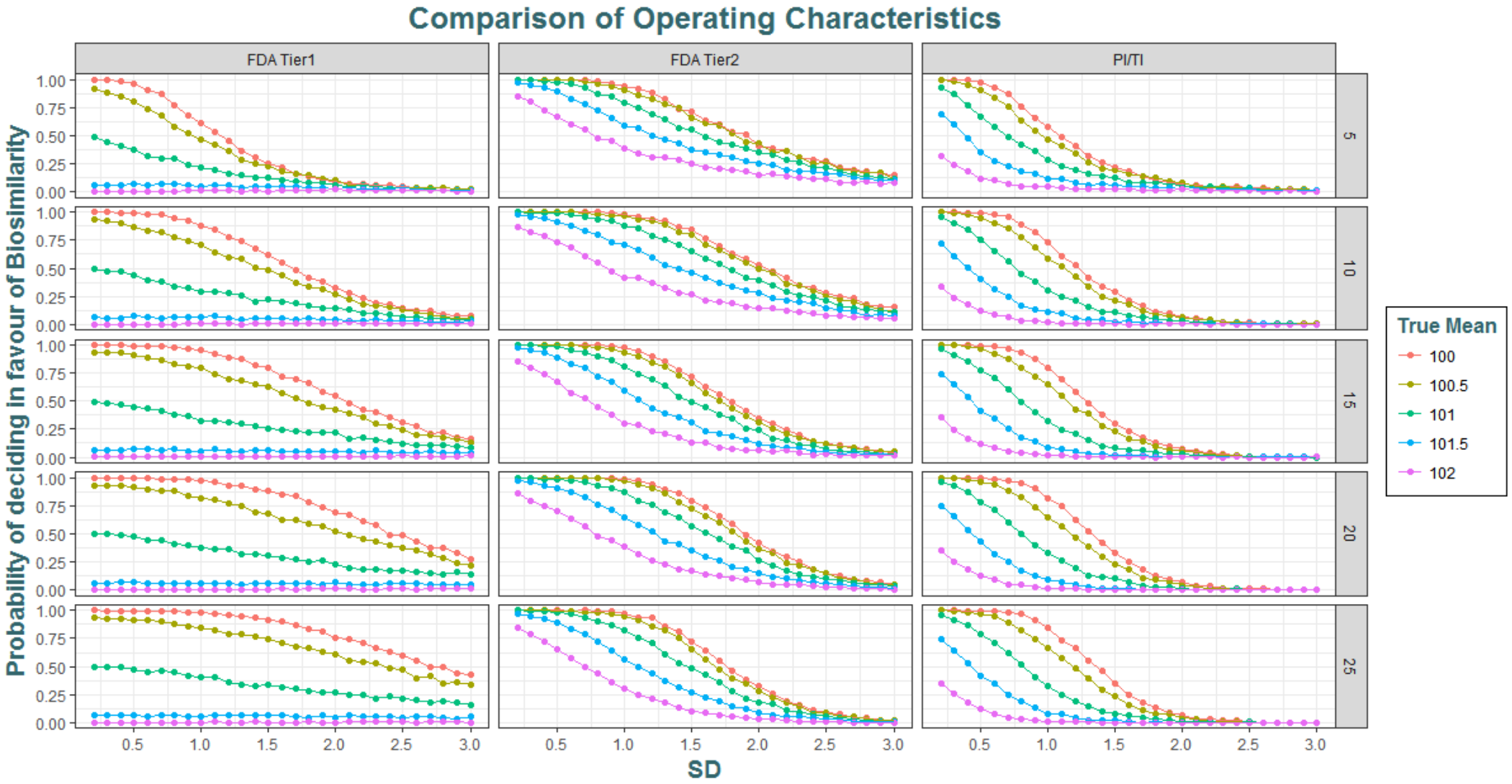

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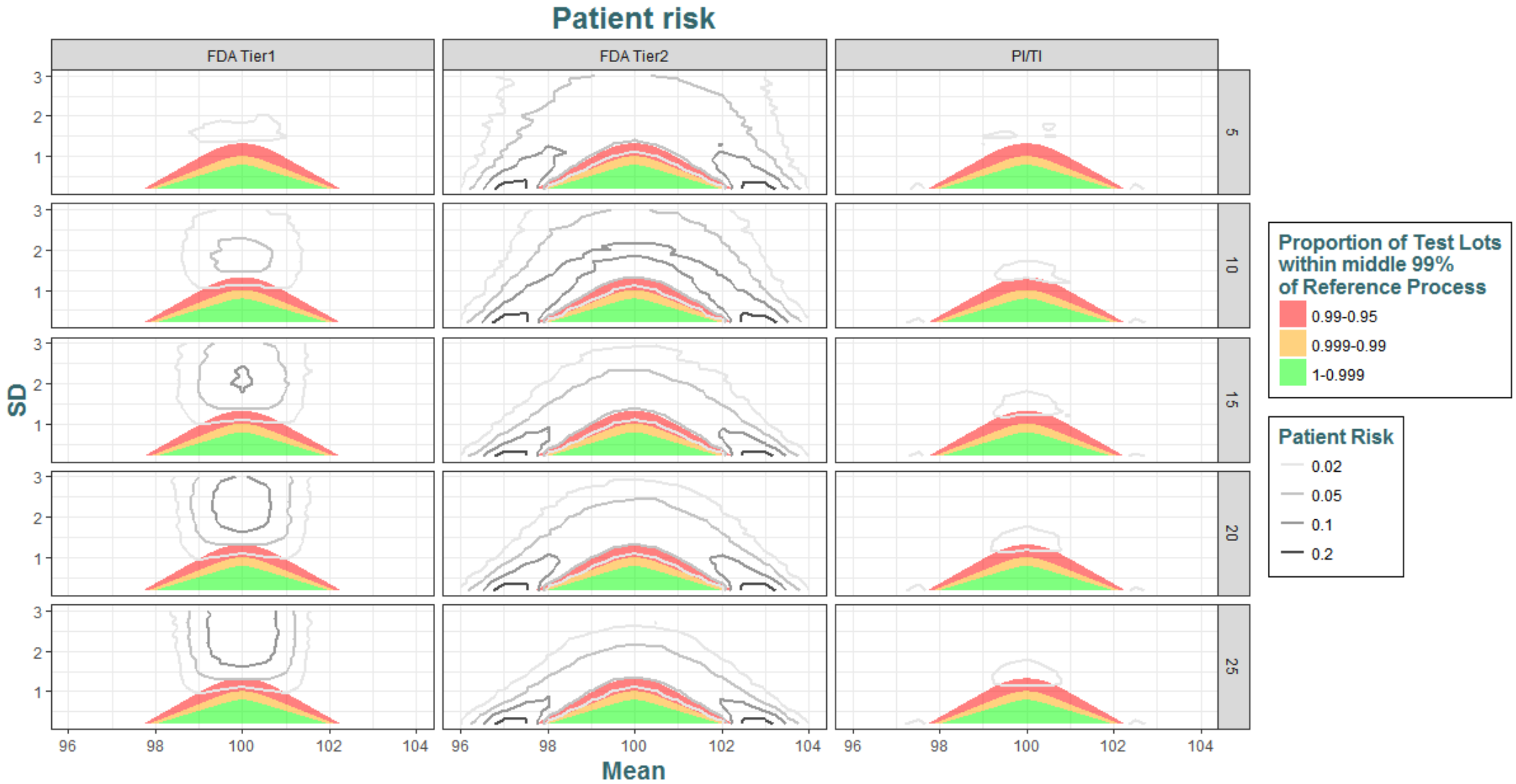

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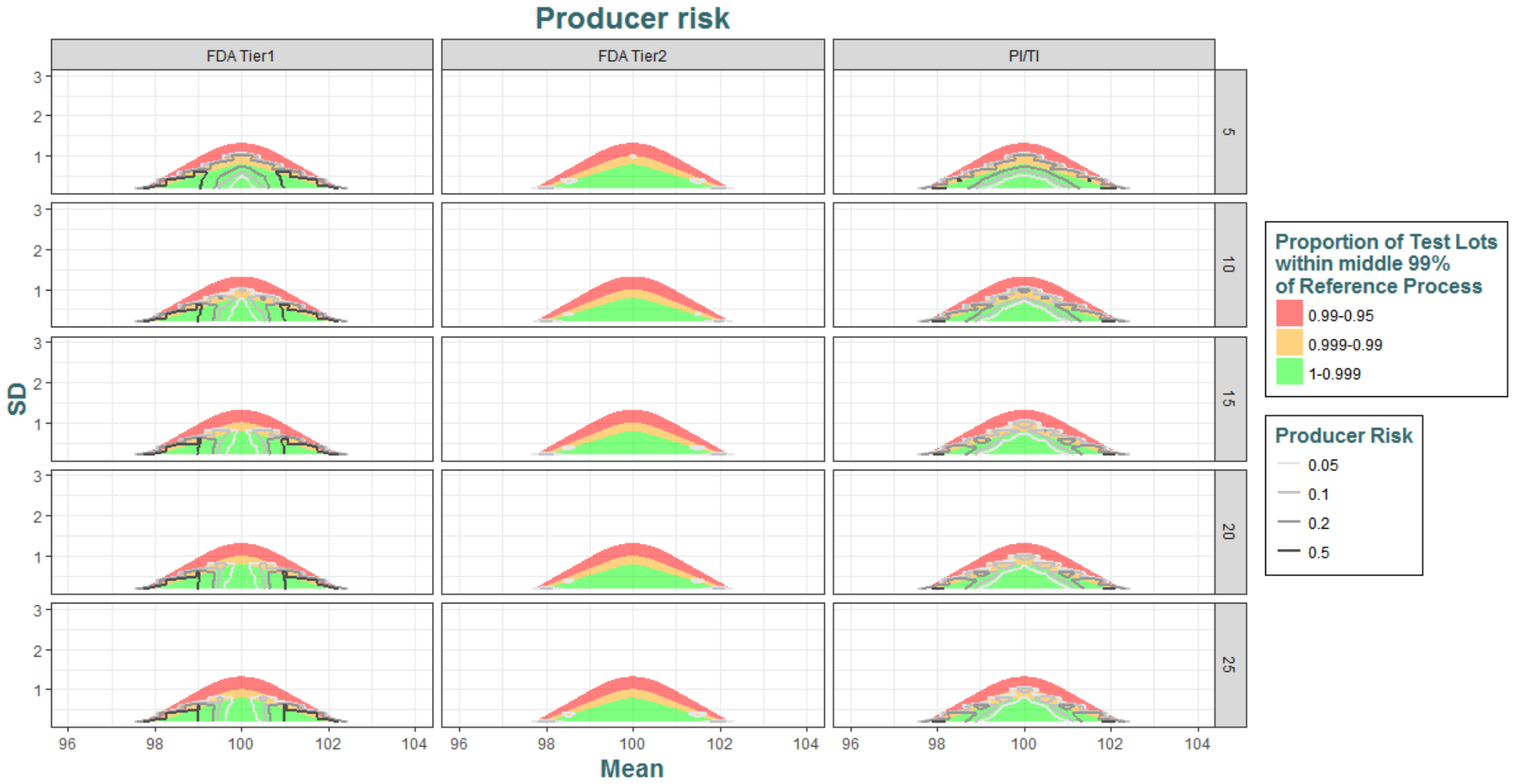

99% PI within 99/95% TI

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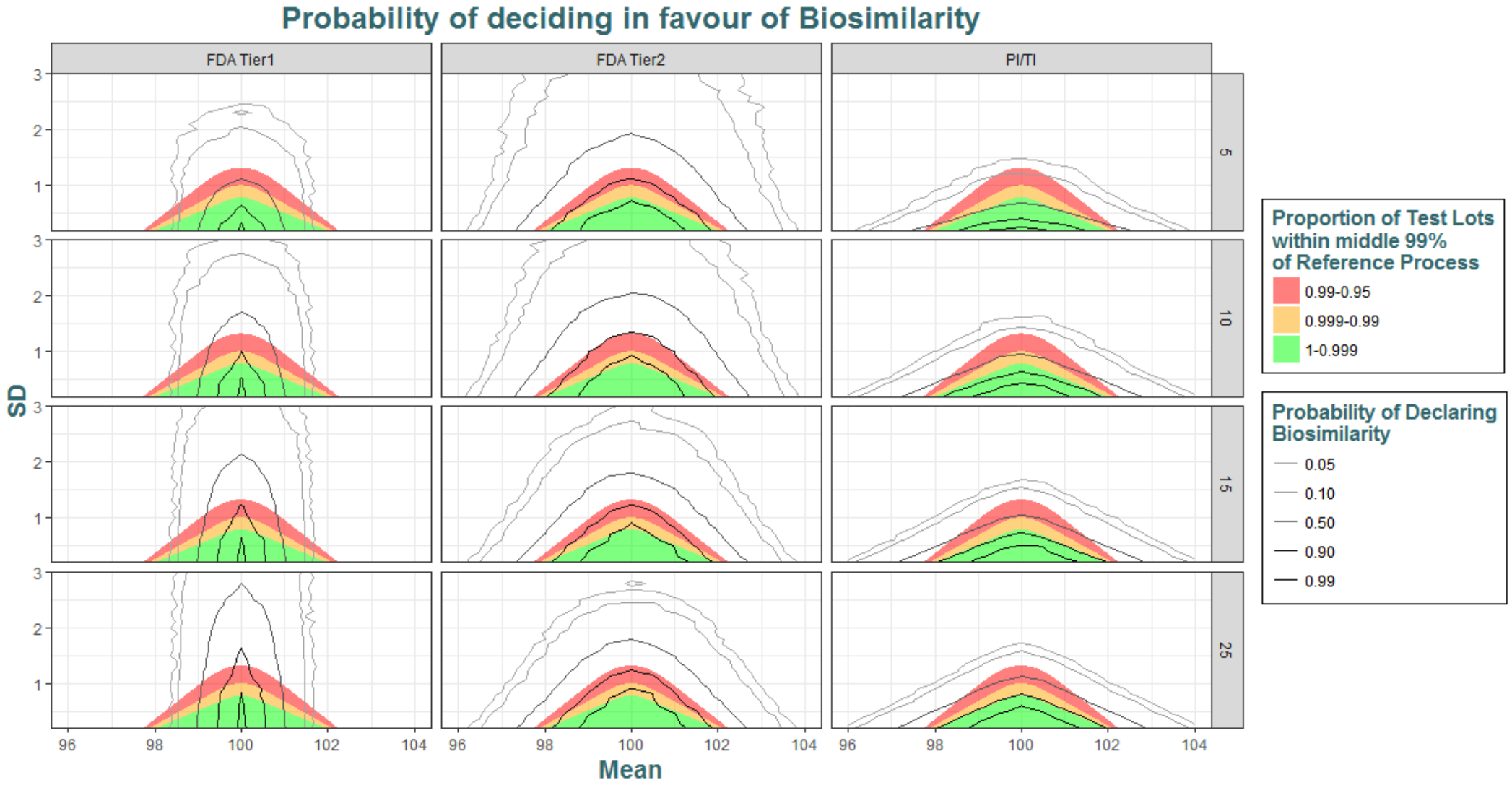

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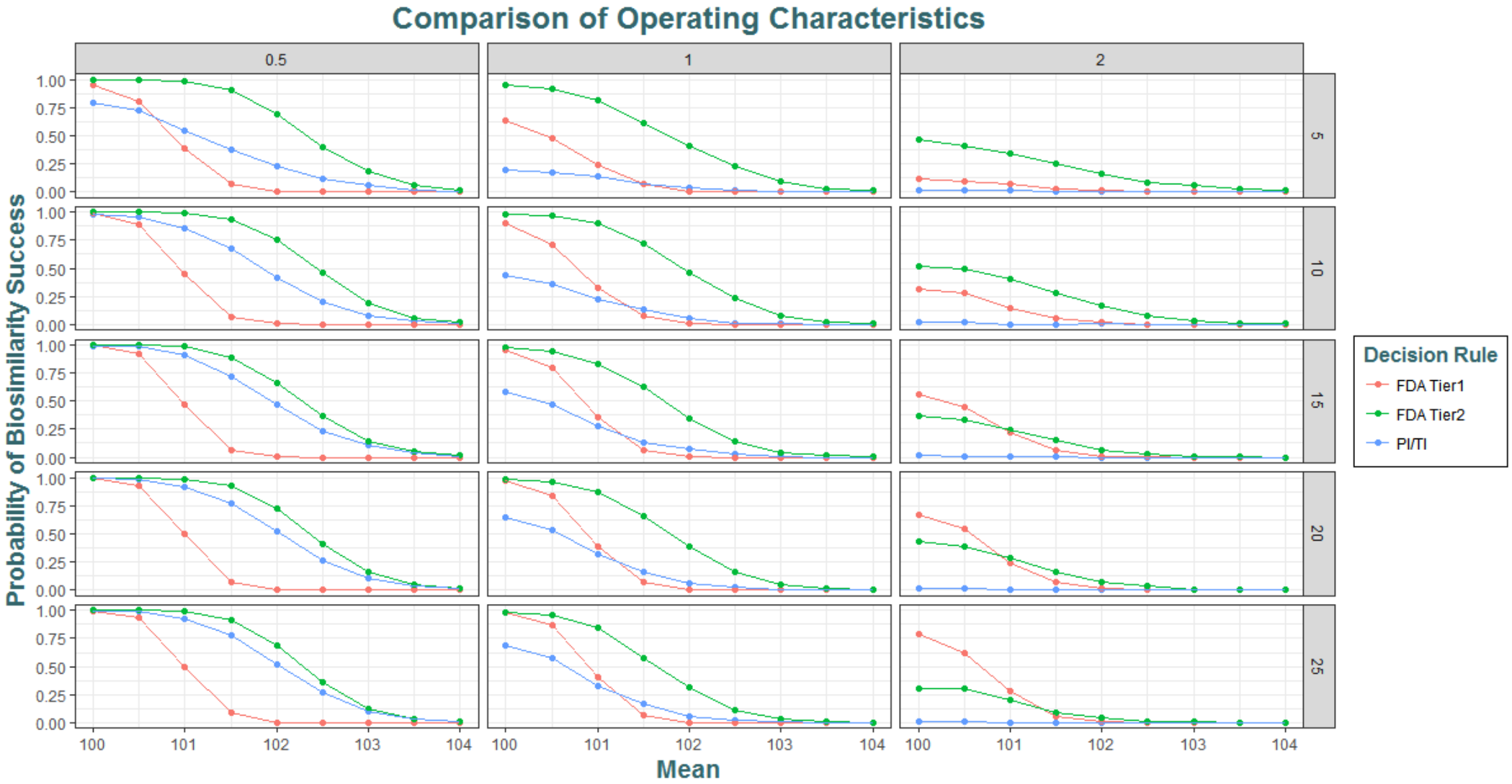

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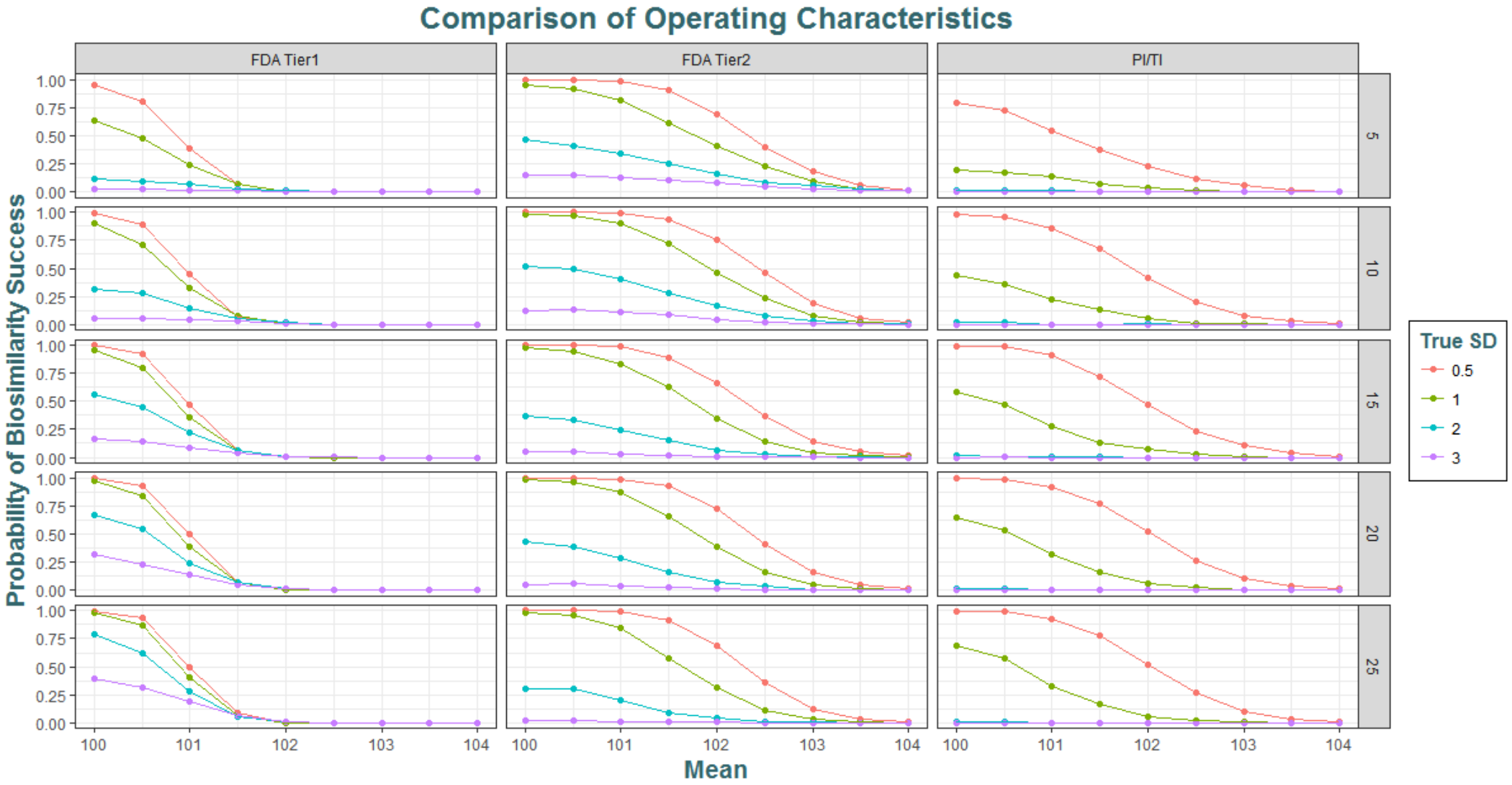

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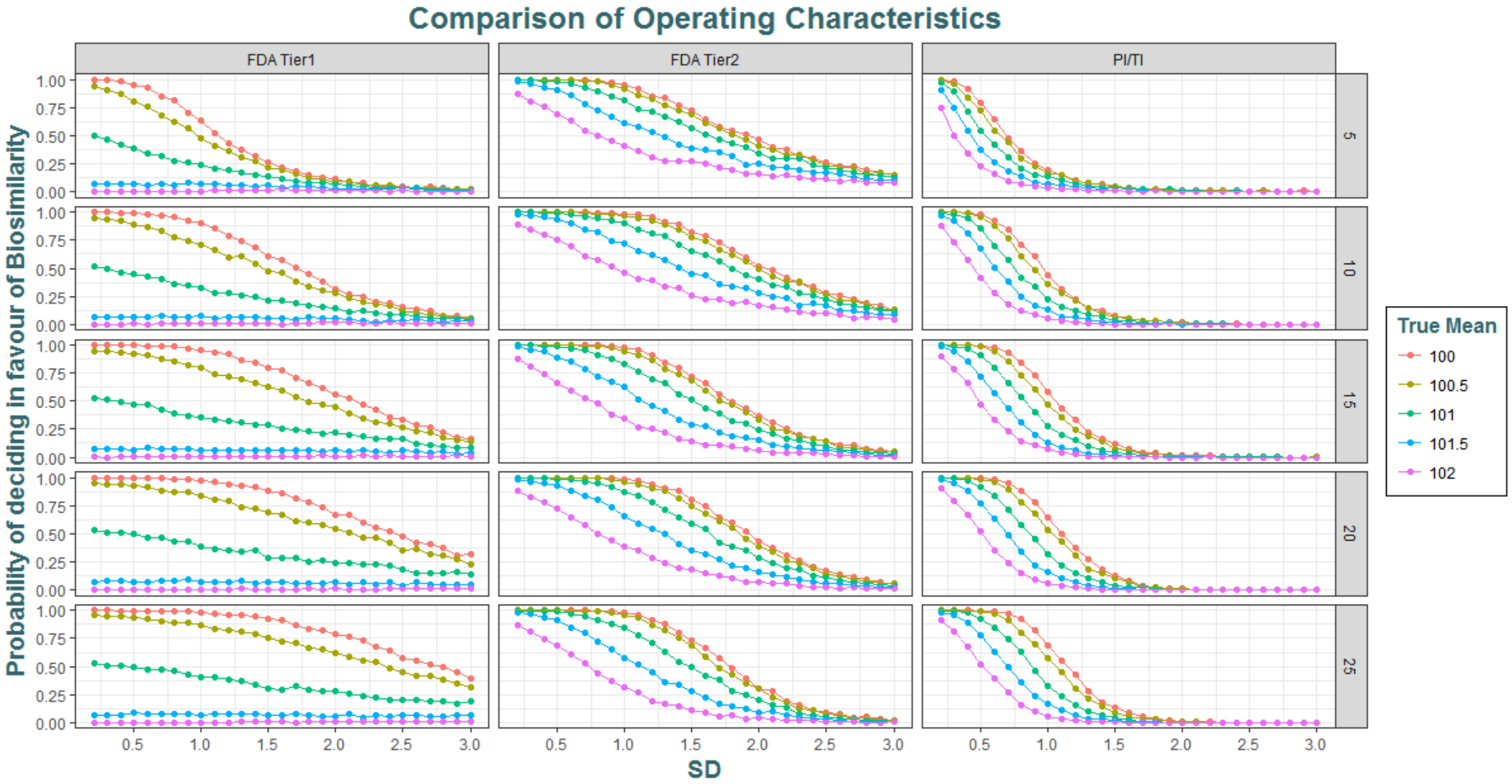

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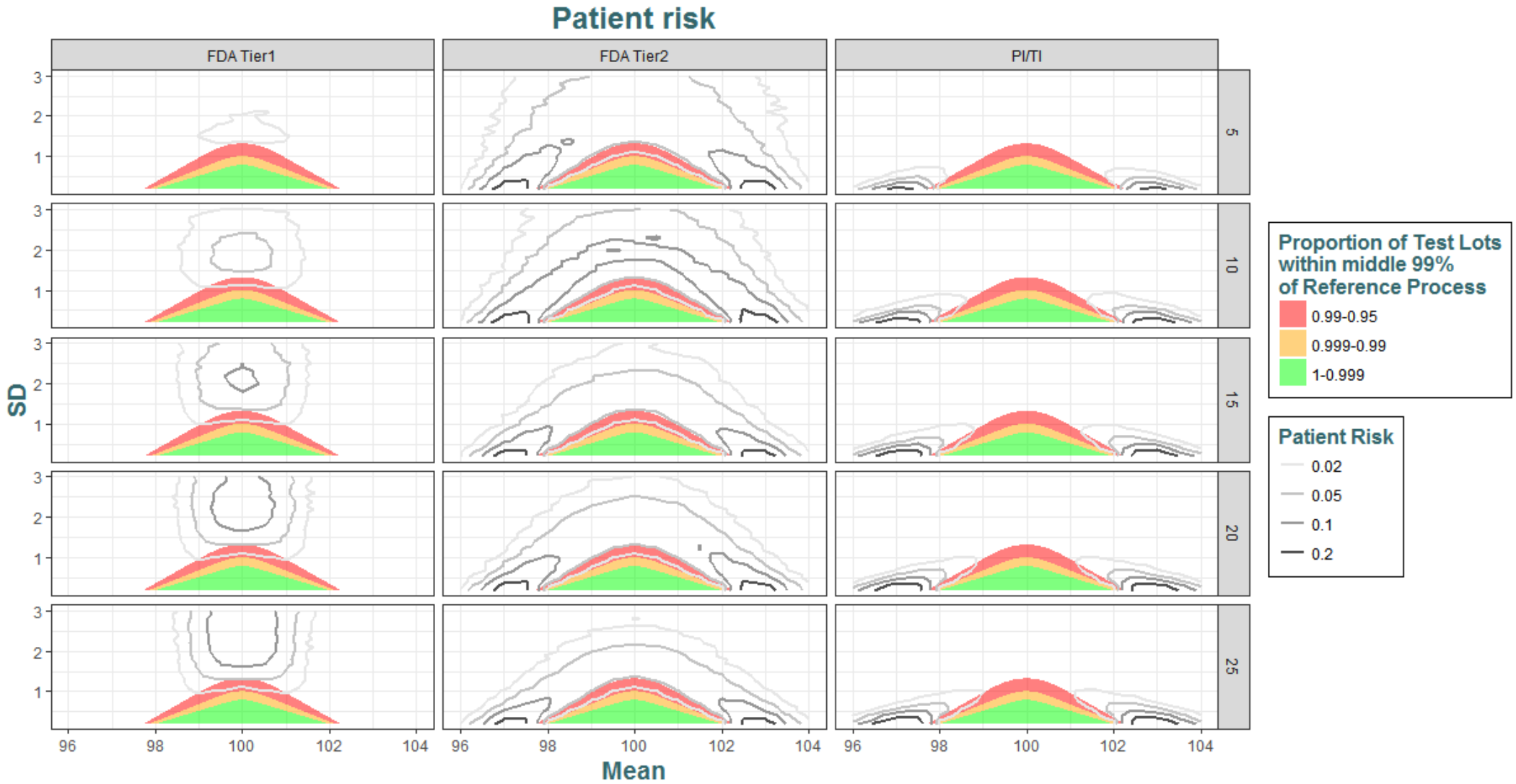

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