Innovative Bayesian Designs in Clinical Trials

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OUTLINE

- **Background; Bayesian design.**
- **Examples:**
  - **1. Early stopping.**
  - **2. Allocate treatments to maximize benefit to patients in & out of trial.**
  - **3&4. Two variations on a theme: seamless phases II and III, sequential sampling, surrogate endpoints.**
    - **Drug for NSCLC.**
    - **Drug for stroke.**

BACKGROUND

- Bayesian approach
  - Fully Bayesian
  - Partially Bayesian
  - Bayes as a frequentist tool
- Bayes and modeling
- Bayes and smoothing
- Hierarchical modeling
- Using historical data
- Predictive probabilities
- Decision making
- Adaptive (efficient) designs

Example 1
MDACC trial in stage III breast cancer; HDCT vs SDCT

- **Based on continual (or regular) monitoring of results.**
- **Maximal sample size: 94 (=47+47)**
  - **1α = 0.05**
  - **Power 80% for pCR of 10% ↑ 30%**

Goals

- **Treat patients better.**
- **Learn efficiently, but**
- **Save patient resources.**
- **Continue to explore only if likely to show benefit.**

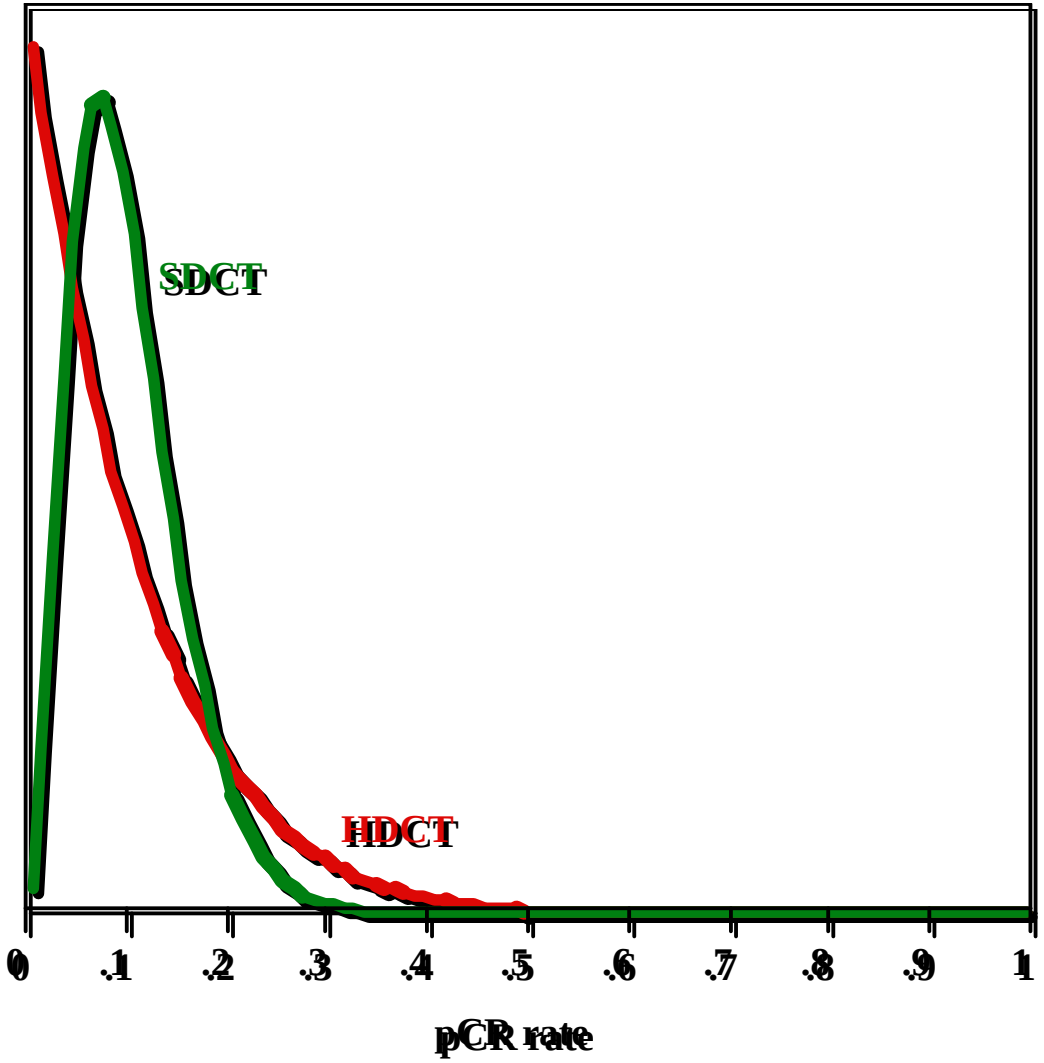
Early stopping

- **Monitoring based on Bayesian predictive probabilities.**
  - **If HDCT is doing sufficiently poorly then stop.**
  - **If HDCT is doing sufficiently well then stop.**
- **Monitor as often as possible.**

Stop before n = 94 for

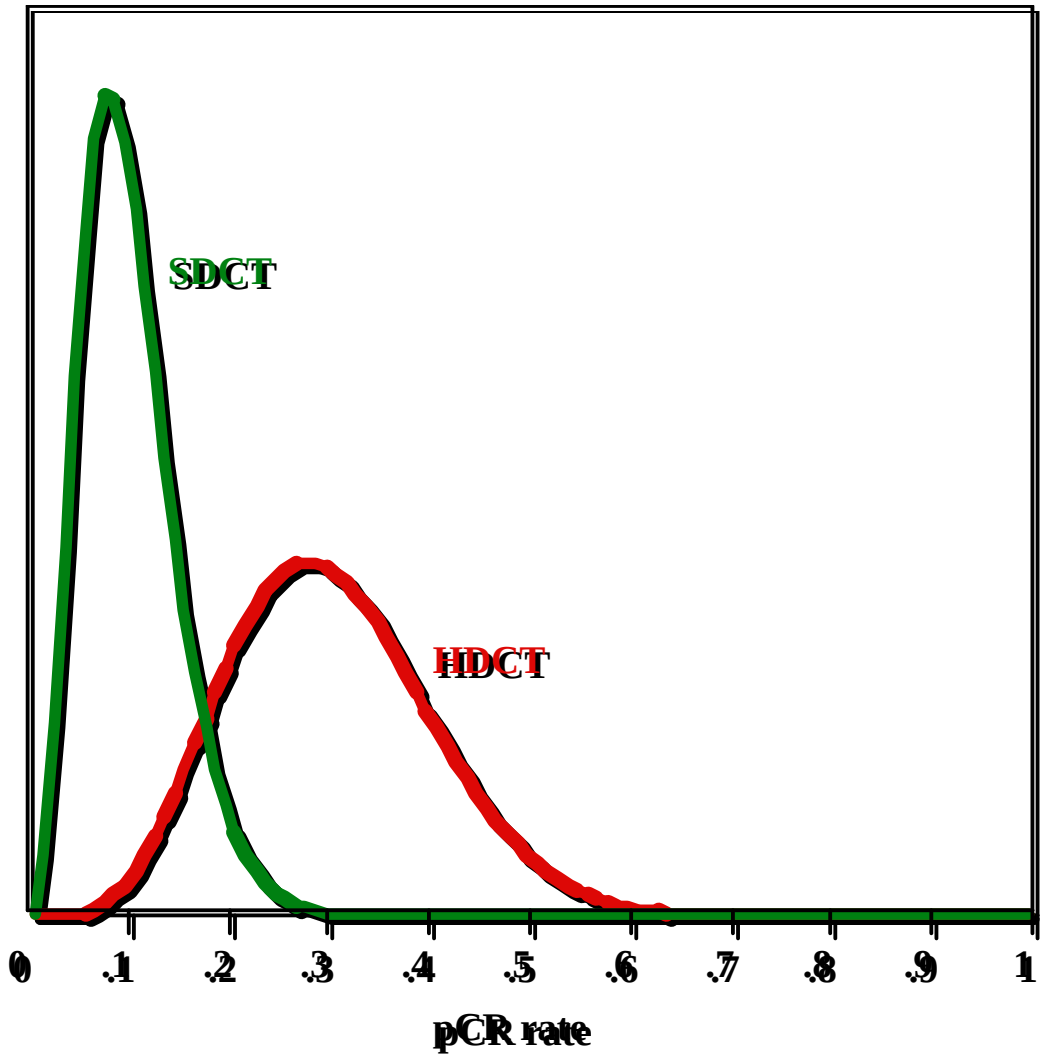
- **Superiority:**
  P(HDCT stat sig|data) > 95%
- **Futility:**
  P(No stat sig|data) > 99%

Prior density for SDCT: beta(3,27)
Prior density for HDCT: beta(1,9)



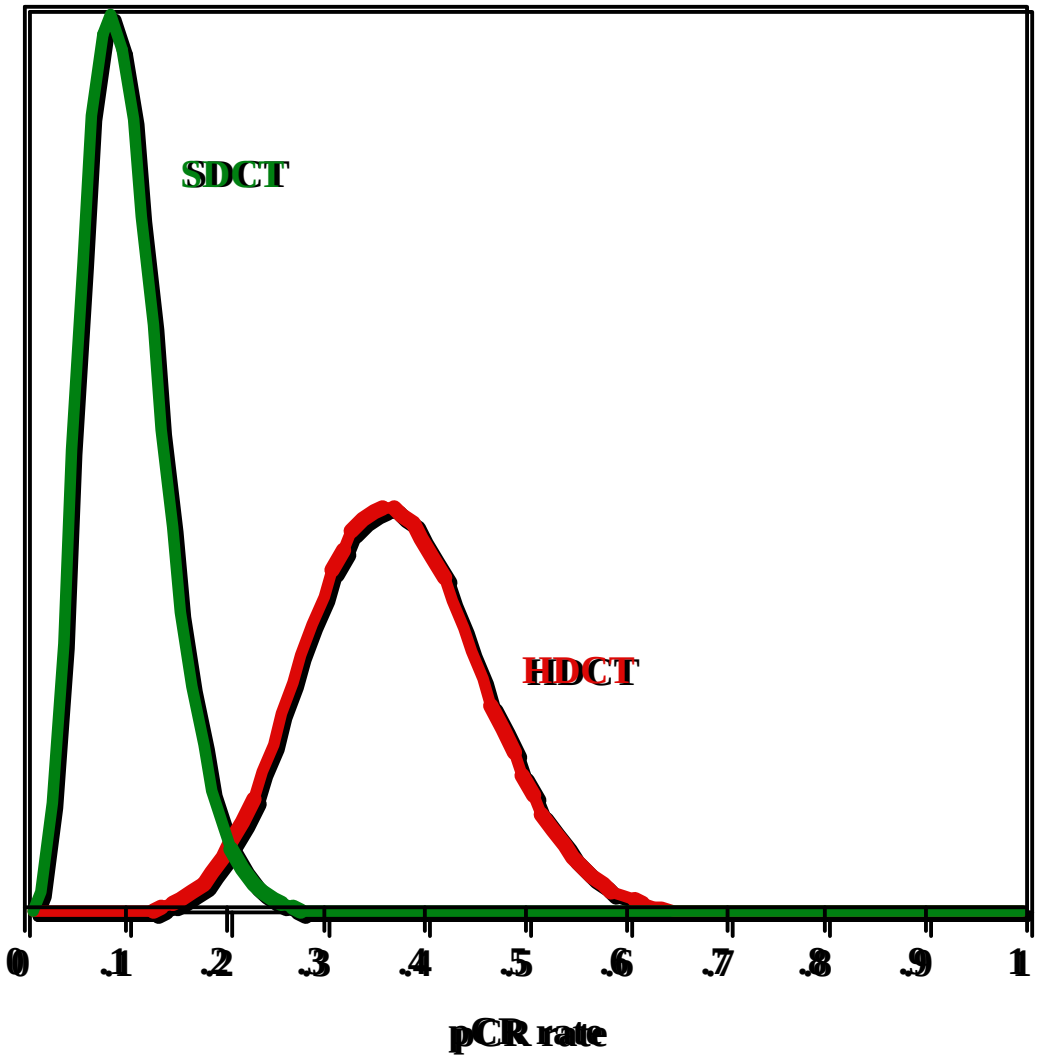
Updated densities:

1 of 10 on SDCT, 5 of 10 on HDCT



Updated densities:

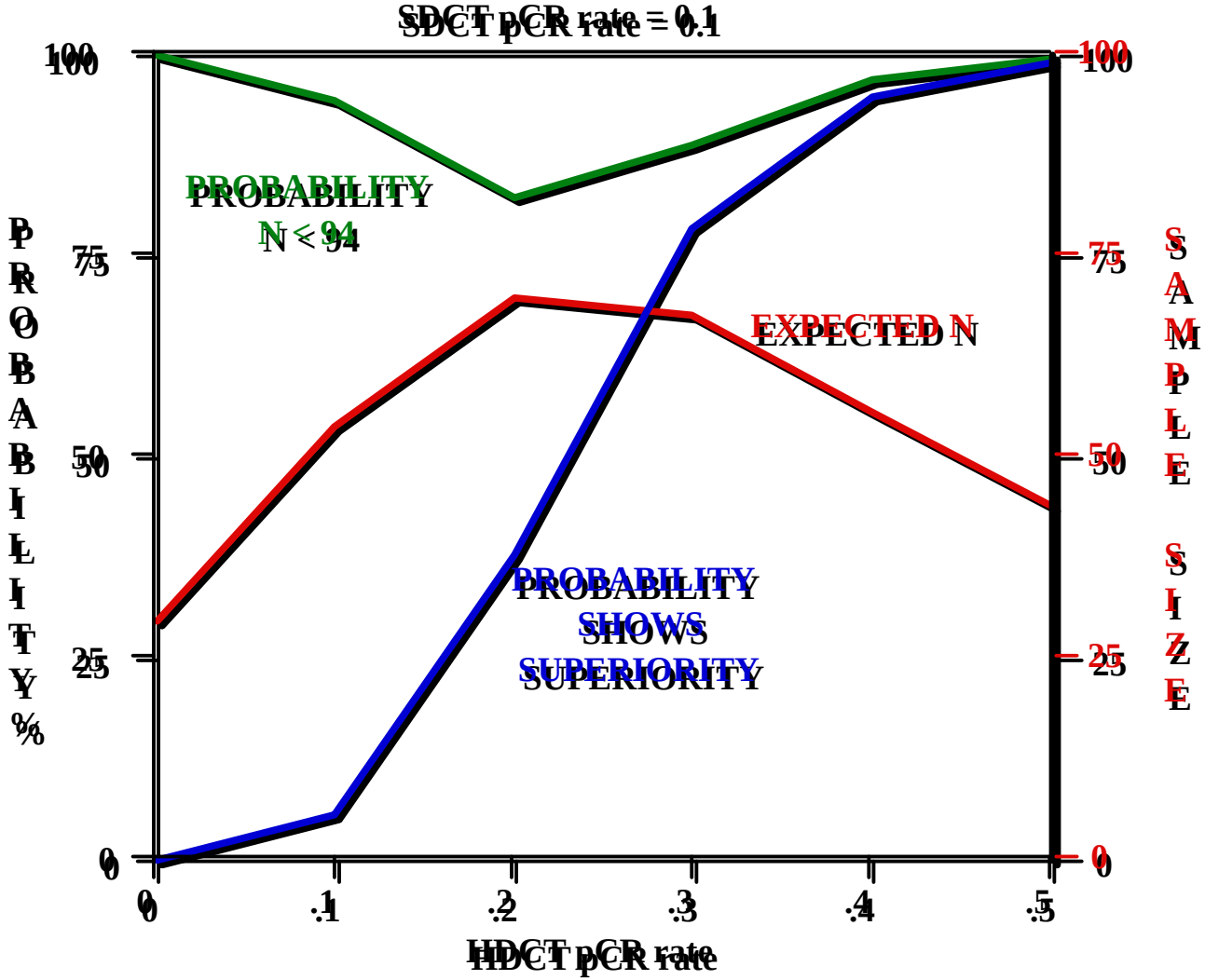
2 of 20 on SDCT, 10 of 20 on HDCT



Operating characteristics

- **Probability n < 94.**
- **Expected sample size.**
- **Probability show superiority.**
- **[Above depend on pCR rates for two arms.]**

Operating characteristics, assuming SDCT rate is 10%



Example 2
Adaptive allocation of therapies

- **Design for phase II trial:**
  Many drugs, & placebo
- **Goals:**
  - **Treat effectively**
  - **Learn quickly**

Adaptive allocation —Application to cancer

- **Endpoint: Tumor response (success = CR or PR). [Or, survival—gradually.]**
- **Weigh randomization toward better performing drugs.**
- **Start w/drug 1 & placebo; add other drugs as become available.**

Adaptive allocation (cont'd)

Typical point in future:

Placebo:	**10 succ, 22 fail**
Drug 1:	**3 succ, 23 fail**
Drug 2:	**8 succ, 18 fail**
Drug 3:	**20 succ, 11 fail**
Drug 4:	**4 succ, 7 fail**
Drug 5:	**7 succ, 2 fail**

[Plus some data in bank]

Example Bayesian measures:

- **Probability drug k is better than placebo, given current evidence (MDACC leuk study).**
- **Probability drug k is best of all in trial.**
- **Number of responses in patient horizon.**

Typical point in future:

Placebo:	10 succ, 22 fail
Drug 1:	3 succ, 23 fail
Drug 2:	8 succ, 18 fail
Drug 3:	20 succ, 11 fail
Drug 4:	4 succ, 7 fail
Drug 5:	7 succ, 2 fail

Possible assignment:

Placebo:	10%
Drug 1:	→ dump
Drug 2:	15%
Drug 3:	→ phase III
Drug 4:	15%
Drug 5:	60%

Typical point in future:

Placebo:	**10 succ, 22 fail**
Drug 1:	**3 succ, 23 fail**
Drug 2:	**8 succ, 18 fail**
Drug 3:	**20 succ, 11 fail**
Drug 4:	**4 succ, 7 fail**
Drug 5:	**7 succ, 2 fail**

What happened?

- **Drug 1 dropped.**
- **Drug 3 moved through quickly.**
- **Drug 5 is moving through quickly.**

Consequences

- **Recall goals:**
  - **(1) Treat effectively**
  - **(2) Learn quickly**
- **Attractive to patients, in and out of the trial.**

Example 3
NSCLC and local control

- **Rates of local control in NSCLC (surrogate endpoint for survival?)**
- **Local control → prolong survival? (depending on treatment)**
- **Drug → prolong survival?**
- **Modeling**
  - **Exponential**
  - **Weibull**
- **Joint with P. Thall and L. Inoue**

Conventional design (with placebo comparison)

Seamless phases

- **Phase II: One or two centers; 10-20 pts/mo. If predictive probabilities look good then expand to**
- **Phase III: Many centers; 30+ pts/mo. (Takes time to gear up, but initial centers keep rolling.)**

- **Single trial: survival data from both phases combined in final analysis.**

Early stopping

- **Use predictive probs of stat. signif.**
- **Frequent analyses (total of 18) using predictive probabilities:**
  - **To switch to Phase III**
  - **To stop accrual**
    - **For futility**
    - **For efficacy**
  - **To submit to FDA (during follow-up)**

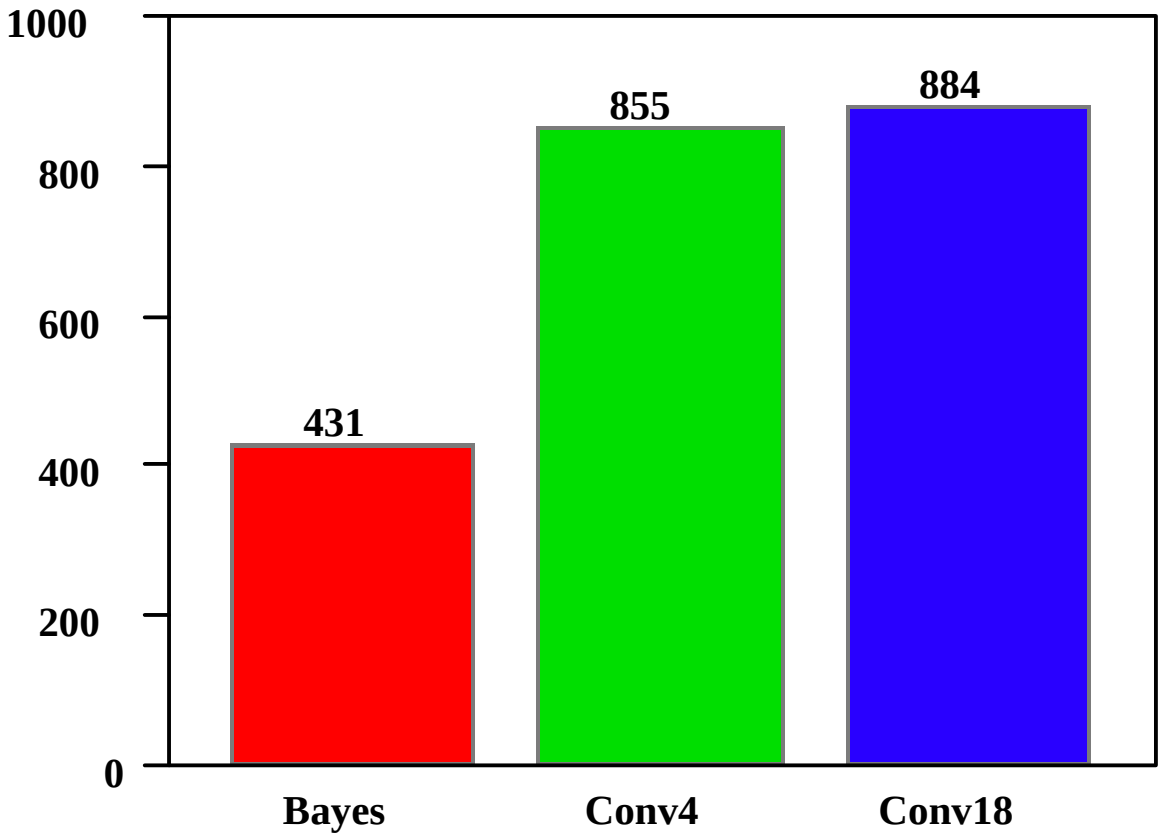
- **Maximal sample size: 900 (phase III of a conventional design)**

  α = 0.05, power = 80% (at 25% improvement)

- **Comparison designs: Conv4 & Conv18, max N = 900.**

- **(Sample size in following doesn't count phase II pts in conventional designs.)**

Expected N under H_0



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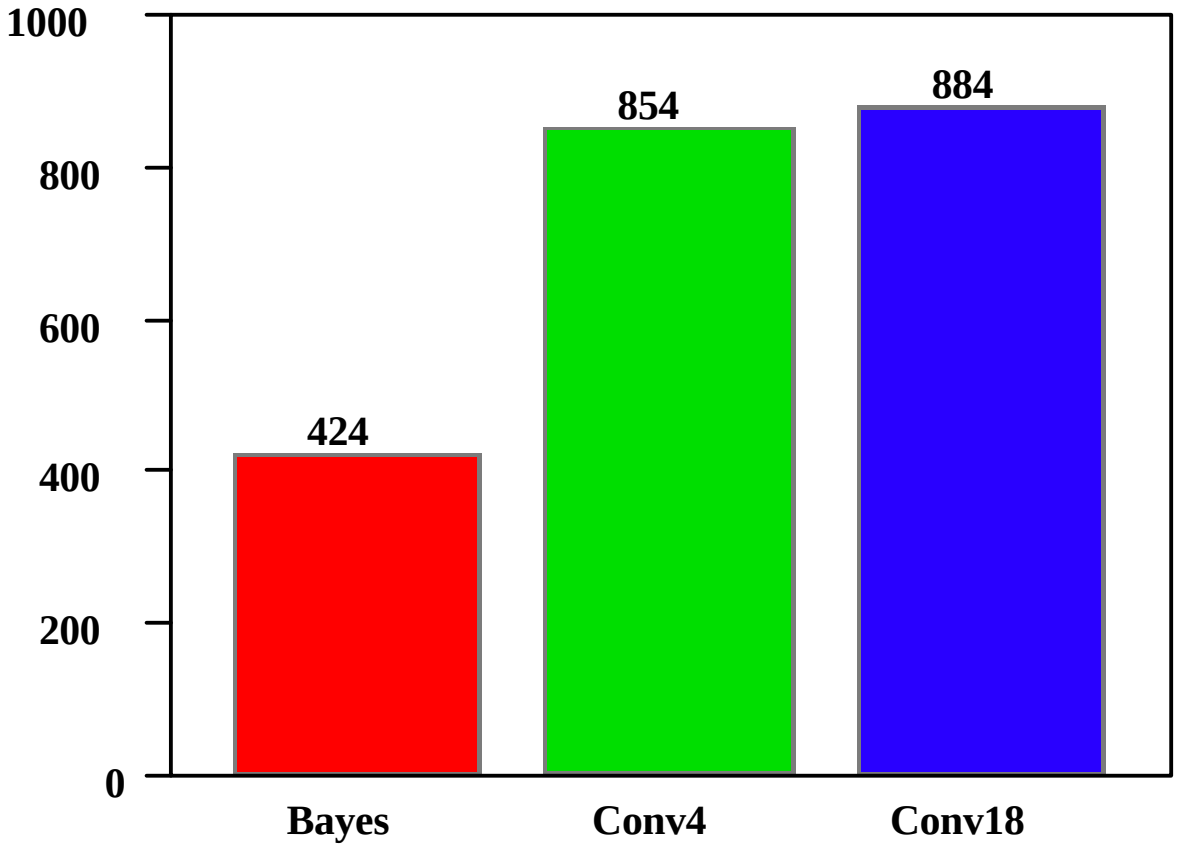

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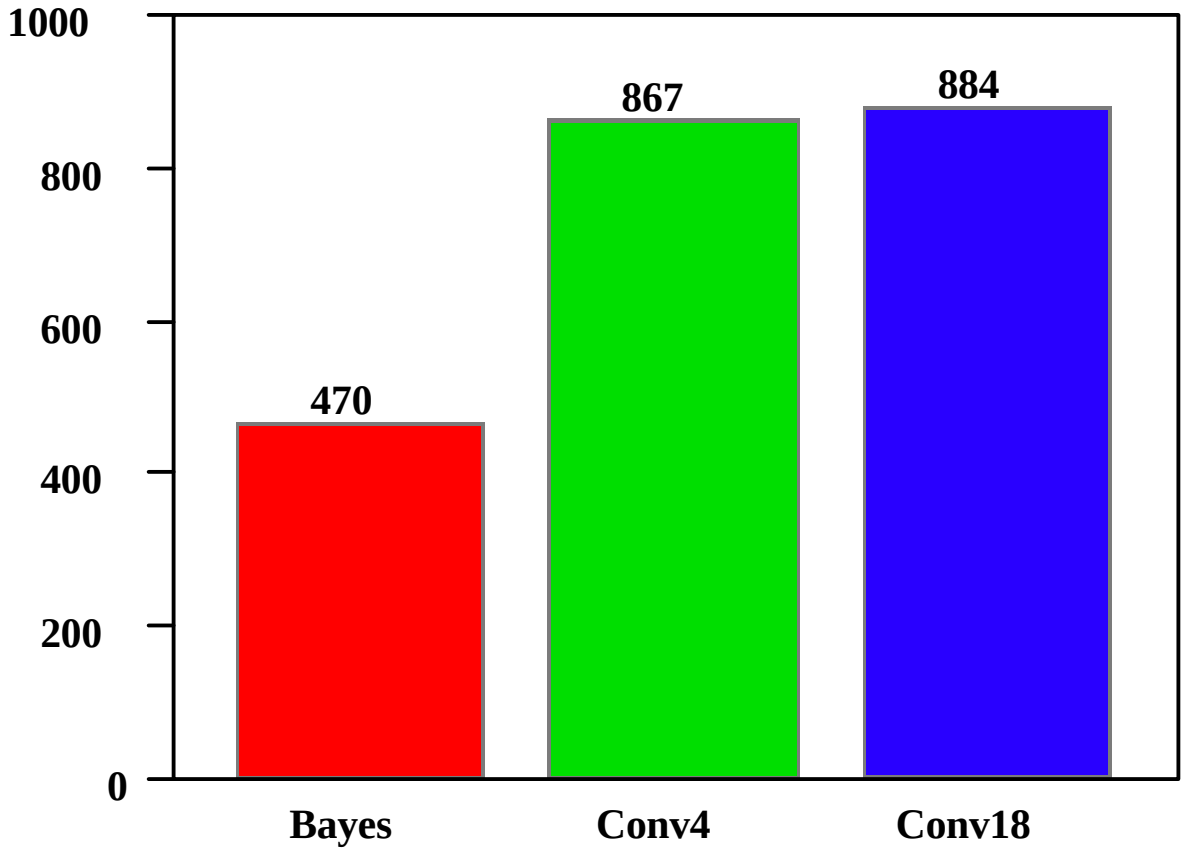
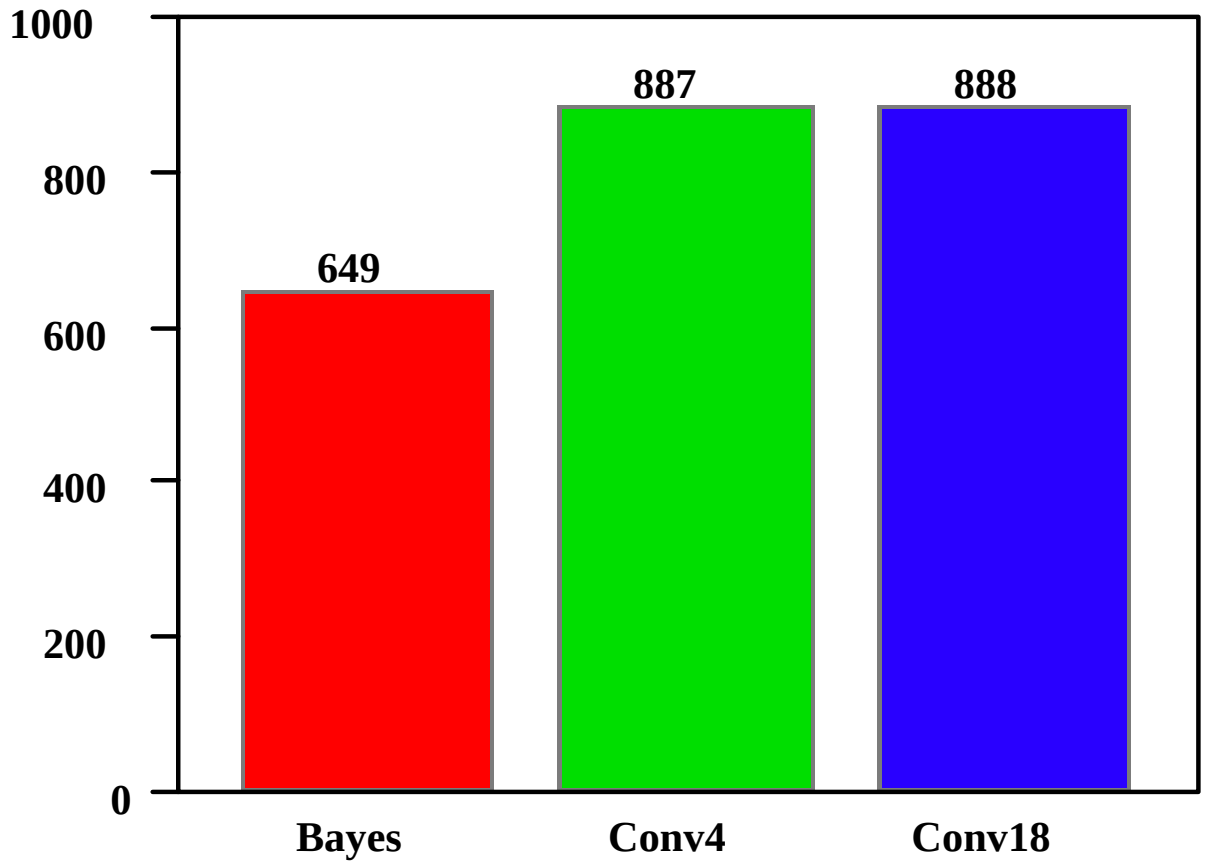
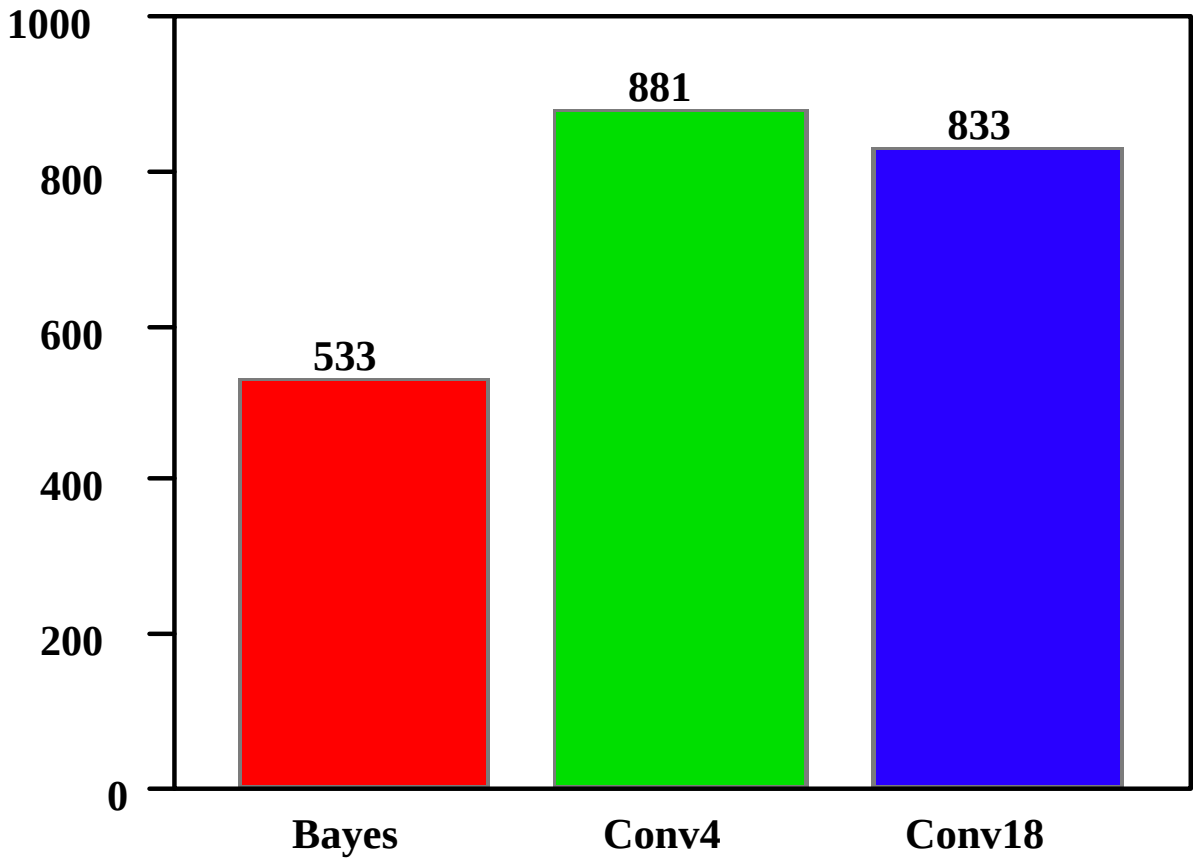


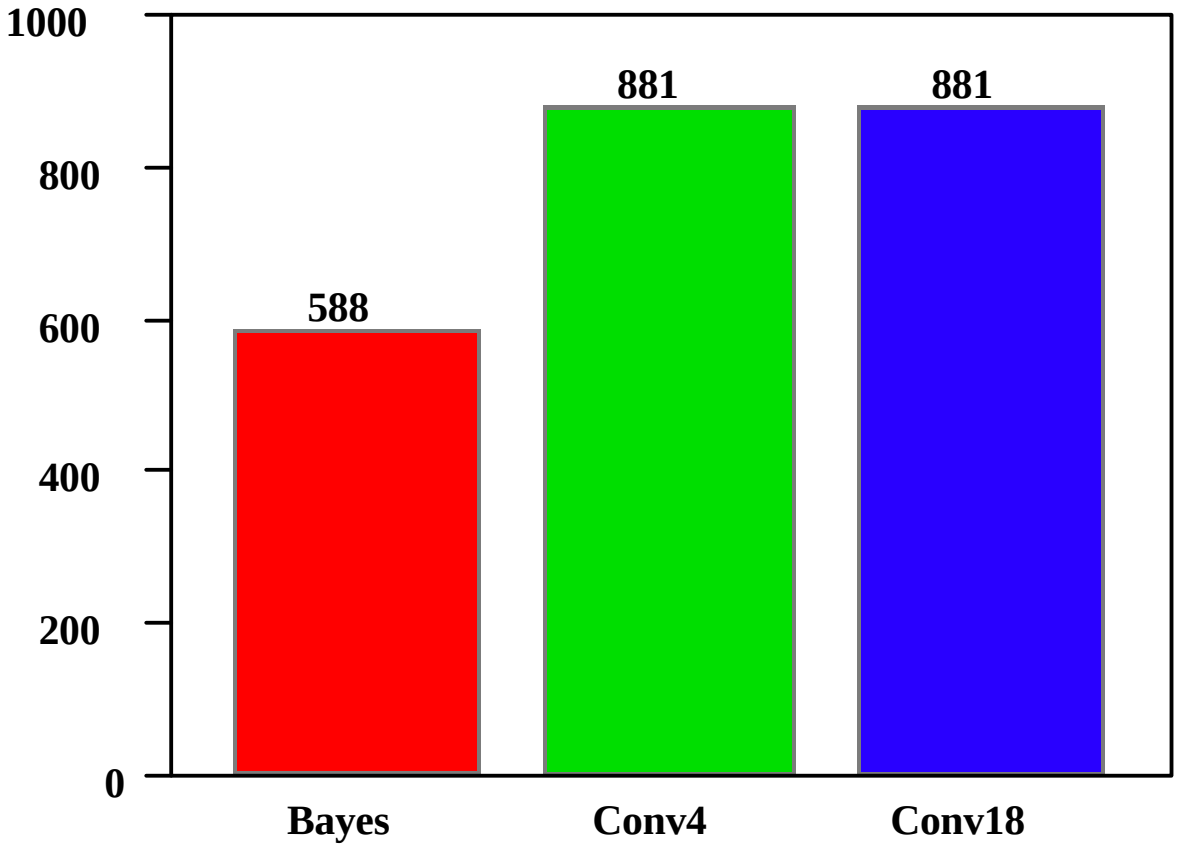
Expected N under H_1



Expected N under H_1*



*Expected N under H_1***



Other characteristics

- **Duration of drug development is greatly shortened under Bayesian design:**
  - **Sample size.**
  - **No hiatus for developing phase III.**
  - **Use all patients to assess both endpoints and relationship between endpoints.**

Possibility of large N

- **Seldom get to N near 900**
- **When you do, it's necessary!**
- **This possibility gives Bayesian design its edge.**
- **[Other reason for edge is modeling local control.]**

Example 4
Adaptive dose-response

- **Adaptive doses in Phase II setting: learn efficiently and rapidly about dose-response relationship.**
- **Joint with P. Mueller, A. Grieve, M. Smith, T. Parke, R. Blazek, N. Pritchard, M. Krams.**

Dose-response trial

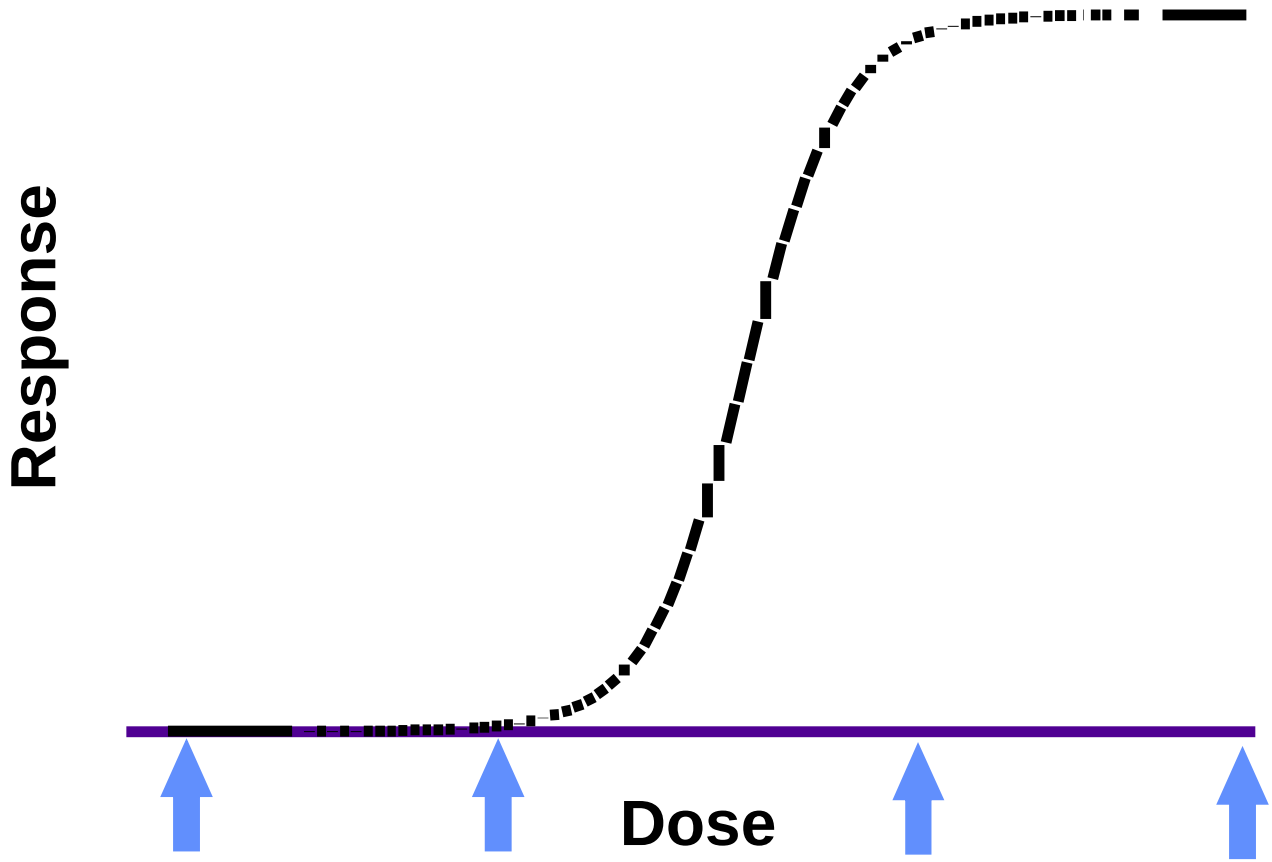
- **Learn efficiently and rapidly about dose-response; if + go to Phase III.**
- **Assign dose to maximize info about dose-response parameters given current info. (Allow for data bank.)**
- **Use predictive probabilities, based on early or surrogate endpoints.**
- **Doses in continuum, or preset grid.**

Dose-response trial (cont'd)

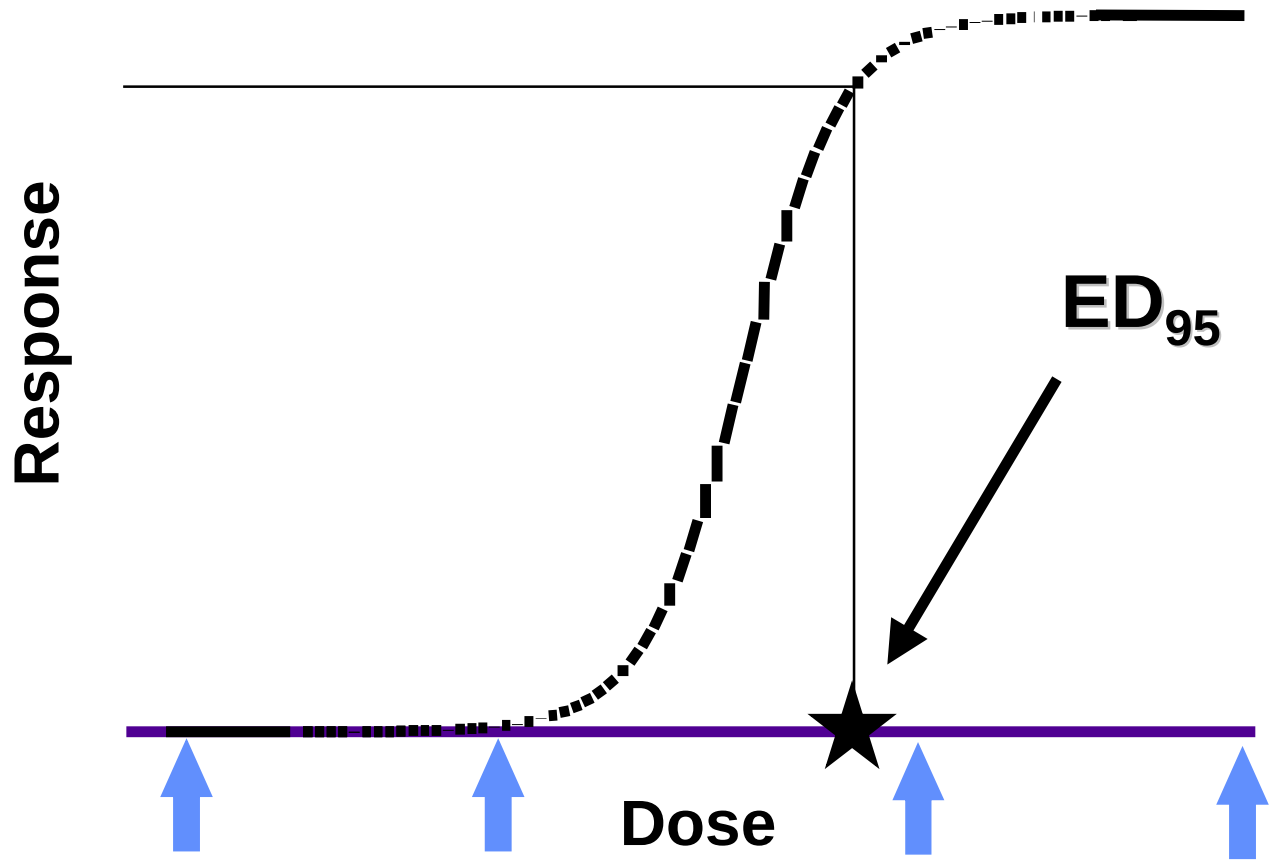
- **Learn about variance on-line.**
- **Halt dose-ranging when know the dose sufficiently well.**
- **Seamless switch from dose-ranging to confirmatory trial—2 trials in 1!**
- **Confirmatory trial dose & sample size chosen using decision analysis.**

Standard Parallel Group Design

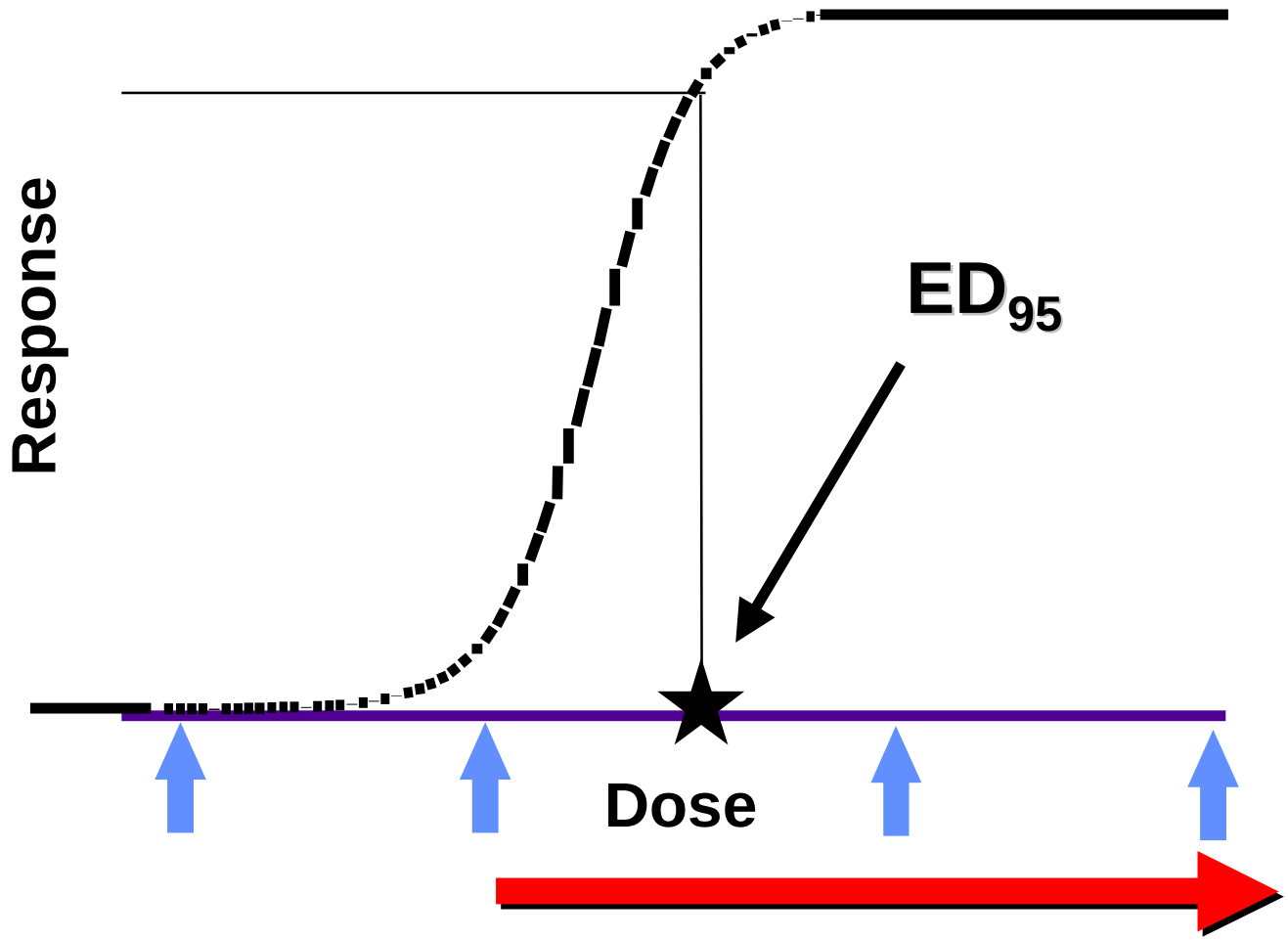
Observe responses (with error) at chosen doses



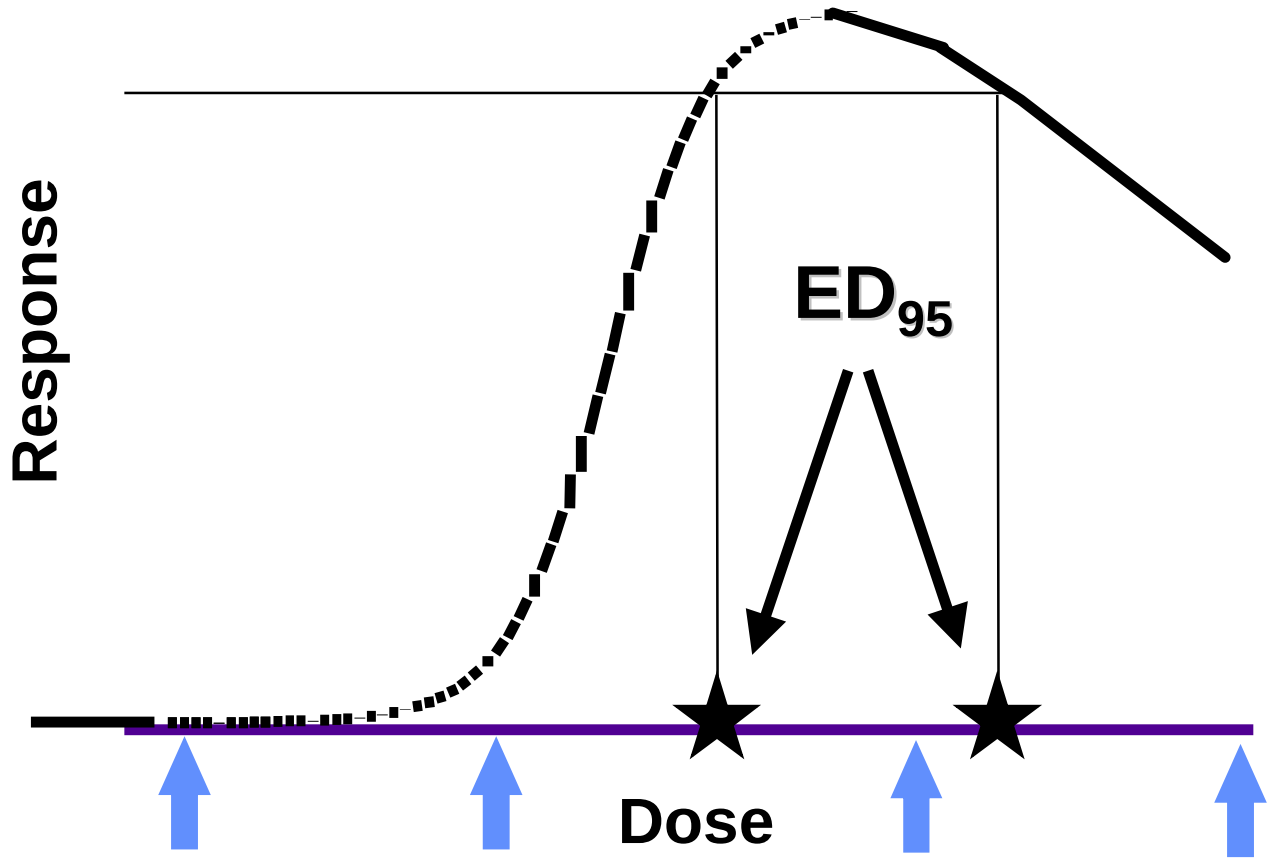
Dose at which 95% max effect



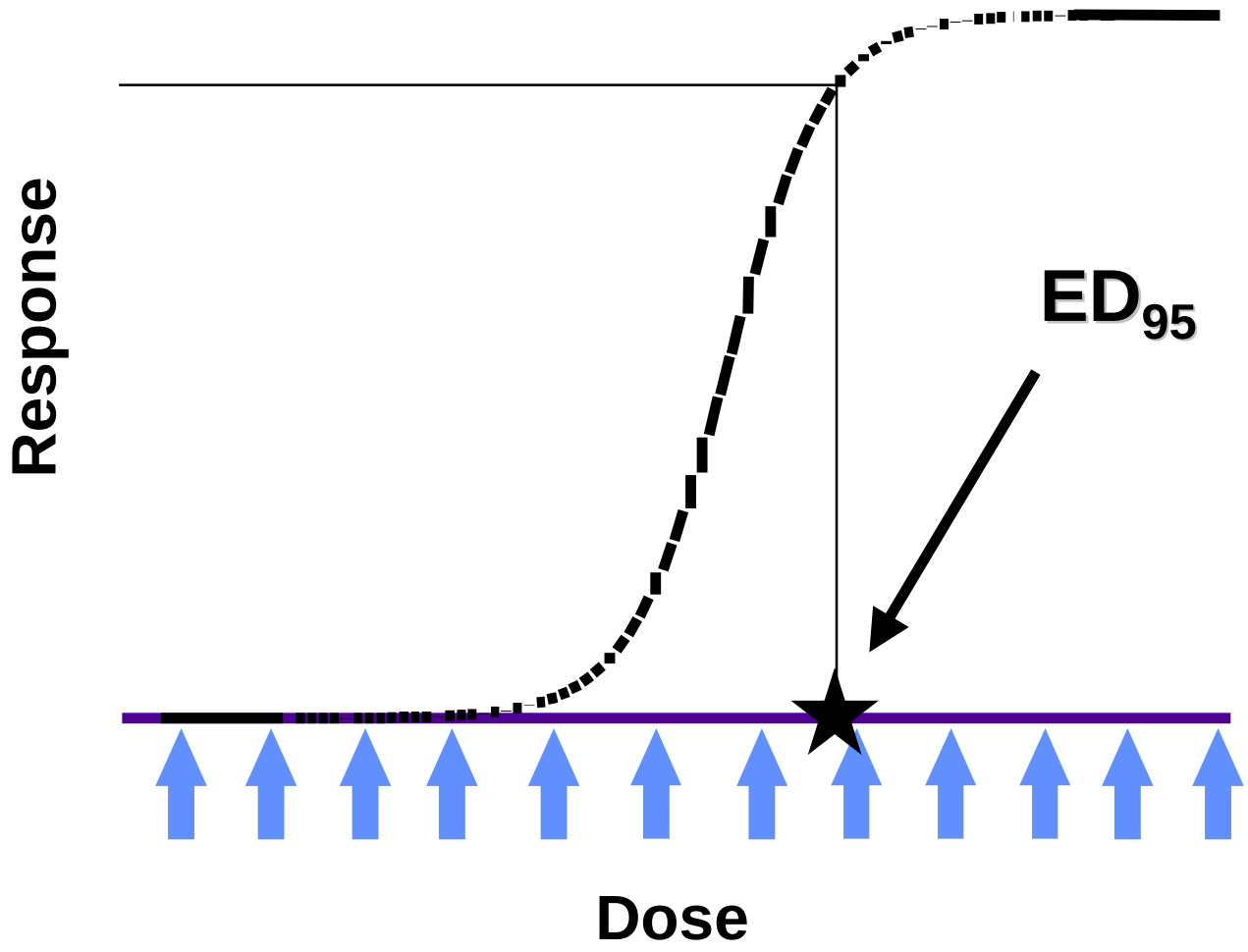
Uncertainty about ED95



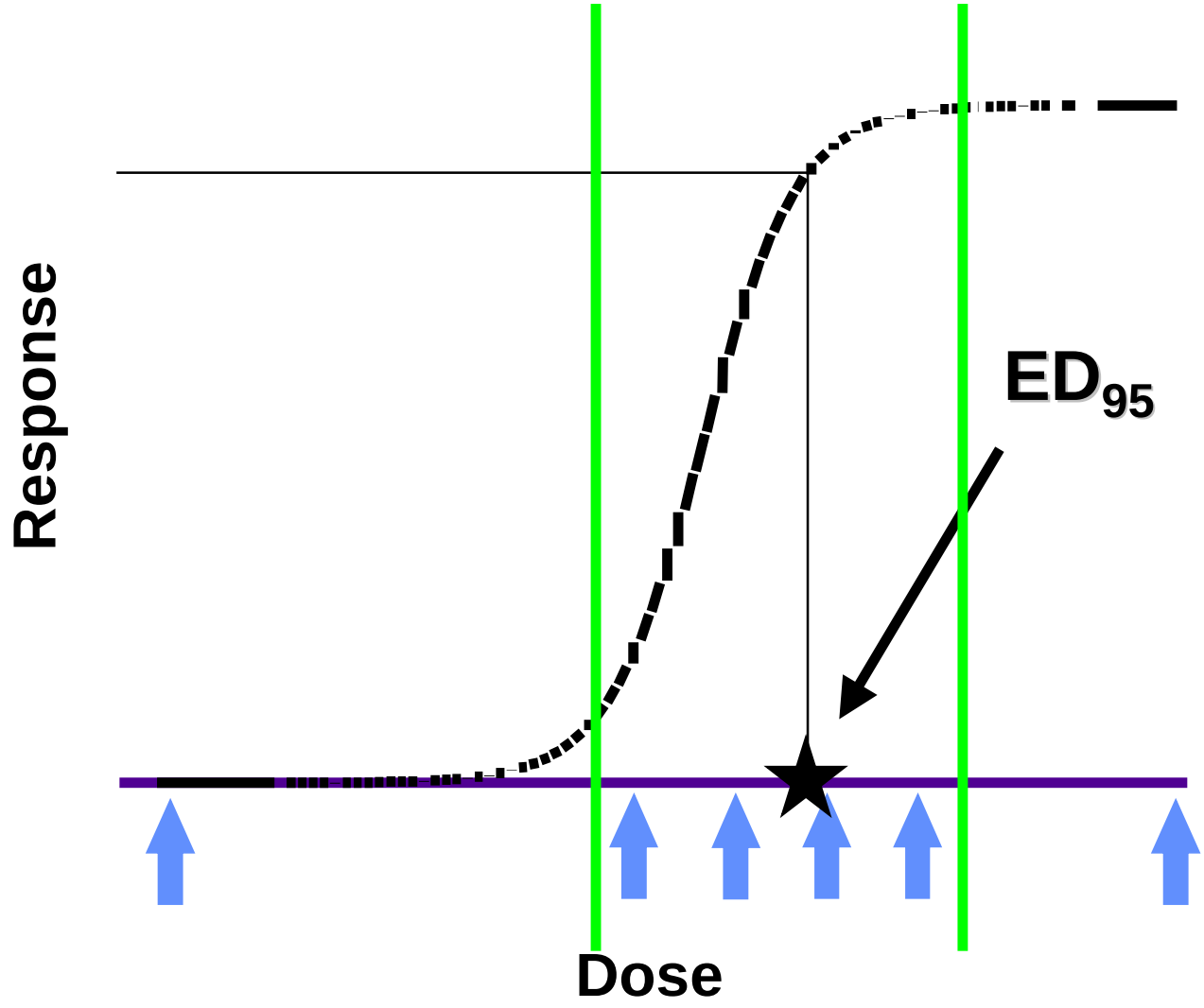
Logically problematic:



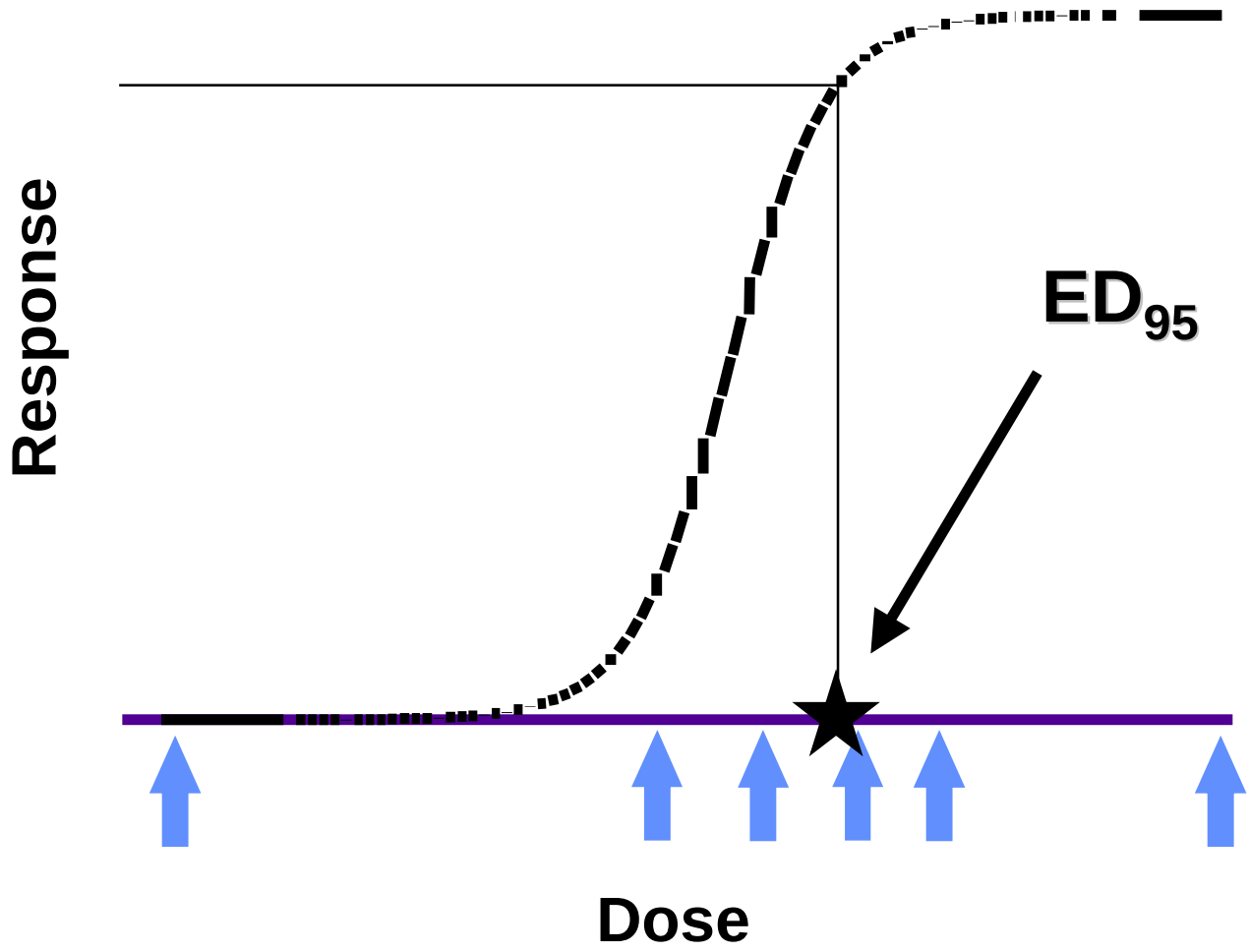
Solution:
Increase number of doses



But, enormous sample size, and . . . wasted doses—always!



Ideal



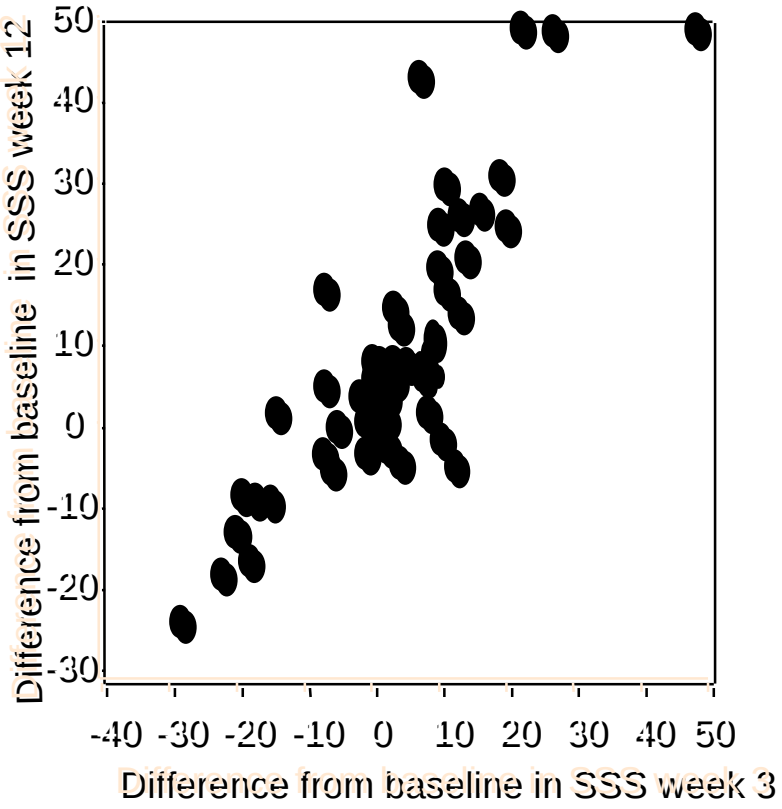
Our adaptive approach

- **Select next dose to maximize information about ED95 & response at ED95, given available evidence.**
- **Stop dose-ranging trial based on**
  - **Decision analysis** +
  - **Statistical significance**
  - **Predictive power**

Our approach (cont'd)

Info accrues gradually about each patient; prediction using longitudinal model.

Longitudinal model based on Copenhagen Stroke Database



Our approach (cont'd)

- **Requires modeling dose-response (we borrow strength from neighboring doses using normal dynamic linear model)**
- **Many doses (logistical issues).**

Possible decisions each day:

- **Stop trial and drop drug's development.**
- **Stop and set up confirmatory trial.**
- **Continue dose-finding trial.**

Choice by decision analysis. (Human safeguard: DSMB.)

Size of confirmatory trial based on info from dose-ranging phase.

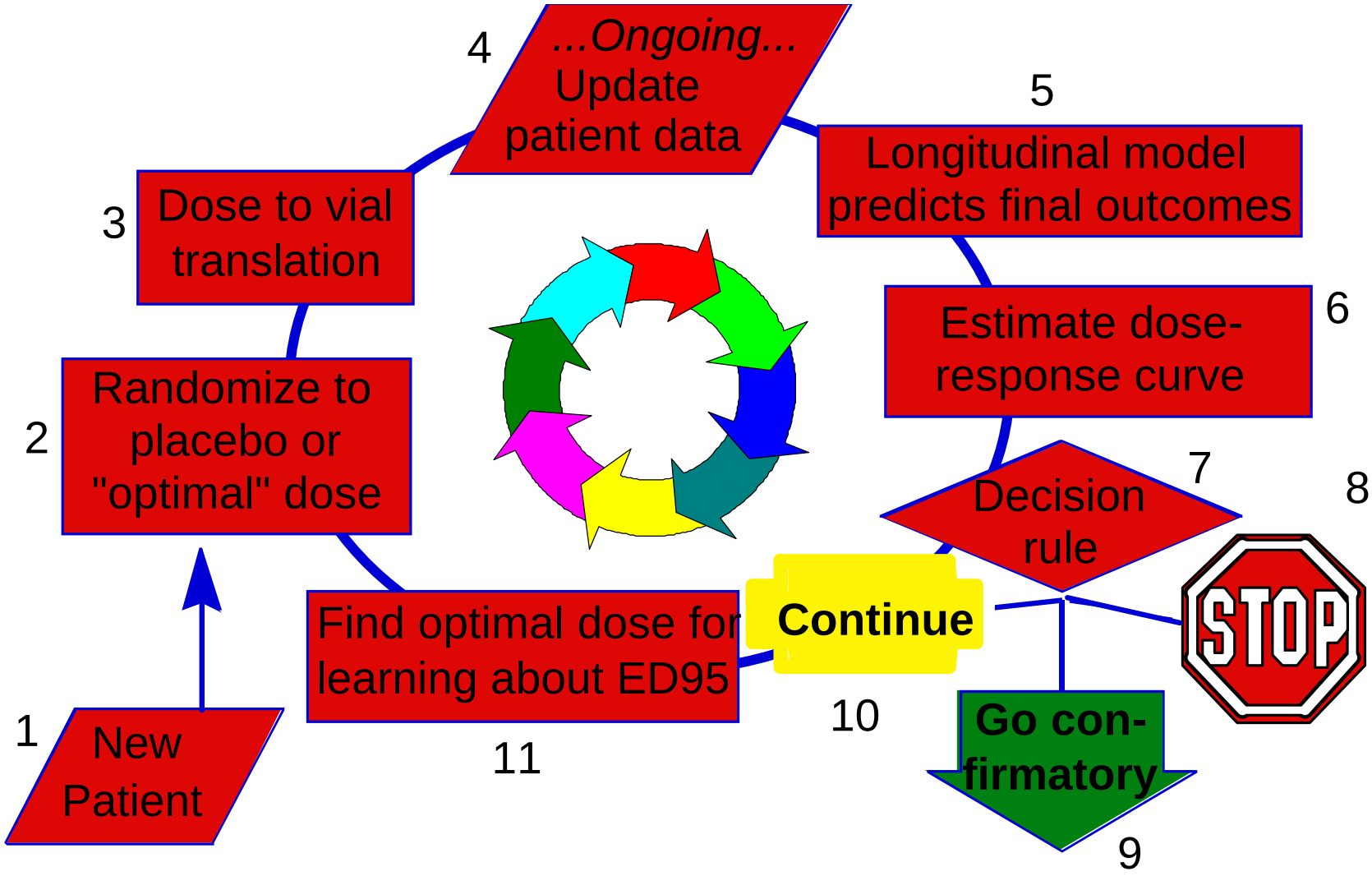
Seamless switch?

- **Two trials in one, with seamless switch from dose-finding to confirmatory comparison (estimated ED95 vs. placebo)—same centers.**
- **Alternative: Two trials.**

Advantages over standard design

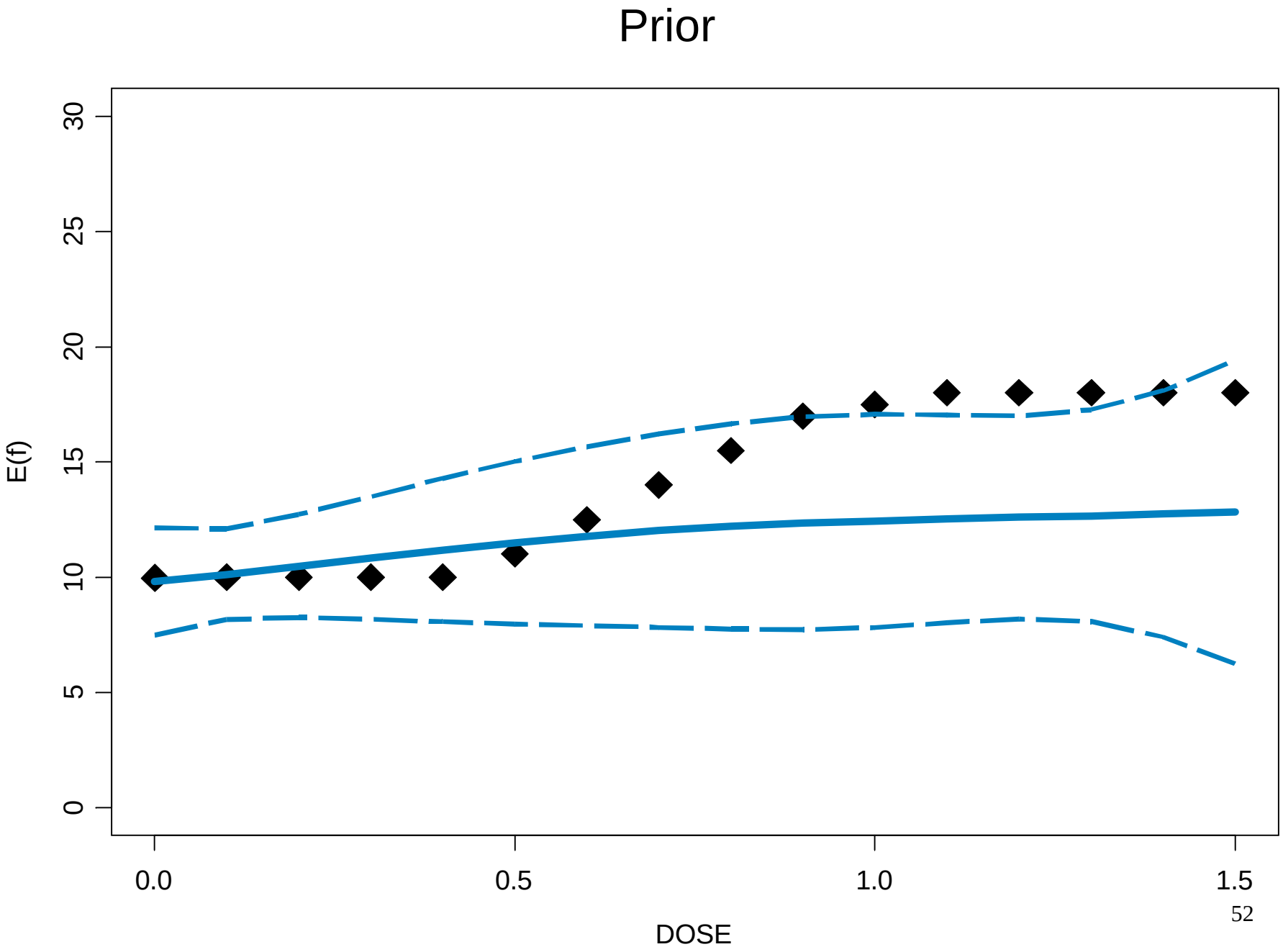
- **Fewer patients (generally); more effective and faster learning.**
- **Better at finding ED95.**
- **Learn about variance on-line.**
- **Tends to treat patients in trial more effectively.**
- **Drops a dud early.**

Design Flow Chart



Simulation

- **Assumes particular dose-response curve**
- **Assumes SD = 12**
- **Shows 25 patients at a time (green circles)**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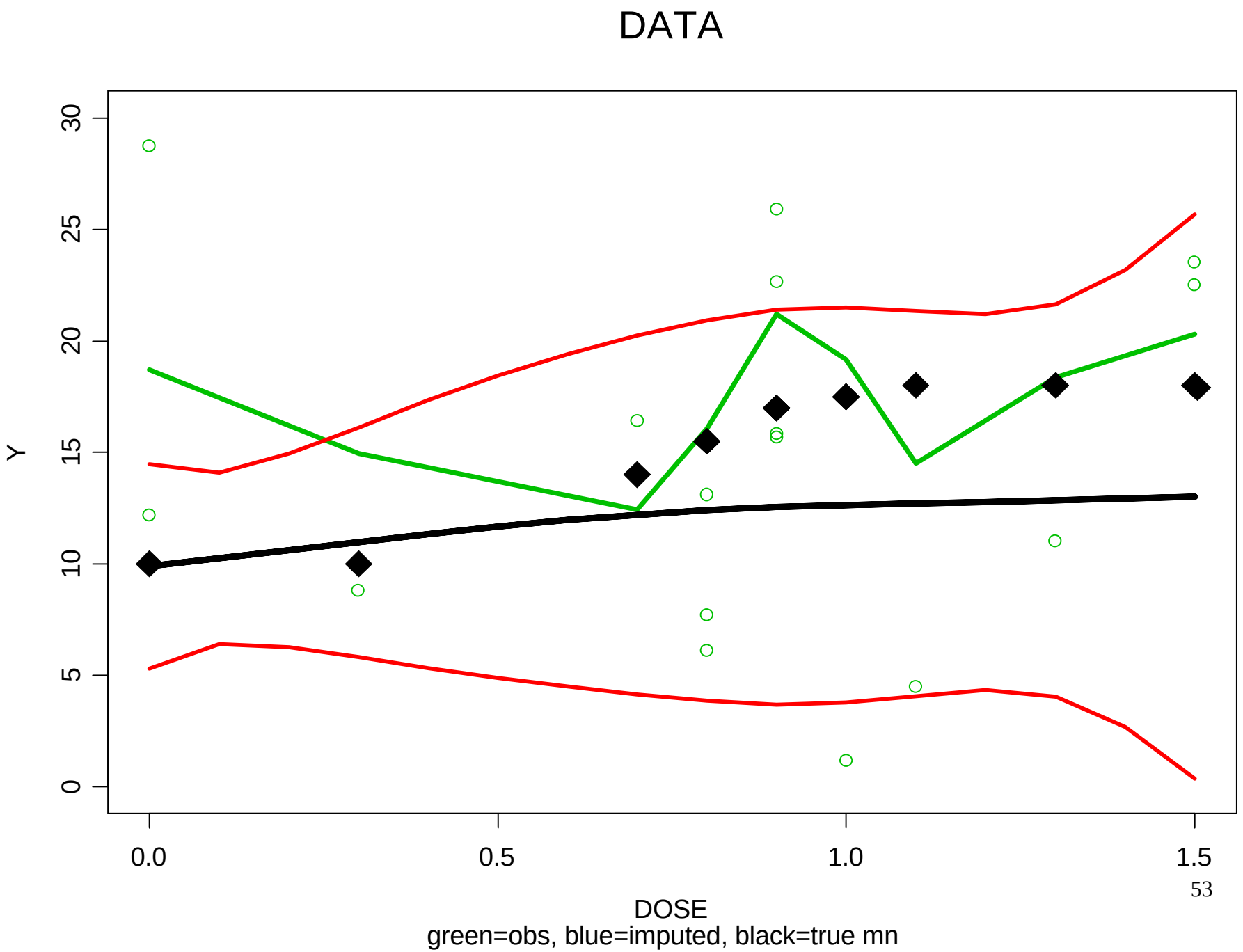
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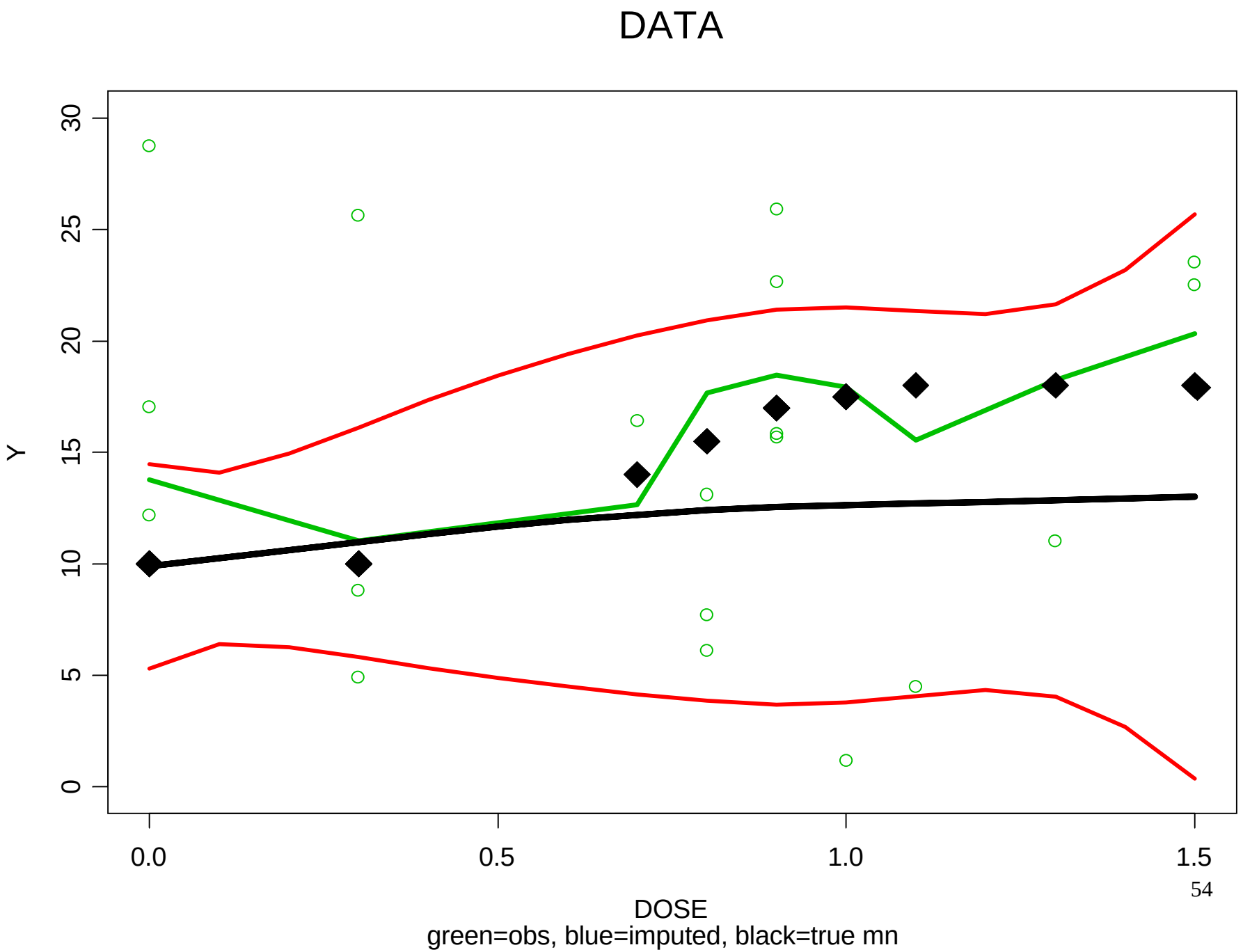
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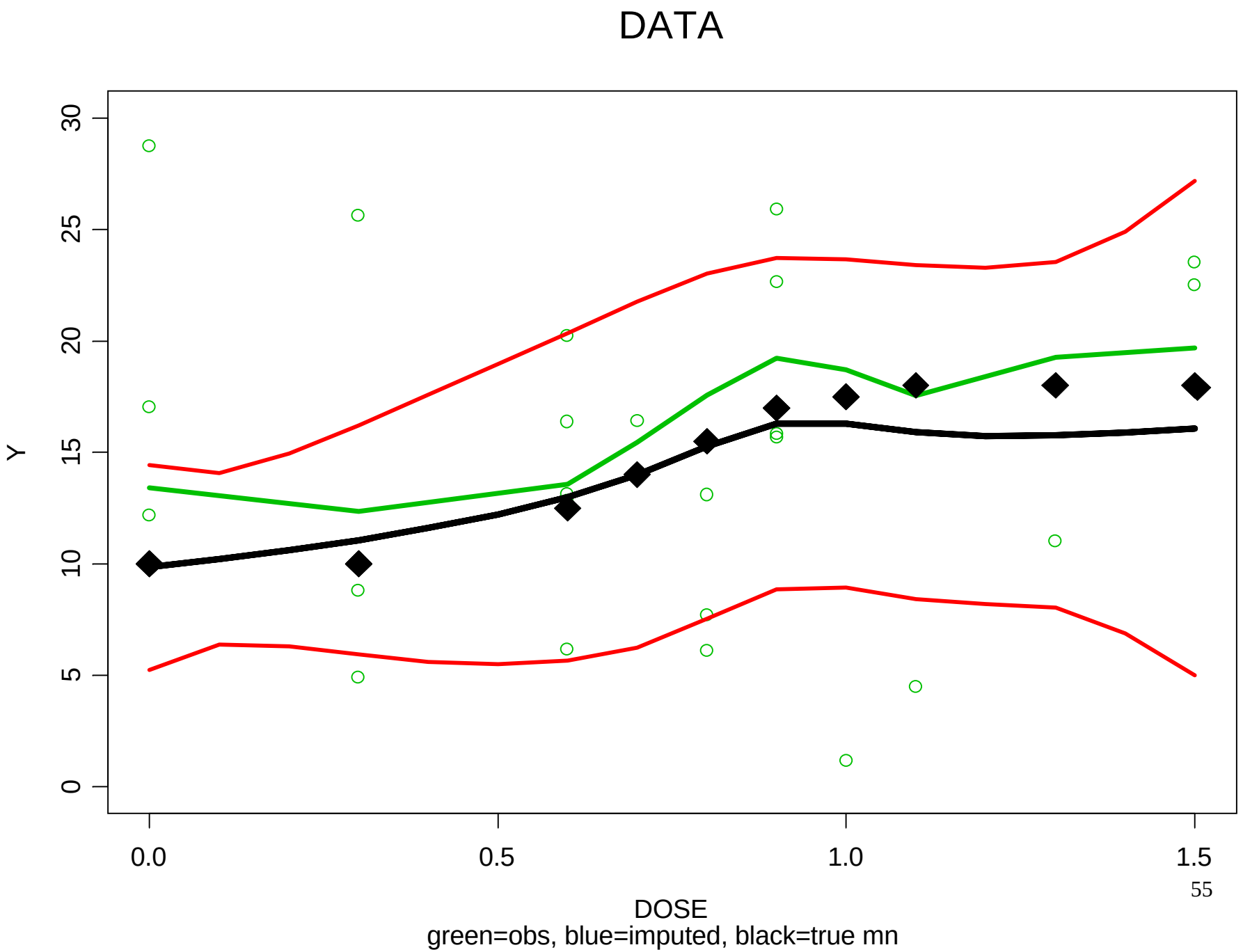
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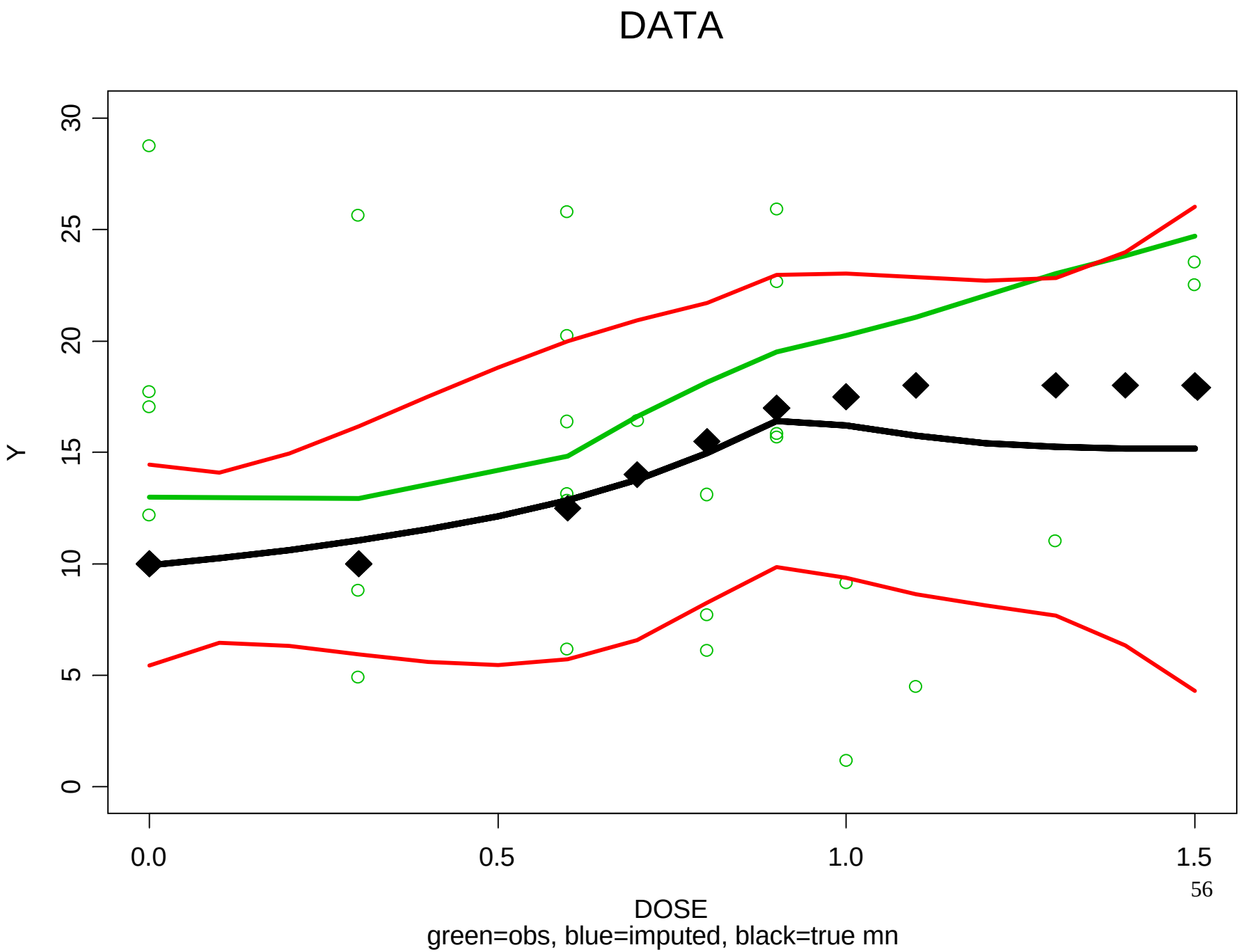
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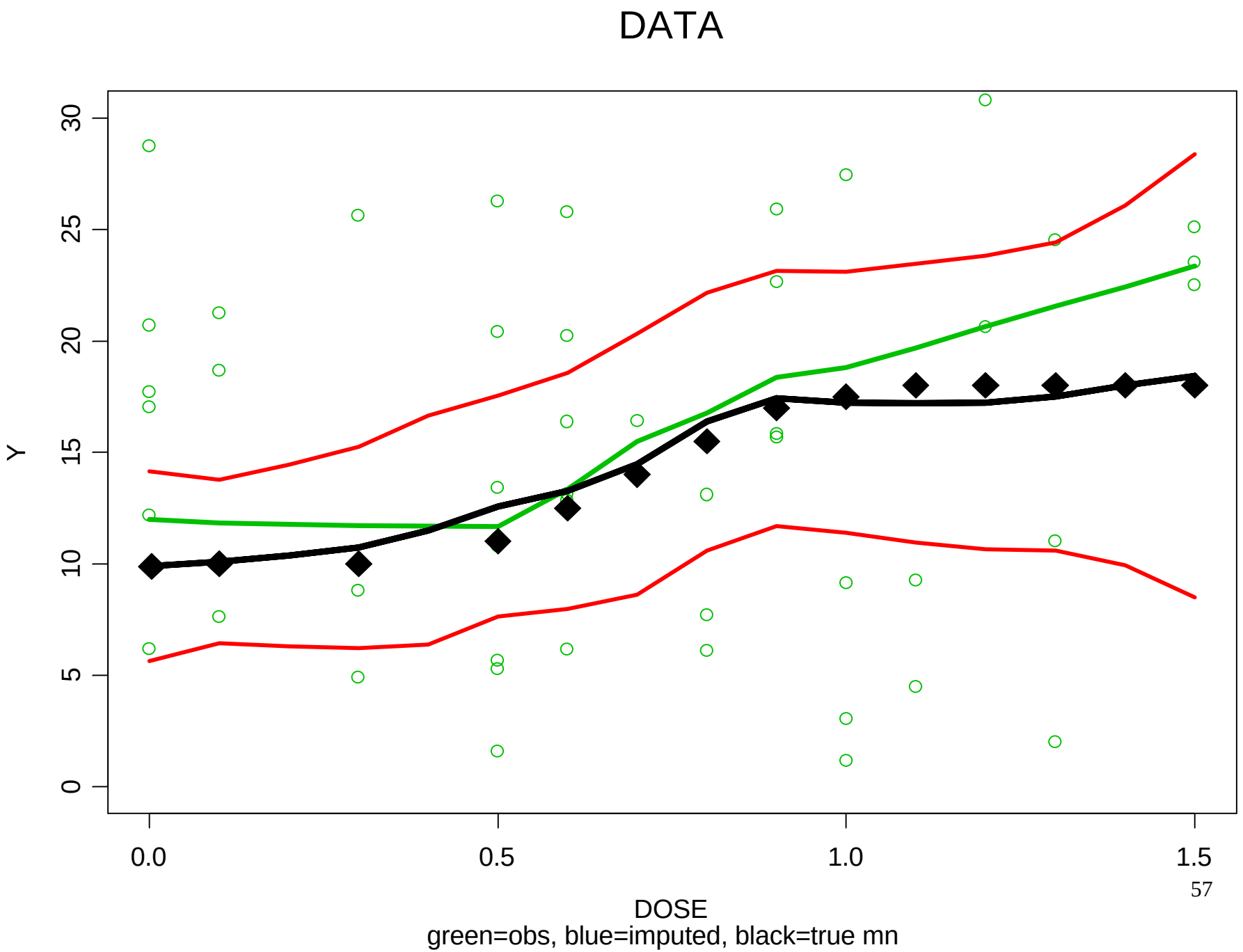
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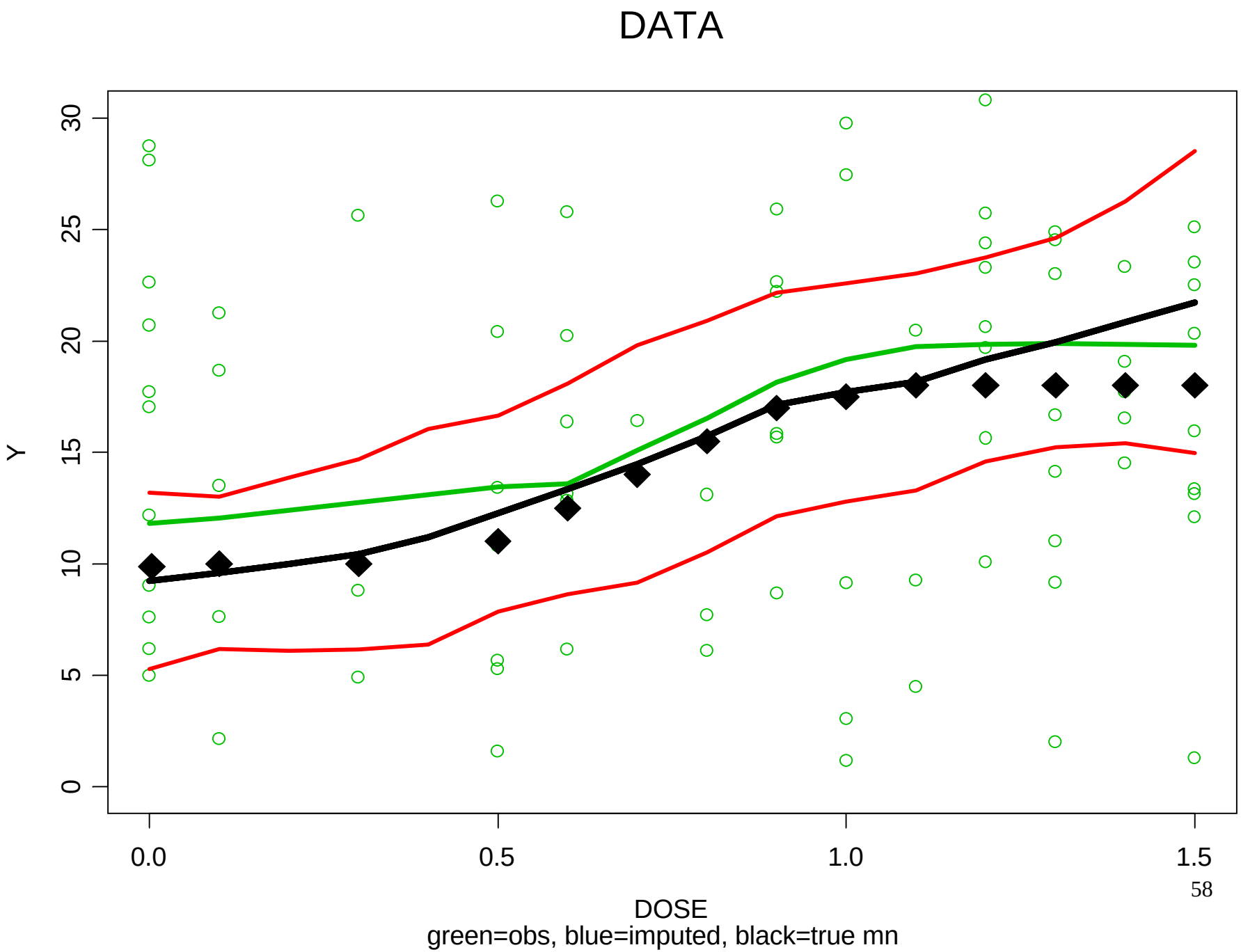
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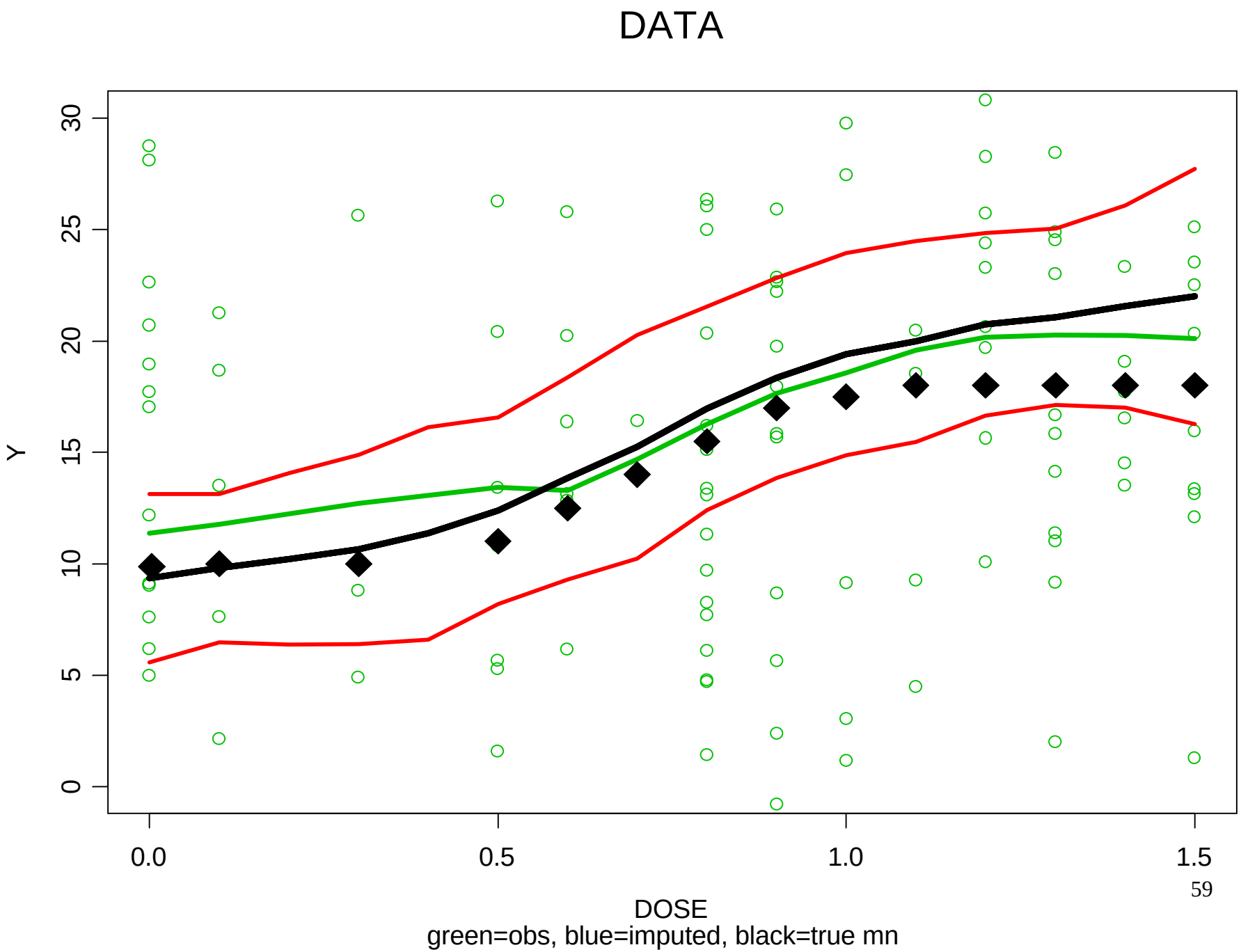
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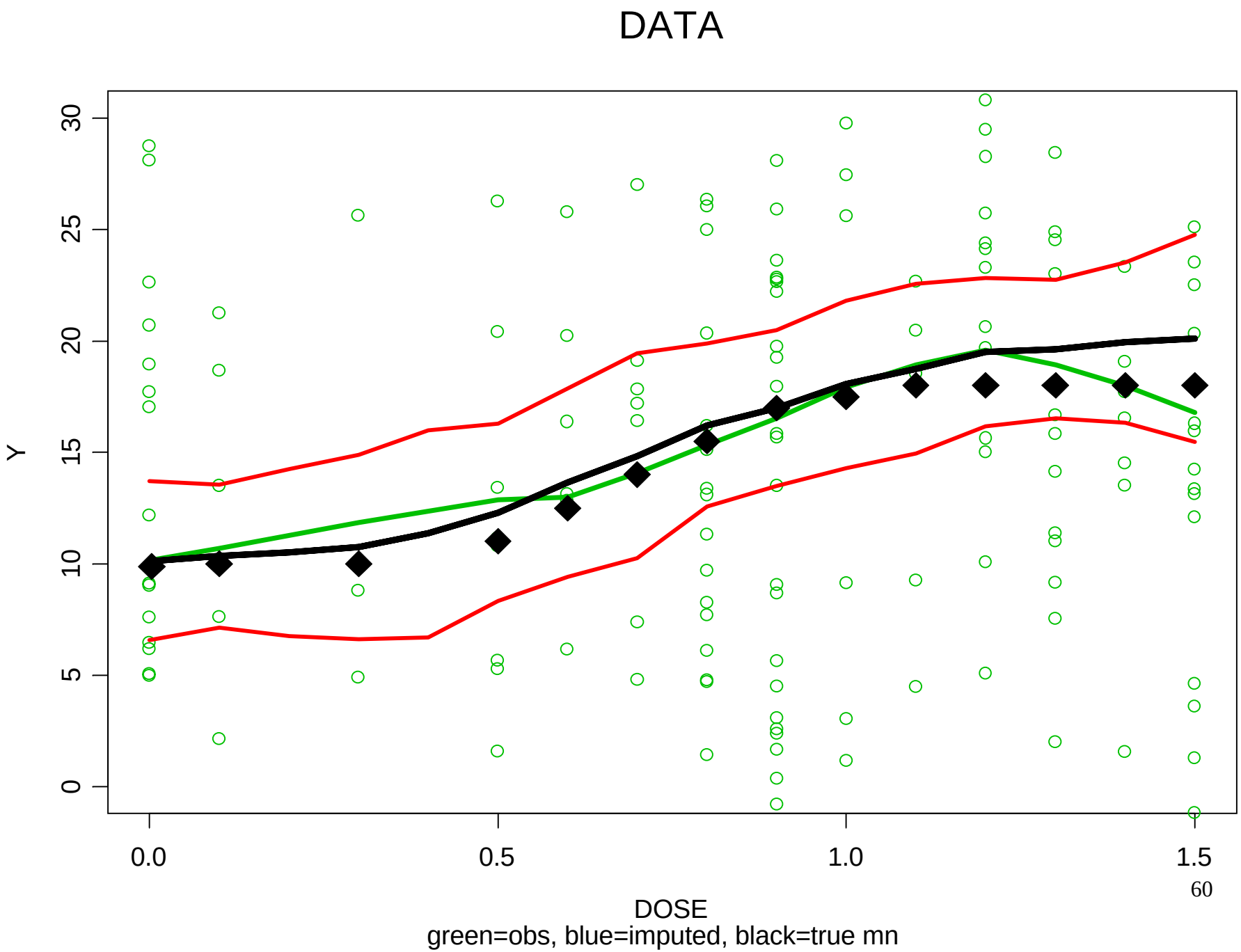
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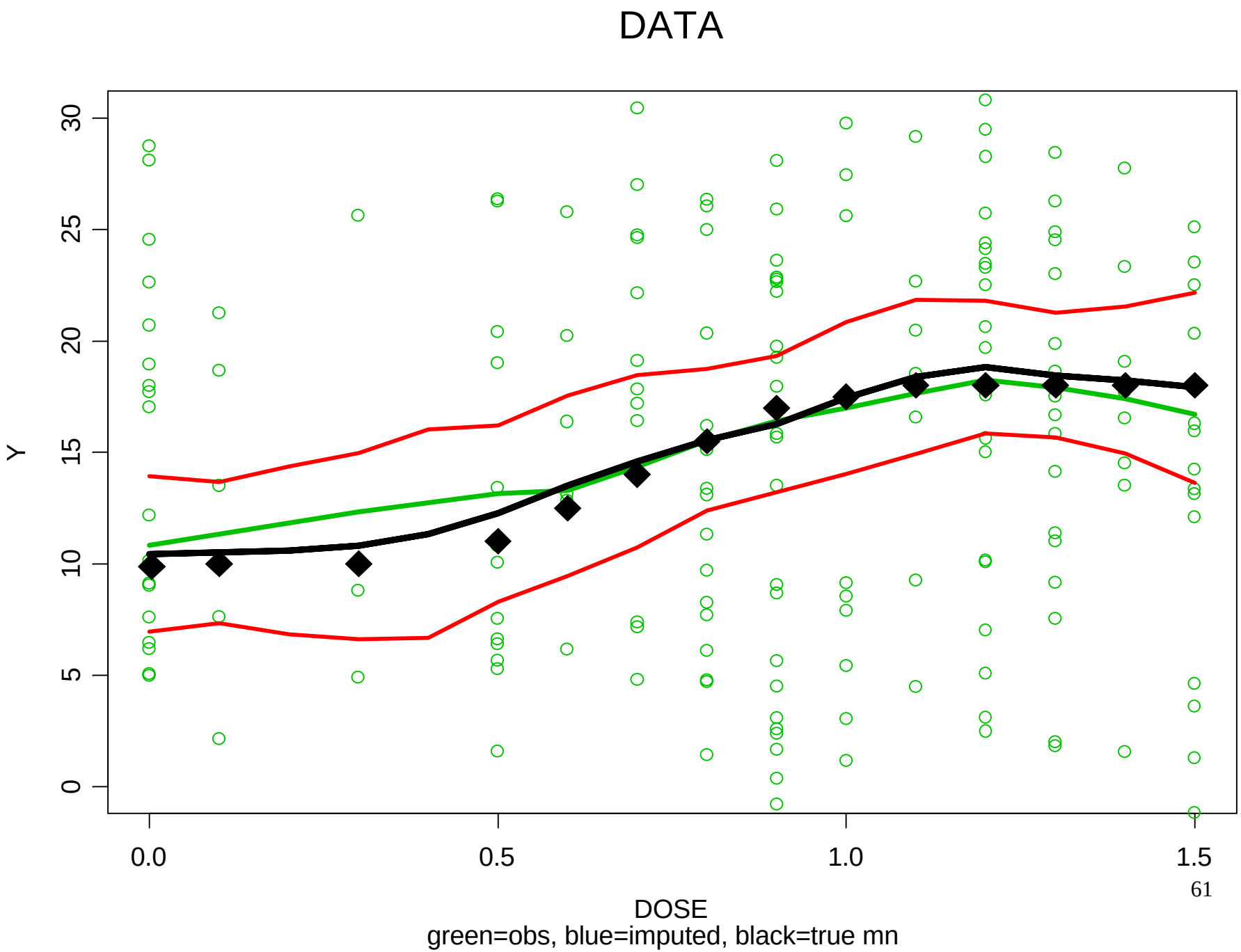
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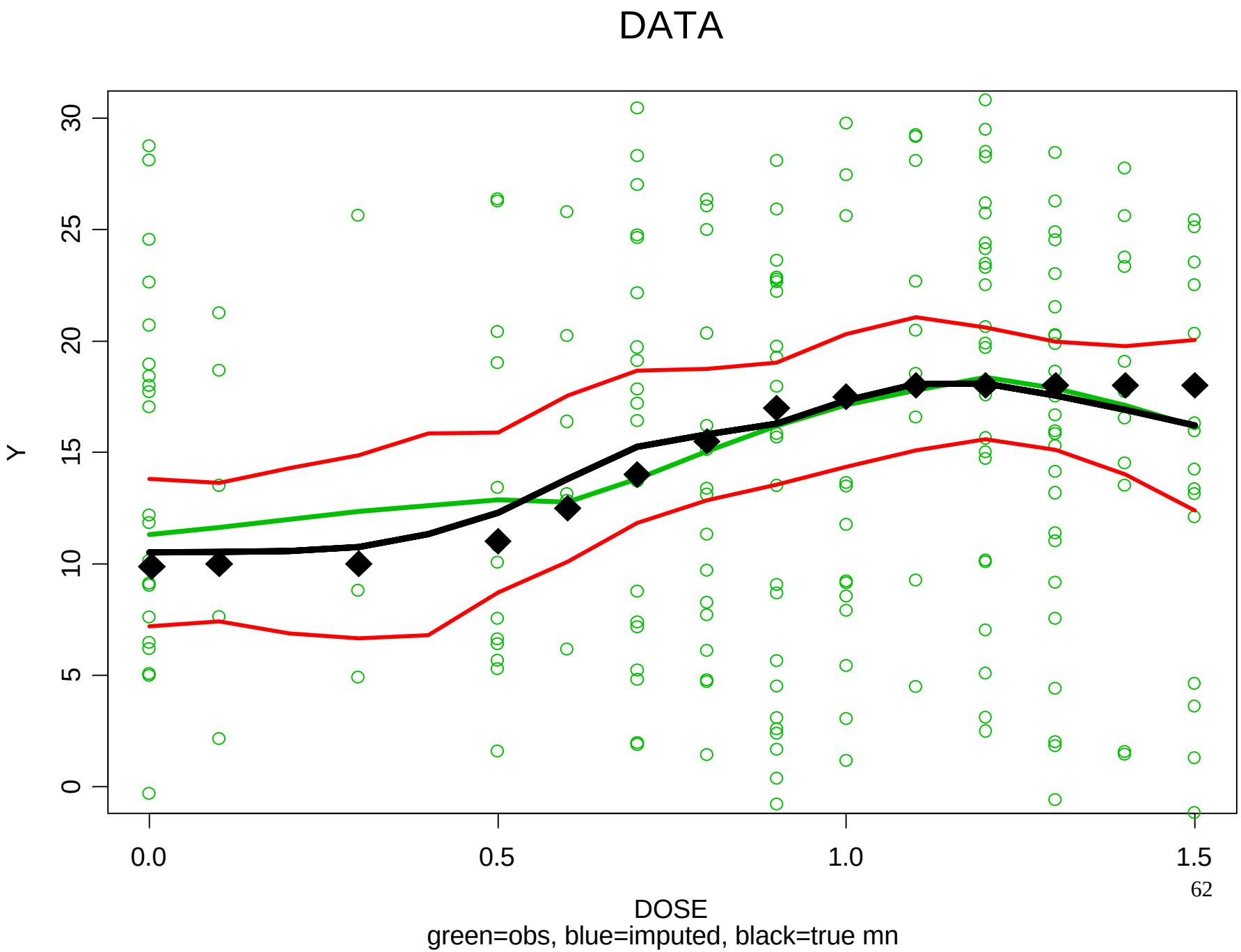
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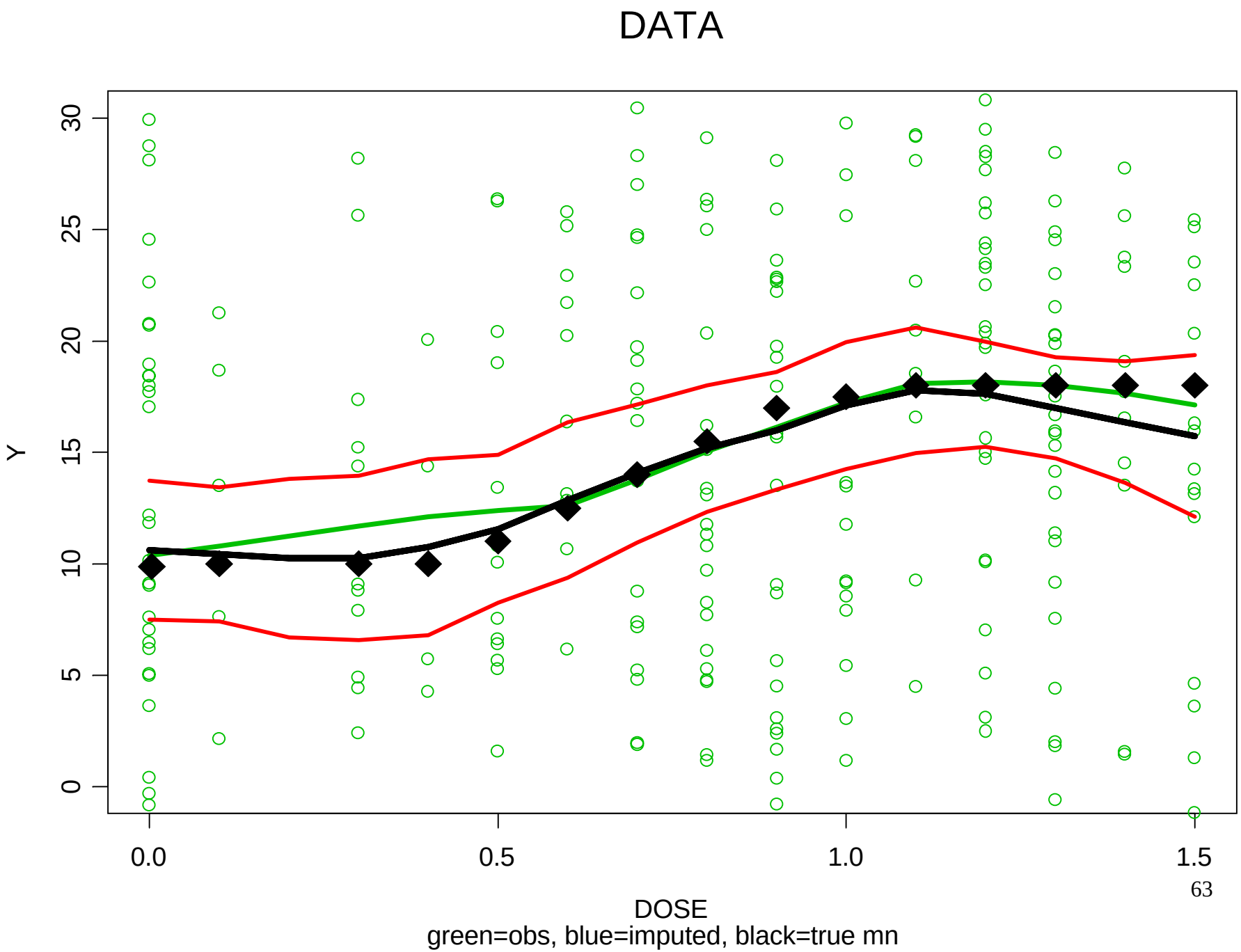
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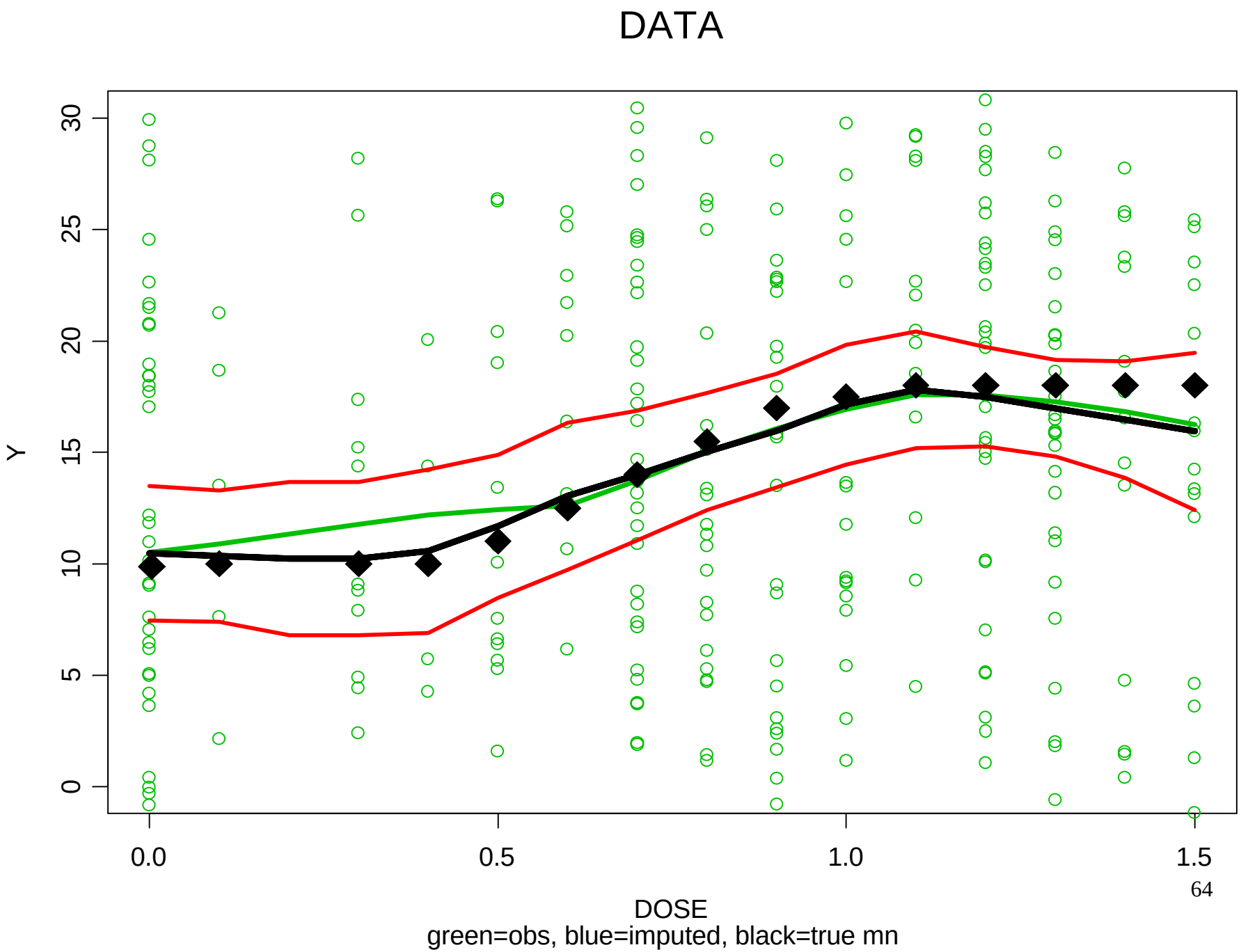
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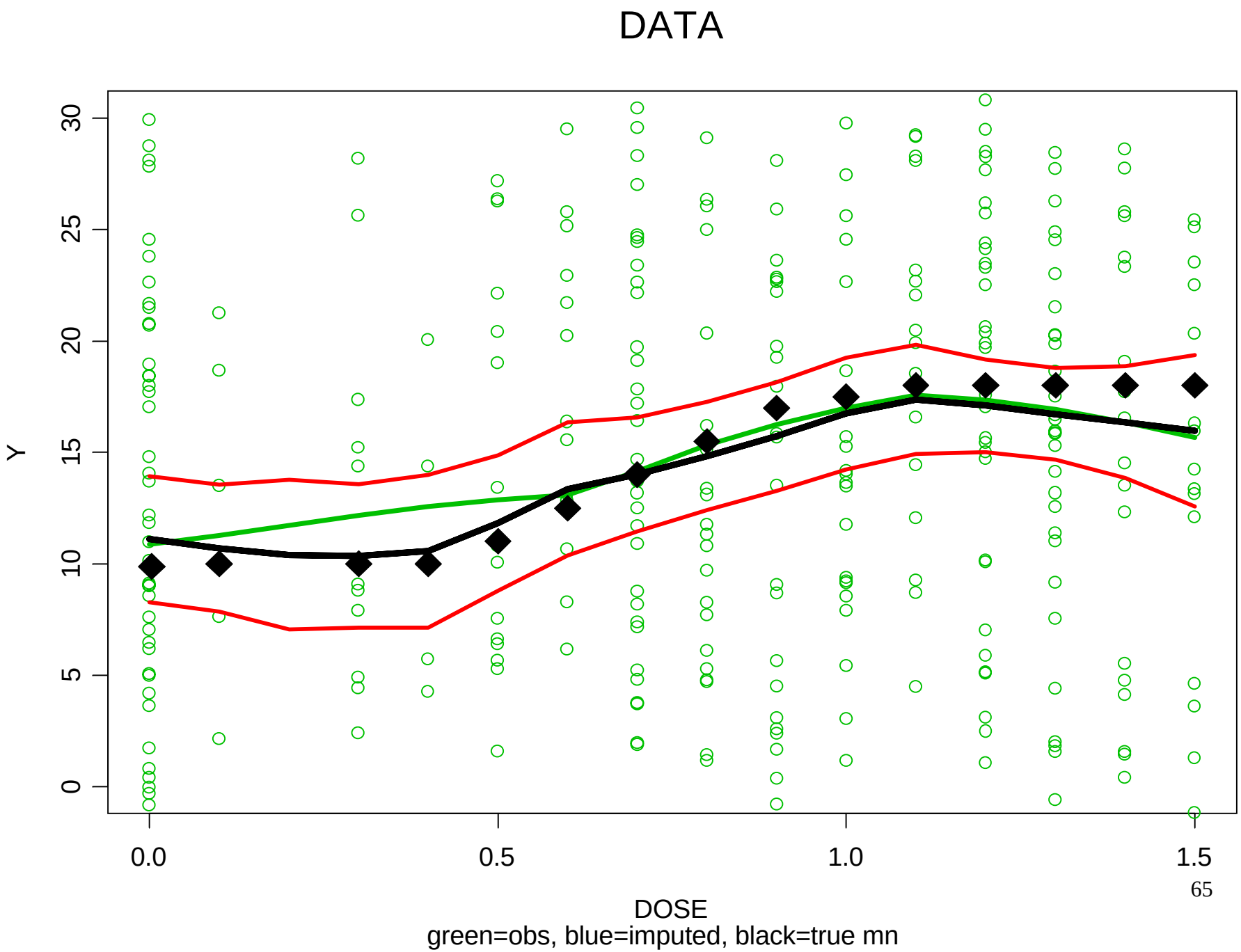
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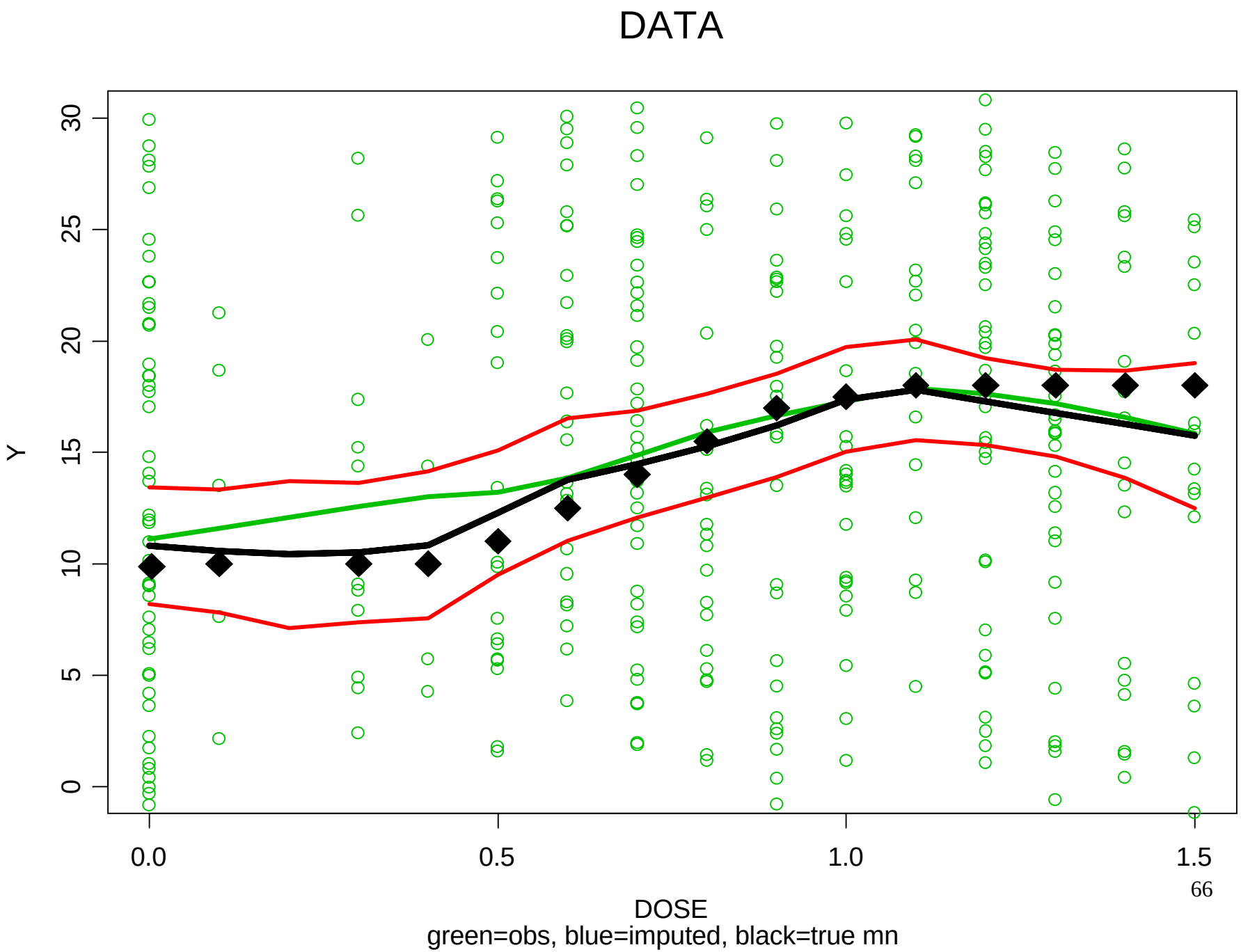
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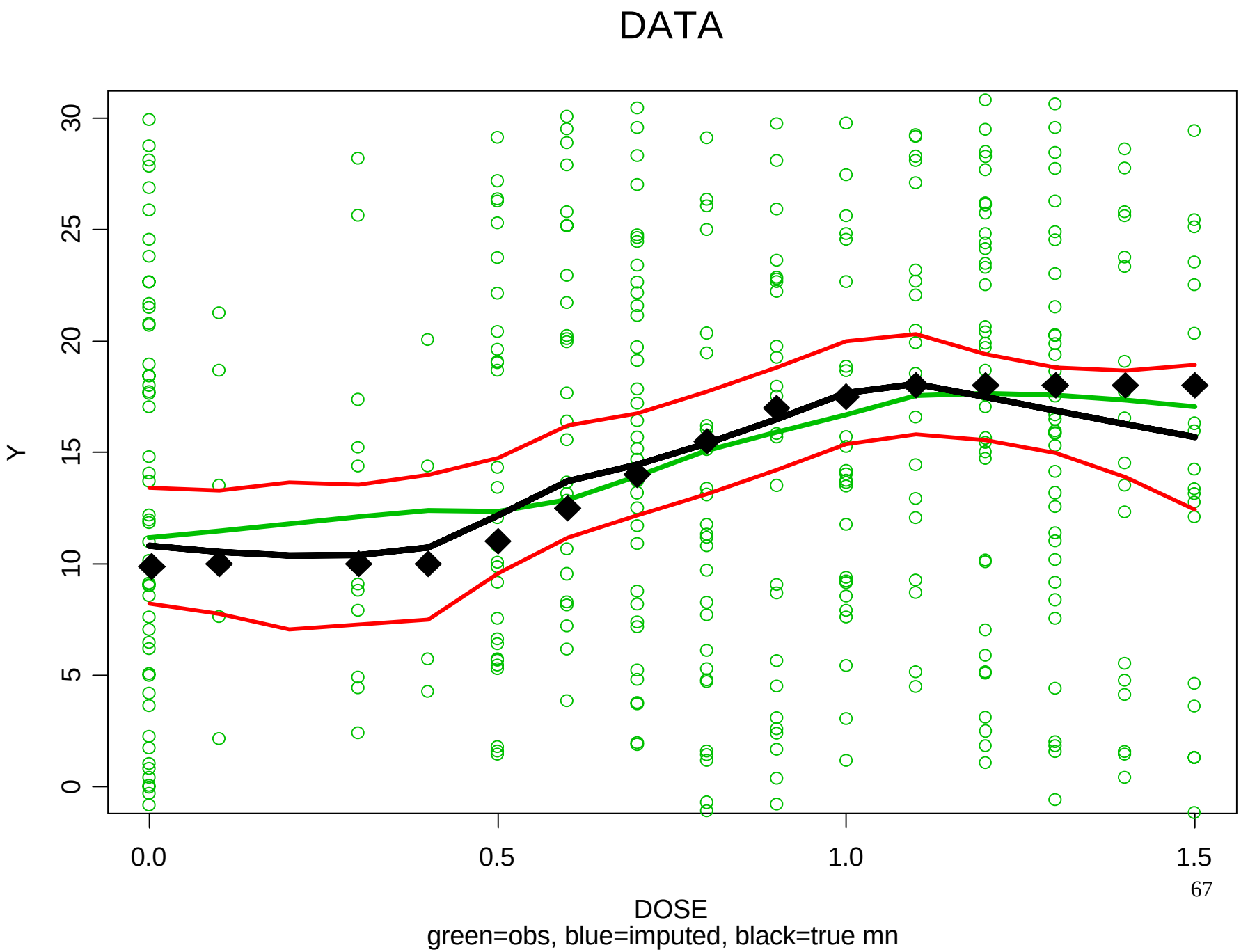
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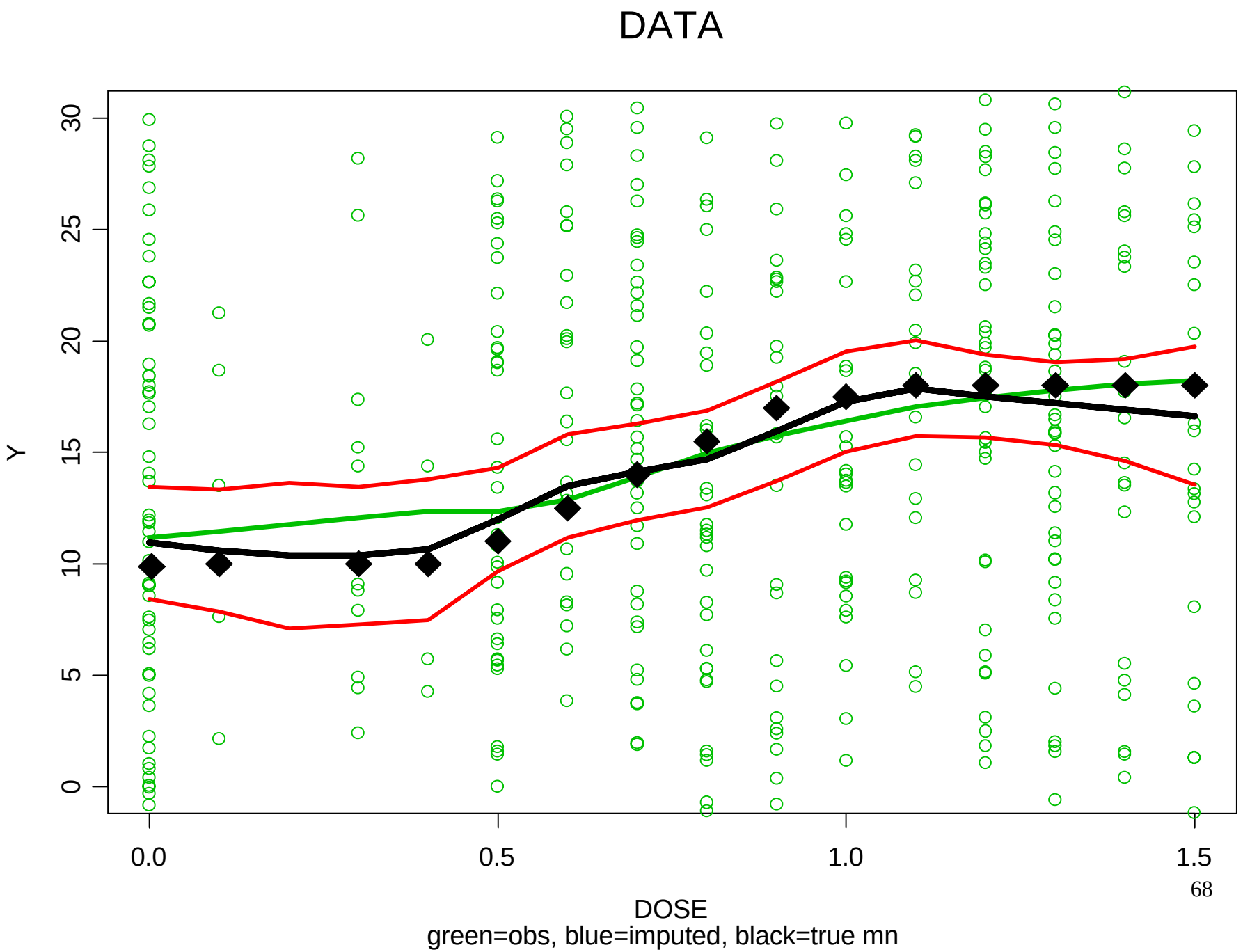
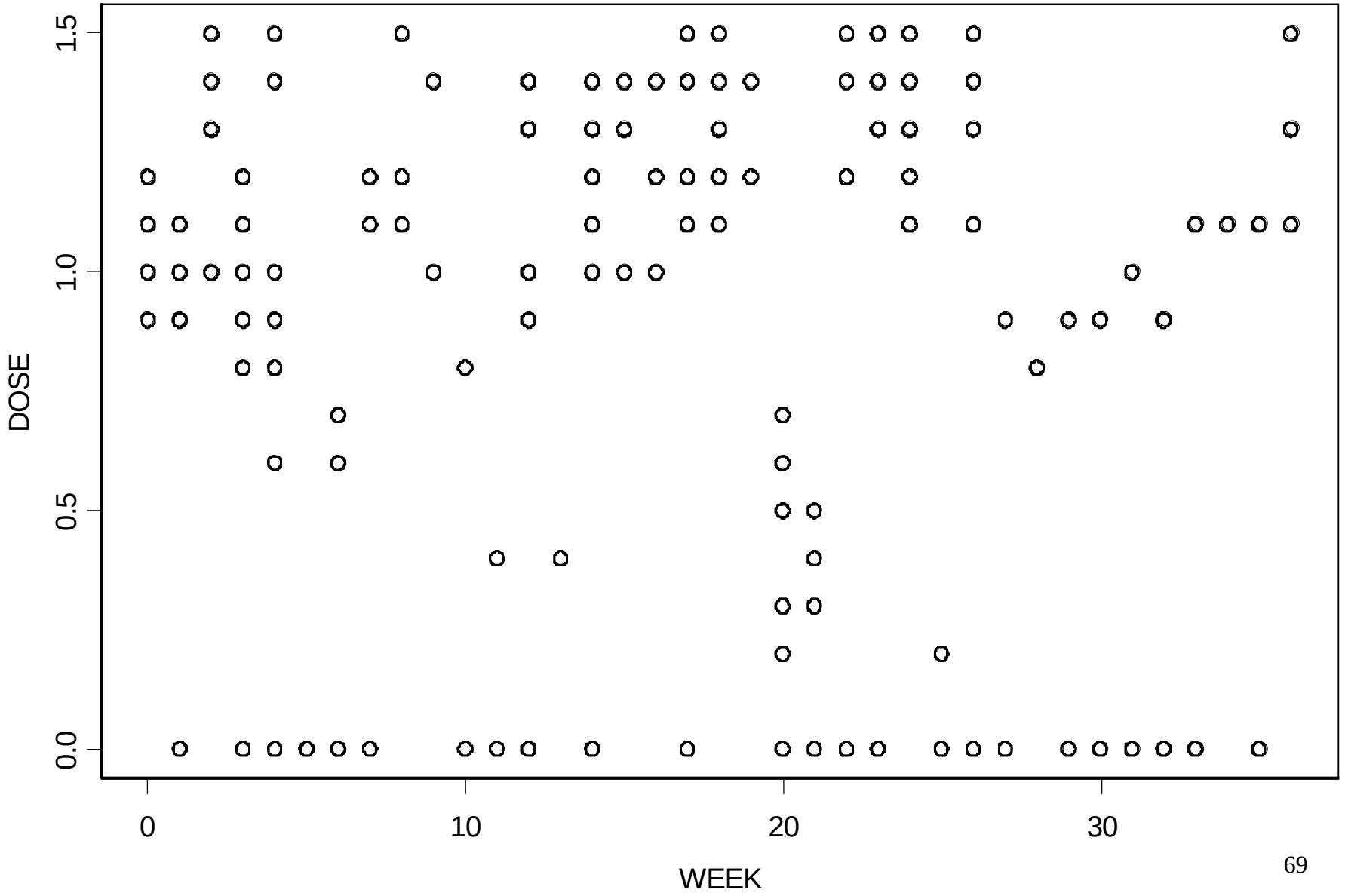
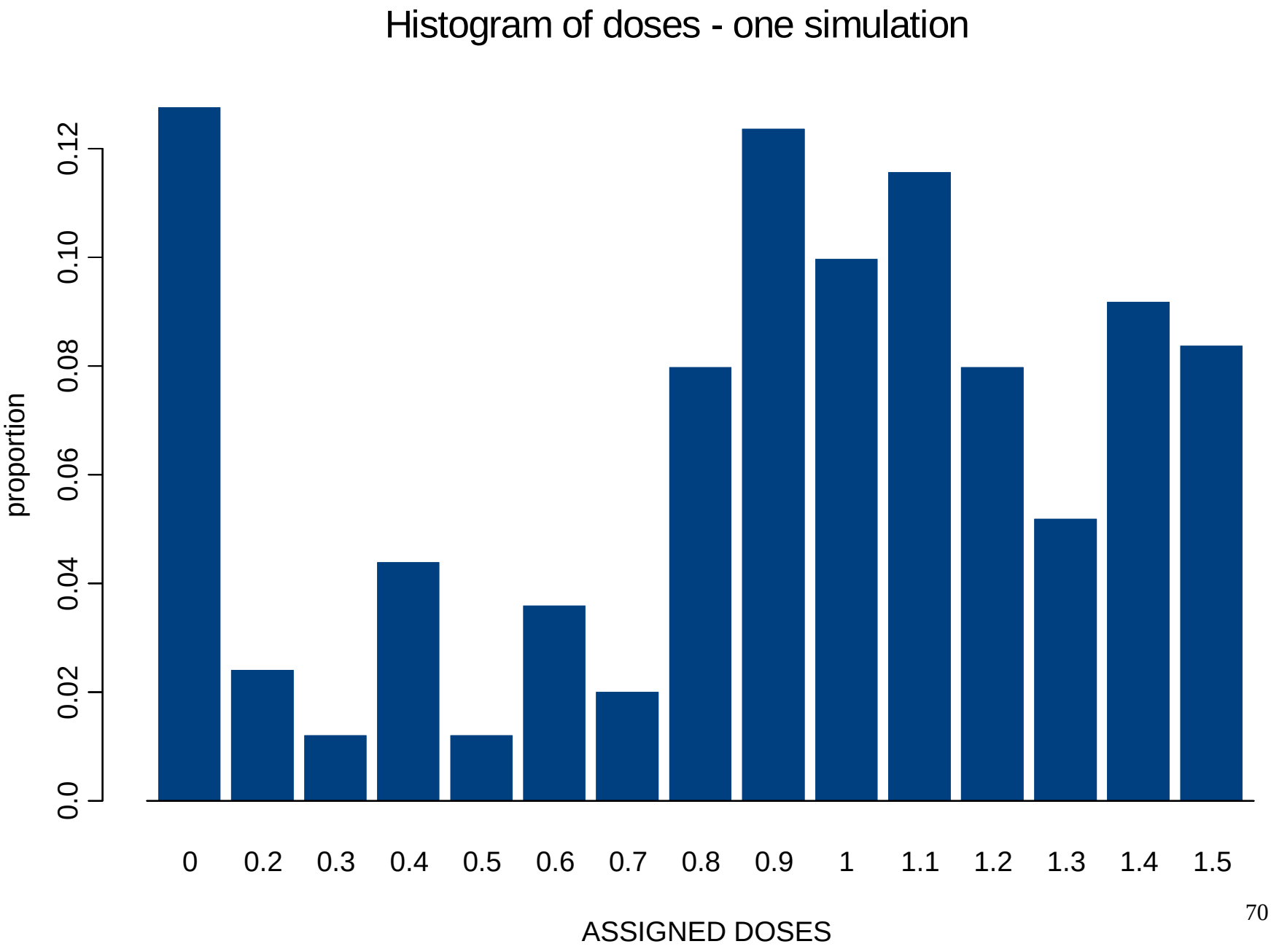
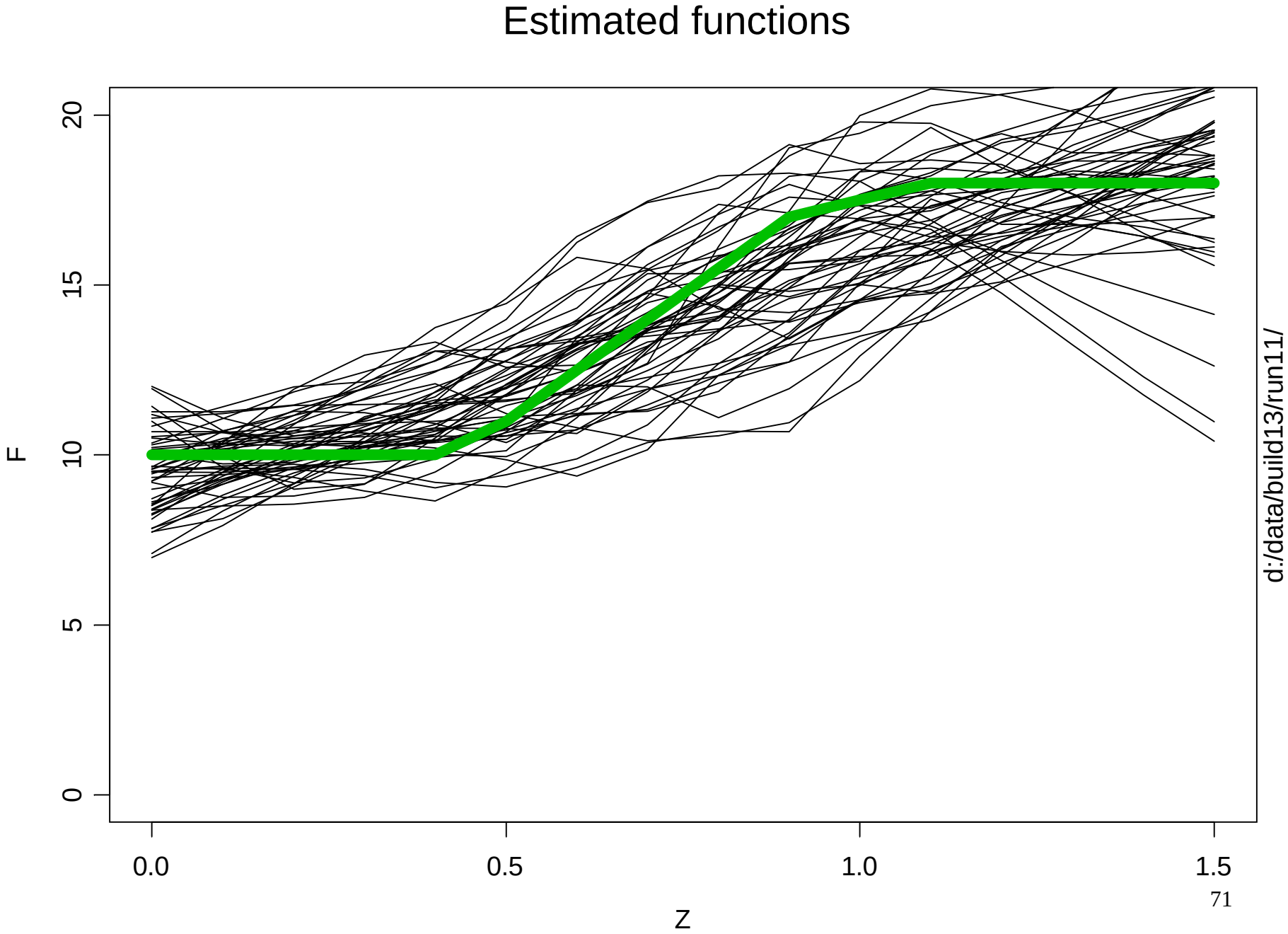
DOSE
green=obs, blue=imputed, black=true mn

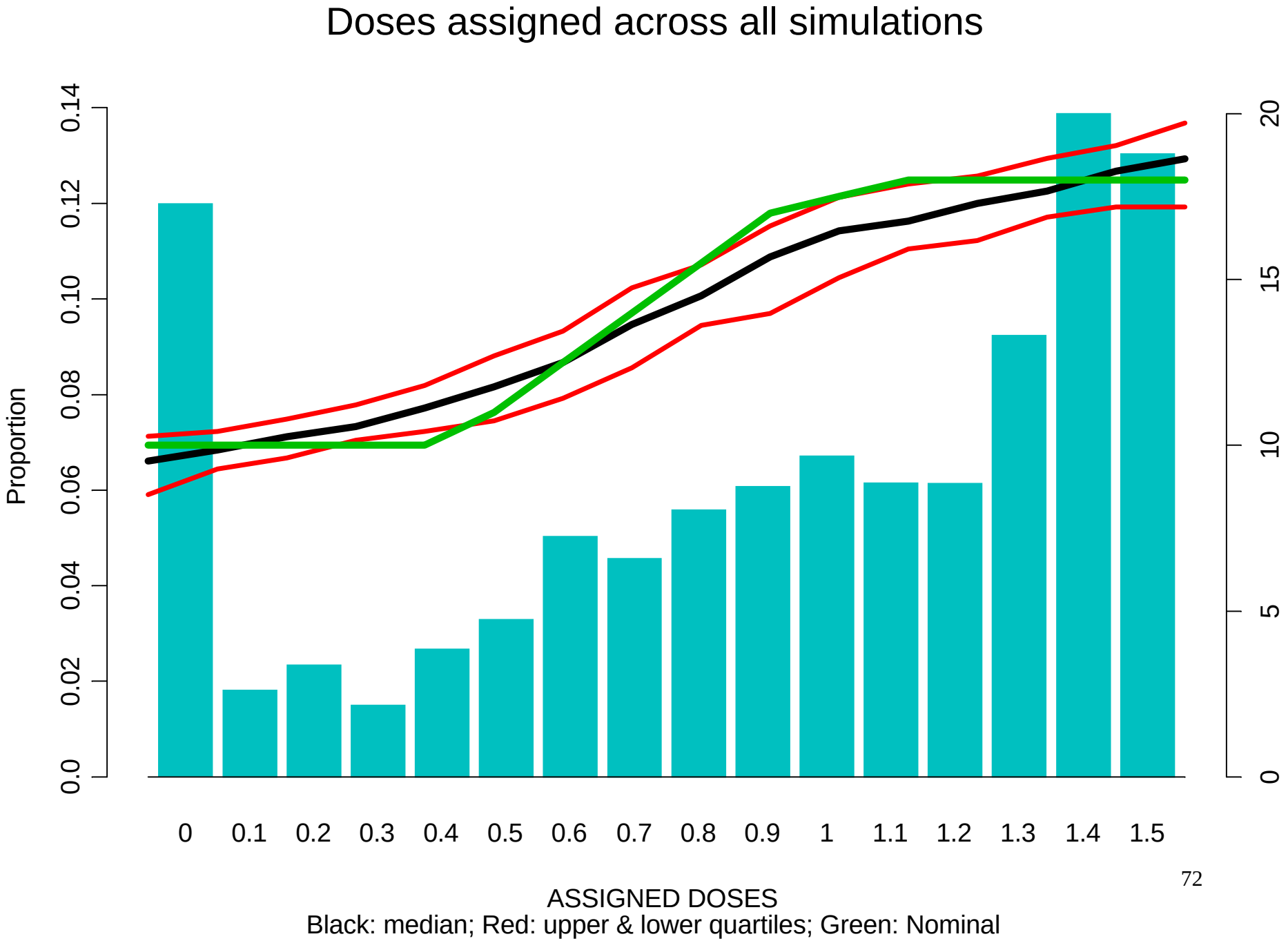

DATA
Y
0
5
10
15
20
25
30
0.0
0.5
1.0
1.5
DOSE
green=obs, blue=imputed, black=true mn

Assigned Doses by Week - one simulation

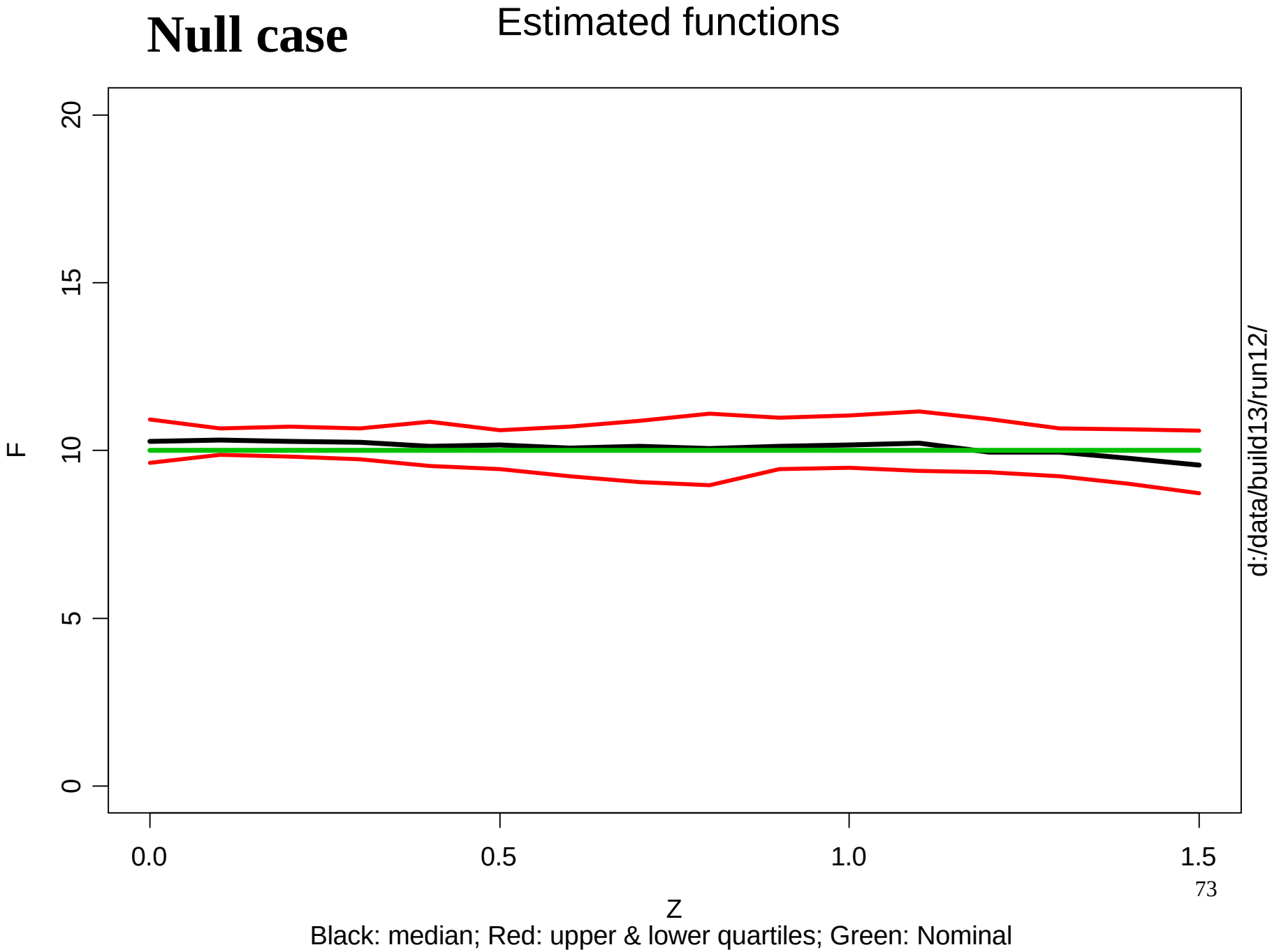


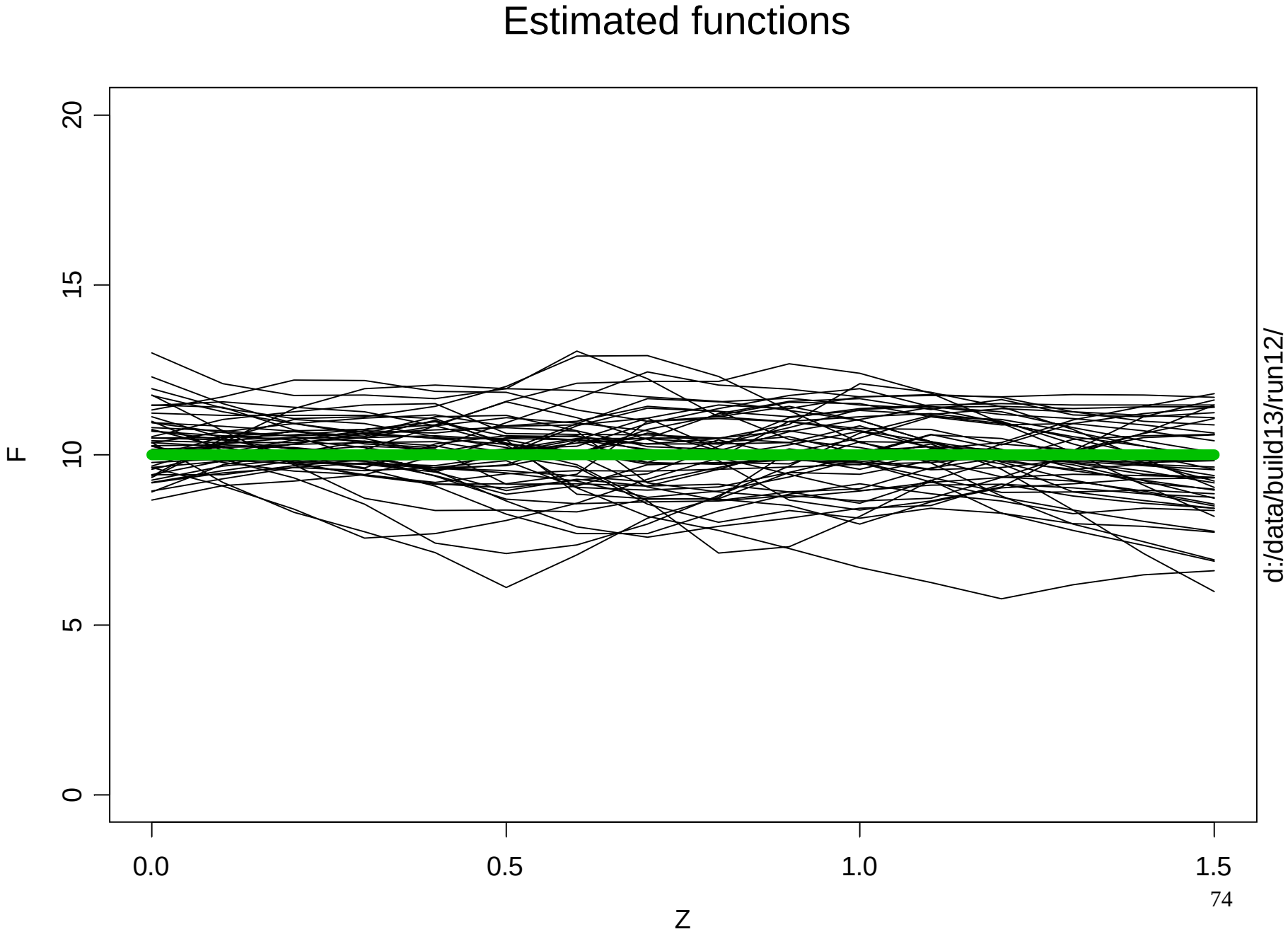

Histogram of doses - one simulation
proportion
0.0
0.02
0.04
0.06
0.08
0.10
0.12
0
0.2
0.3
0.4
0.5
0.6
0.7
0.8
0.9
1
1.1
1.2
1.3
1.4
1.5
ASSIGNED DOSES

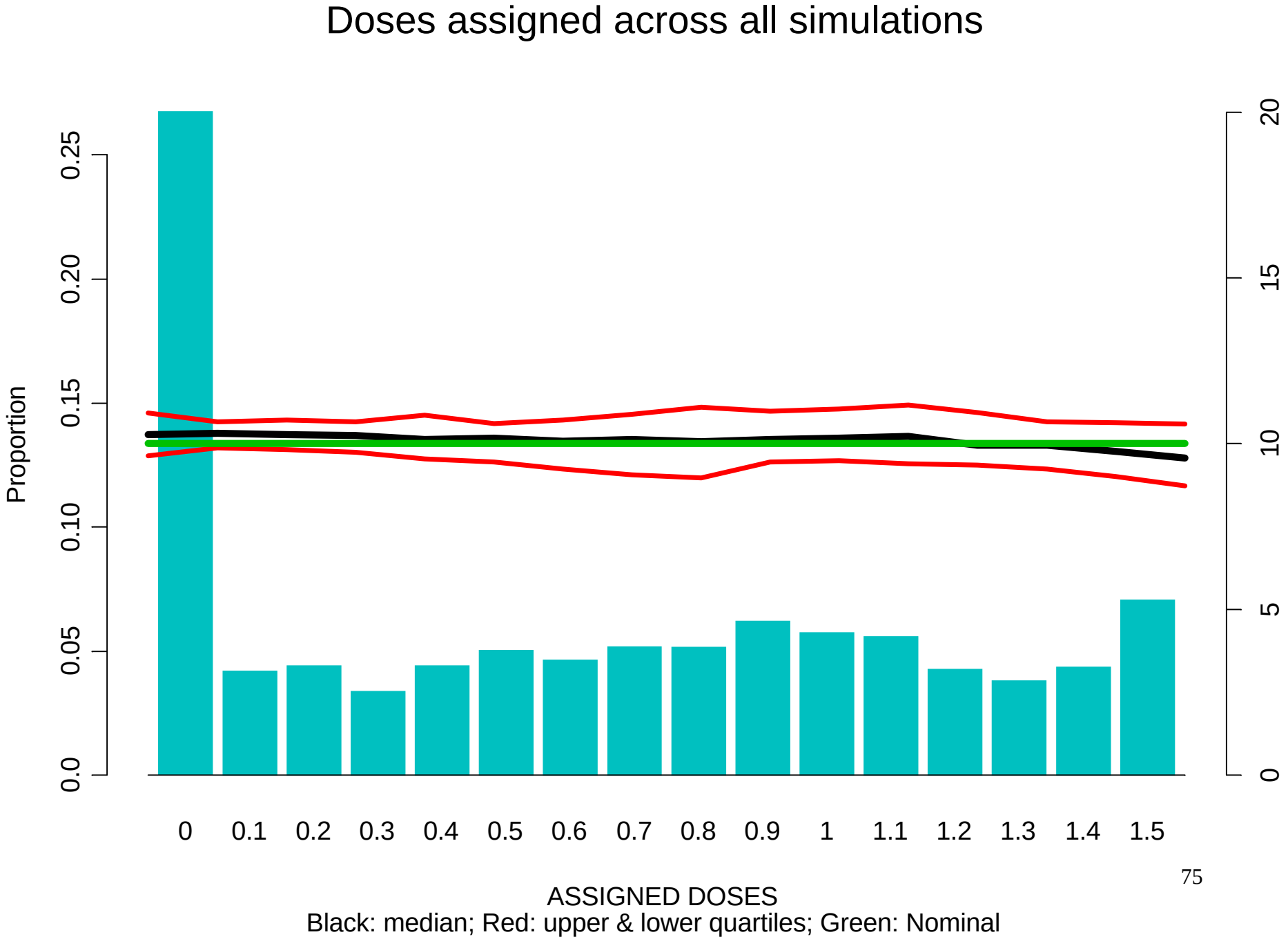

Estimated functions
F
0
5
10
15
20
0.0
0.5
1.0
1.5
Z
d:/data/build13/run11/


Doses assigned across all simulations
Proportion
0.0
0.02
0.04
0.06
0.08
0.10
0.12
0.14
0
5
10
15
20
0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0.8
0.9
1
1.1
1.2
1.3
1.4
1.5
ASSIGNED DOSES
Black: median; Red: upper & lower quartiles; Green: Nominal

Null case


Estimated functions
F
0
5
10
15
20
0.0
0.5
1.0
1.5
Z
d:/data/build13/run12/
Black: median; Red: upper & lower quartiles; Green: Nominal


Estimated functions
F
0
5
10
15
20
0.0
0.5
1.0
1.5
Z
d:/data/build13/run12/


Doses assigned across all simulations
Proportion
0.0
0.05
0.10
0.15
0.20
0.25
0
5
10
15
20
0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0.8
0.9
1
1.1
1.2
1.3
1.4
1.5
75
ASSIGNED DOSES
Black: median; Red: upper & lower quartiles; Green: Nominal

Consequences

- **Fundamental change in the way we do medical research.**
- **More rapid progress; more drugs considered.**
- **Better treatment of patients.**
- **. . . at less cost.**

SUMMARY

- **Background.**
- **Early stopping (HDCT vs SDCT).**
- **Adaptive allocation to treatment.**
- **Seamless design; drug for NSCLC.**
- **Adaptive dose-finding; drug for stroke.**