Precision Generalized Phase I-II Designs

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Outline

Section Overview

Early phase dose-finding designs typically rely on **short-term outcomes**.

- **BOIN design** (phase I): finding the maximum tolerated dose (MTD) based on toxicity.
- **BOIN12 design** (phase I-II): identifies the optimal biological dose (OBD) by considering both toxicity and short-term efficacy.

These designs rely on the assumption that selecting a dose based on short-term outcomes ensures **long-term therapeutic success**.

However, the selected dose may result in **suboptimal** survival due to high relapse rates.

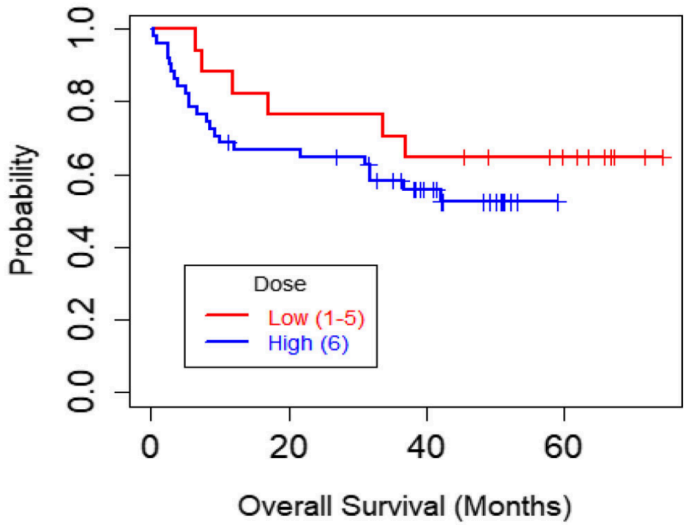


Figure 1: A dose-finding trial that failed.

Thall et al. (2023) proposed a generalized Bayesian phase I-II (**Gen I-II**) design to optimize the **long-term** therapeutic success.

- First, a conventional phase I-II design based on short-term outcomes identifies **a set of candidate doses**.
- Additional patients are then randomized among these candidates, and the final dose is selected based on long-term therapeutic success.

- The trial considered in the Gen I-II design aims to optimize the dose of chimeric antigen receptor (CAR) natural killer (NK) cells for advanced hematologic malignancies.

Table 1: Three Disease Subgroups in the CAR NK Cell Trial

Disease Group	Description
1	AML, ALL, CMML, MDS, and blastic CML
2	Non-T-cell Hodgkin's and non-Hodgkin's lymphoma
3	T-cell non-Hodgkin's lymphoma

AML = acute myelogeneous leukemia, ALL = acute lymphocytic leukemia, CMML = chronic myelomonocytic leukemia, MDS = myelodysplastic syndrome, and CML = chronic myelogeneous leukemia.

- The Gen I-II design assumed homogeneous outcome distributions across these subgroups and ignored patient **heterogeneity**.

Section Overview

To solve this issue, we paopose PGen I-II designs to refine Gen I-II design by accounting for patient heterogeneity across subgroups.

Notations:

- $Y_j \in \{0, \cdots, L_j - 1\}$ denotes **ordinal** efficacy ($j = E$) and toxicity ($j = T$) outcomes over $[0,\ t_1]$.
- Y_S denotes the time to failure over the longer follow-up period $[0, t_2]$.
- Dose values d_j for levels $j = 1, \cdots, J$.
- $g \in \{1, \cdots, G\}$ represents pre-specified subgroups.
- **Latent cluster membership variables** $\boldsymbol{z} = (z_1, \cdots, z_G)$: $z_1 = 1$ and for $g \geq 2$, if subgroup $j \in \{1, \ldots, g-1\}$ is in the same cluster as g, set $z_g = z_j$. Otherwise, $z_g = \max_{i \in \{1,\ldots,g-1\}} z_i + 1$.
- Thus, if $z_g = z_{g'}$ for $g \neq g'$, subgroups g and g' are combined into the same cluster.

To construct a parametric model for $p(Y_E, Y_T \mid d, g)$, we adopt the **multivariate probit latent variable approach**.

- (X_E, X_T) denote **real-valued latent variables** following the **bivariate normal distribution**

$$(X_E,\ X_T) \,\Big|\, d, g \ \sim\ N_2\Big(\big(\mu_E(d,g),\ \mu_T(d,g)\big),\ \begin{pmatrix} \sigma_{11} & \sigma_{12} \\ \sigma_{12} & \sigma_{22} \end{pmatrix}\Big),$$

  where $\sigma_{11} = \sigma_{22} = 1$ and $-1 \le \sigma_{12} \le 1$.

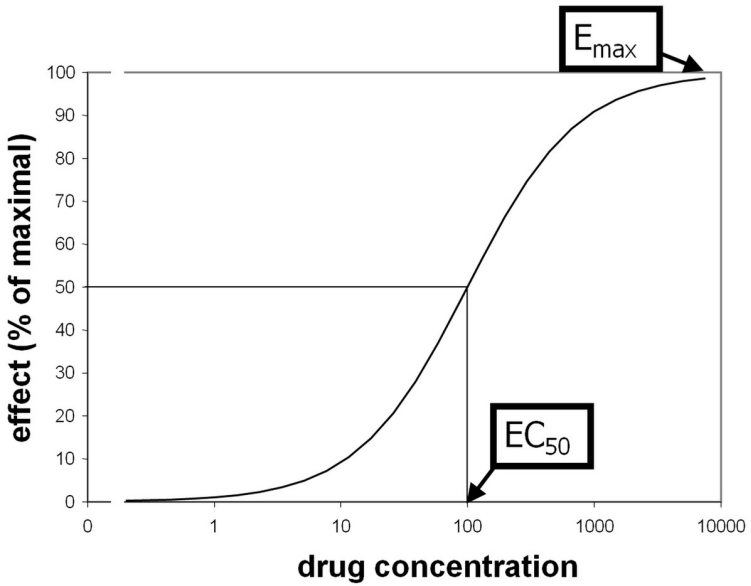
- Given real-valued **cutpoints**, we obtain

$$Y_E = \begin{cases} 0 & \text{if } \eta_0 < X_E < \eta_1 \\ 1 & \text{if } \eta_1 \le X_E < \eta_2 \\ \dots & \\ L_E - 1 & \text{if } \eta_{L_E-1} \le X_E < \eta_{L_E} \end{cases}, Y_T = \begin{cases} 0 & \text{if } \zeta_0 < X_T < \zeta_1 \\ 1 & \text{if } \zeta_1 \le X_T < \zeta_2 \\ \dots & \\ L_T - 1 & \text{if } \zeta_{L_T-1} \le X_E < \zeta_{L_T} \end{cases},$$

  where $\eta_1 = \zeta_1 = 0$ to ensure identifiability.

- For efficacy, we assume the flexible four-parameter Emax model

$$\mu_E(d,g) = \alpha_{0,g} + \frac{\alpha_{1,g} d^{\alpha_{3,g}}}{\alpha_{2,g}^{\alpha_{3,g}} + d^{\alpha_{3,g}}}.$$



- For toxicity, we model more simply as $\mu_T(d,g) = \beta_{0,g} + \beta_{1,g} d$.

- Given an elicited utility function $U(y_E, y_T)$, **the early outcome optimality criterion** for dose d in subgroup g is the mean utility

$$\phi_{ET}(d, g) = \sum_{y_E, y_T} \pi(y_E, y_T \mid d, g, \boldsymbol{\theta}_{ET})\, U(y_E, y_T).$$

- In the CAR NK Cell Trial, Y_S is progression-free survival (PFS) time and $[Y_E = 0]$ means progressive disease (PD).
- Define $Y_S' = (Y_S - t_1)\, I(Y_E > 0)$ as the treatment failure time starting from t_1. If $Y_E = 0$, then $Y_S' = 0$.
- **The long-term dose optimality criterion** is defined as the long-term success probability

$$\begin{aligned}\phi_S(d, g) &= \Pr(Y_S > t_2 \mid d, g) = \Pr(Y_S' > t_2 - t_1 \mid d, g) \\ &= \sum_{y=1}^{L_E - 1} \Pr(Y_E = y \mid d, g) \Pr(Y_S' > t_2 - t_1 \mid d, g, Y_E = y).\end{aligned}$$

- For robustness, we assume that Y_S' follows a **piecewise exponential** (PE) distribution, with the following PE hazard function

$$h_S(t \mid Y_E^+, Y_T, d, g, \boldsymbol{\theta}_S) = \left\{ \sum_{k=1}^{K} \lambda_k \, I(c_{k-1} \leq t < c_k) \right\} \times \exp\left(\gamma_{E,Y_E^+,g} + \gamma_{T,Y_T,g} + \sum_{j=1}^{J} \gamma_{D,j,g} \mathrm{I}(d = d_j) \right), \quad t > 0,$$

  where Y_E^+ represents values of $Y_E > 0$, λ_k represents the baseline PE hazard on the k^{th} subinterval and $\gamma_{E,1,g} = \gamma_{T,0,g} = \gamma_{D,1,g} = 0$.
- Let $\mathcal{D}_{TE}^n$ represent the data on (Y_T, Y_E), $\mathcal{D}_S^n$ represent the data on Y_S, and $\mathcal{D}^n$ represent the complete dataset for the first n patients.

We use the latent cluster membership vector $\boldsymbol{z}$ to adaptively cluster similar subgroups:

- Each possible configuration of $\boldsymbol{z}$ represents a model, indexed by $\nu = 1, \cdots, M$. If $G = 3$, there are $M = 5$ possible models

$$\begin{aligned} \nu &= 1 \quad \text{if} \quad \boldsymbol{z} = (1,1,1), \\ \nu &= 2 \quad \text{if} \quad \boldsymbol{z} = (1,1,2), \\ \nu &= 3 \quad \text{if} \quad \boldsymbol{z} = (1,2,1), \\ \nu &= 4 \quad \text{if} \quad \boldsymbol{z} = (1,2,2), \\ \nu &= 5 \quad \text{if} \quad \boldsymbol{z} = (1,2,3). \end{aligned}$$

- Assume a discrete uniform prior: $\Pr(\nu = k) = 1/5$, $k = 1, \cdots, 5$.
- Due to the adaptive model dimension change, we use **Reversible-Jump Markov Chain Monte Carlo (RJMCMC)** to obtain posterior samples on spaces of varying dimensions.

The following criteria will be used by the PGen I-II design:

- **The early-term dose optimality criteria**:

$$\widehat{\phi}_{ET}(d, g \mid \mathcal{D}_{ET}^n) = \int \phi_{ET}(d, g \mid \boldsymbol{\theta}_{ET}^\star, z_g)\ p(\boldsymbol{\theta}_{ET}^\star, z_g \mid \mathcal{D}_{ET}^n)\ d\boldsymbol{\theta}_{ET}^\star\ dz_g.$$

- **The long-term dose optimality criteria**:

$$\widehat{\phi}_S(d, g \mid \mathcal{D}^n) = \int \phi_S(d, g \mid \boldsymbol{\theta})\ p(\boldsymbol{\theta} \mid \mathcal{D}^n)\ d\boldsymbol{\theta}.$$

- The posterior predictive probability that the long-term optimality criterion for dose d in subgroup g is greater than $\underline{\phi}_S$ is given by:

$$\widehat{\Pr}\left\{\phi_S(d, g \mid \mathcal{D}^n) > \underline{\phi}_S \mid \mathcal{D}^n\right\} = \int \Pr\left\{\phi_S(d, g) > \underline{\phi}_S \mid \boldsymbol{\theta}\right\} p(\boldsymbol{\theta} \mid \mathcal{D}^n)\, d\boldsymbol{\theta}.$$

- For $j = E, T$ and each (d, g), denote the vector of L_j marginal early outcome probabilities by:

$$\boldsymbol{\pi}_j(d, g, \boldsymbol{\theta}_j) = (\pi_j(0 \mid d, g, \boldsymbol{\theta}_j), \pi_j(1 \mid d, g, \boldsymbol{\theta}_j), \cdots, \pi_j(L_j - 1 \mid d, g, \boldsymbol{\theta}_j))'.$$

- We say that *a dose d is acceptable for subgroup g* if:

$$\begin{aligned} &\Pr\left\{\boldsymbol{b}_E'\boldsymbol{\pi}_E(d, g, \boldsymbol{\theta}_E) > \underline{\pi}_E \mid \mathcal{D}_{ET}^n\right\} > p_E, \\ &\Pr\left\{\boldsymbol{b}_T'\boldsymbol{\pi}_T(d, g, \boldsymbol{\theta}_T) < \overline{\pi}_T \mid \mathcal{D}_{ET}^n\right\} > p_T, \end{aligned} \tag{1}$$

  where $\boldsymbol{b}_E$ and $\boldsymbol{b}_T$ are design parameter vectors with all entries 0 or 1, and $\underline{\pi}_E$ and $\overline{\pi}_T$ are prespecified fixed limits.
- In our illustration, $\boldsymbol{b}_E = (0, \cdots, 0, 1)'_{L_E}$ and $\boldsymbol{b}_T = (0, \cdots, 0, 1)'_{L_T}$.

The PGen I-II design has **three stages**:

- the sample size for each stage: n_s;
- the overall sample size is $N = n_1 + n_2 + n_3$;
- the sample size for subgroup g in stage s: $n_{s,g}$;
- the sample size for subgroup g with dose d_j: $n_s(d_j)$.

Stage 1:

- Due to limited within-subgroup sample sizes, the PGen I-II design temporarily **ignores subgroups**, using the **BOIN12 design** to assign doses and determine **an acceptable dose set** $\mathcal{A}_{ET}^{n_1}$ for all subgroups combined.
- Other phase I-II designs can also be used in stage 1.

Stage 2:

- For each subgroup g, $n_{2,g}$ additional patients are randomized fairly among the acceptable doses in $\mathcal{A}_{ET}^{n_1}$.
- At the end of Stage 2, for each g, a subgroup-specific acceptable dose set $\mathcal{A}_{ET,g}^{n_{12}}$ is determined using the criteria in (1). The acceptable dose set in subgroup g is defined as

$$\mathcal{A}_{S,g}^{n_{12}} = \left\{ d_j \in \mathcal{A}_{ET,g}^{n_{12}} : \Pr\left\{ \phi_S(d_j, g) > \underline{\phi}_S \mid \mathcal{D}^{n_{12}} \right\} > p_{S,L} \right\}.$$

- The maximum over the set of acceptable doses for subgroup g is

$$\widehat{\phi}_{ET,g}^{max} = \max_{d_j \in \mathcal{A}_{ET,g}^{n_{12}}} \widehat{\phi}_{ET}(d_j, g \mid \mathcal{D}^{n_{12}}).$$

A ***candidate dose set for subgroup*** g then is defined as

$$\mathcal{C}_g^{n_{12}} = \left\{ d_j \in \mathcal{A}_{S,g}^{n_{12}} : \widehat{\phi}_{ET}(d_j, g \mid \mathcal{D}^{n_{12}}) \geq \rho \, \widehat{\phi}_{ET,g}^{max} \right\}.$$

Stage 3:

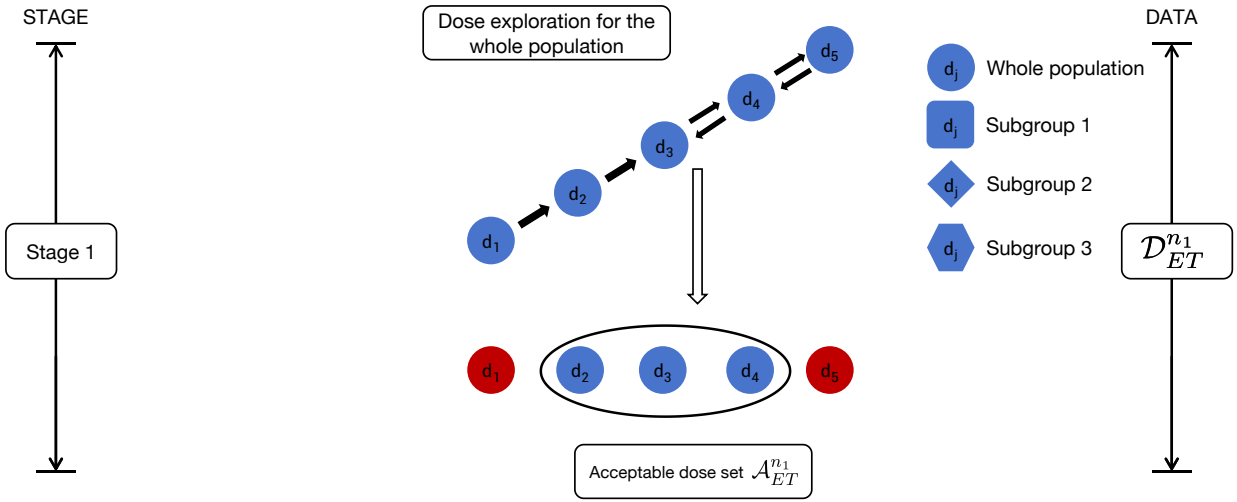
- For each subgroup g, $n_{3,g}$ additional patients are randomized among the doses in $\mathcal{C}_g^{n_{12}}$ and followed to time t_2.
- Denote $n_{123,g} = n_{1,g} + n_{2,g} + n_{3,g}$.
- The updated candidate dose set $\mathcal{C}_g^N$ must satisfy both the toxicity requirement in (1) and the minimal long-term success probability requirement, formally

$$\mathcal{C}_g^N = \Big\{ d_j \in \mathcal{C}_g^{n_{12}} : \Pr\Big\{ \boldsymbol{b}_T' \boldsymbol{\pi}_T(d_j, g, \boldsymbol{\theta}_T) < \overline{\pi}_T \mid \mathcal{D}^N \Big\} > p_{\mathcal{C},T,L}$$
$$\text{and } \Pr\big\{ \phi_S(d_j, g) > \underline{\phi}_S \mid \mathcal{D}^N \big\} > p_{\mathcal{C},S,L} \Big\}.$$

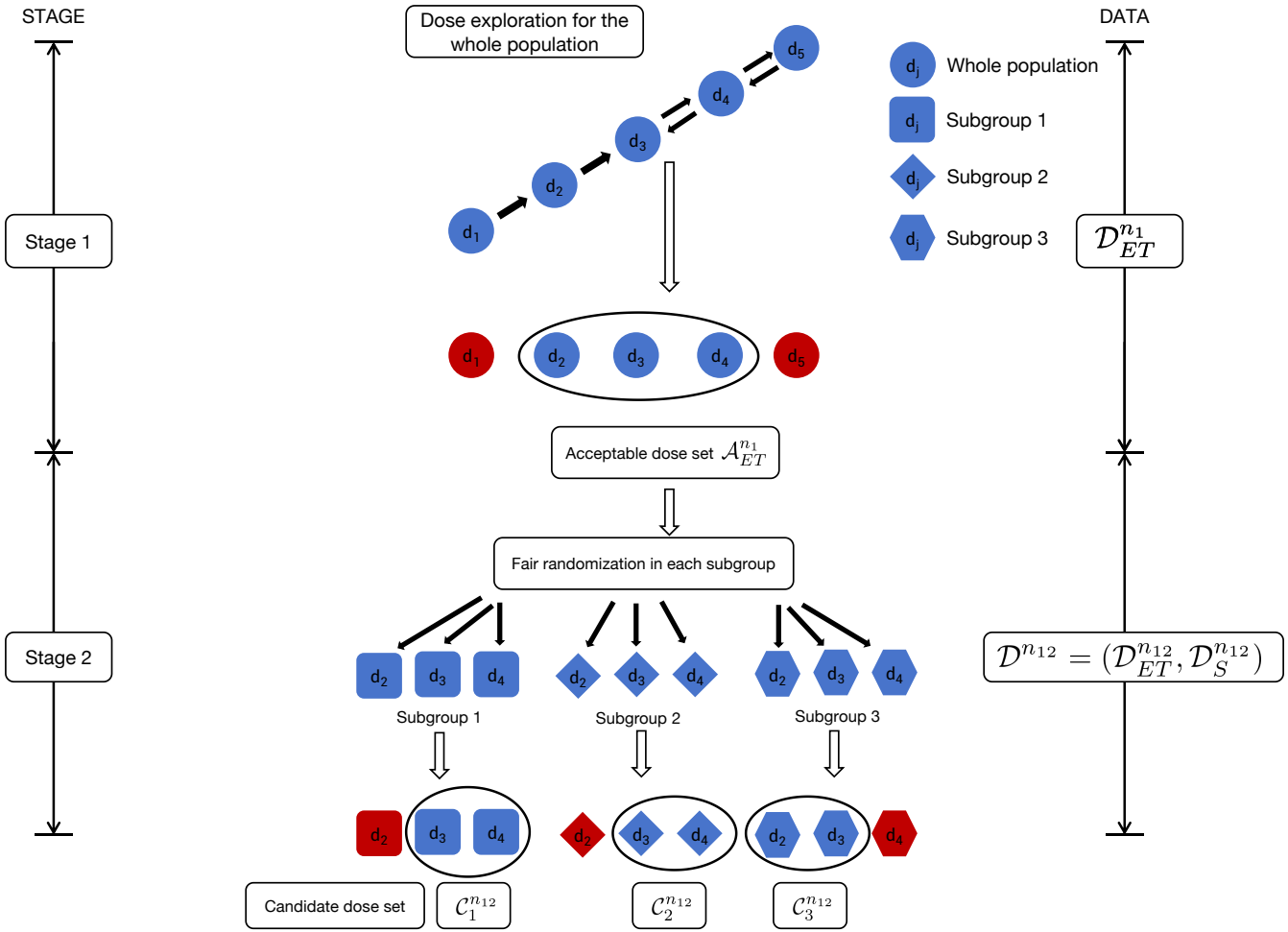
  In our simulated design, we used $p_{\mathcal{C},T,L} = .10$ and $p_{\mathcal{C},S,L} = .50$.
- **The optimal dose** for that subgroup is the acceptable dose that maximizes the estimated long-term benefit criterion,

$$d^{opt,g} = \underset{d_j \in \mathcal{C}_g^N}{\text{argmax}} \ \widehat{\phi}_S(d_j, g \mid \mathcal{D}^N). \tag{2}$$

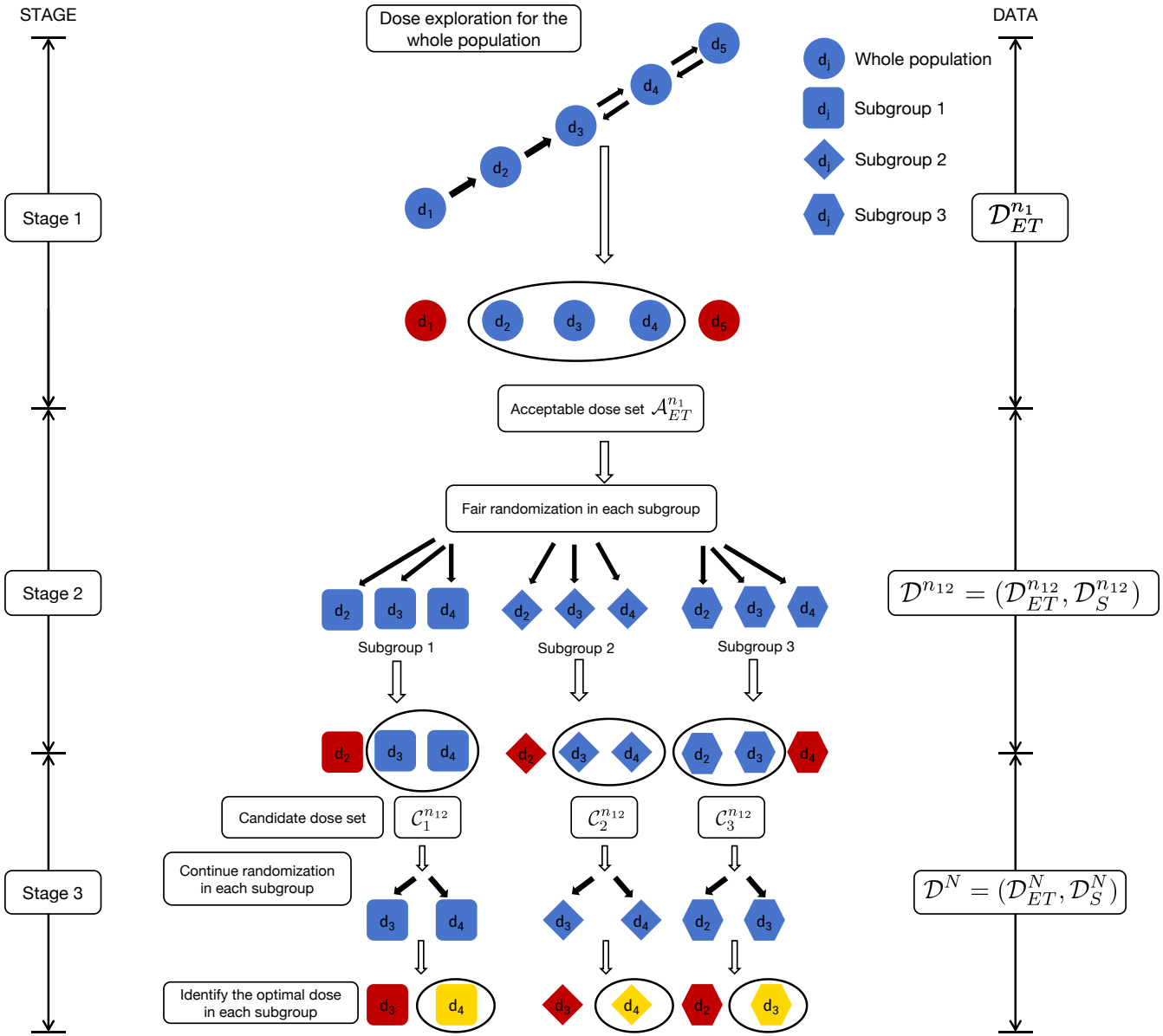
Schematic for the PGen I-II design



Schematic for the PGen I-II design

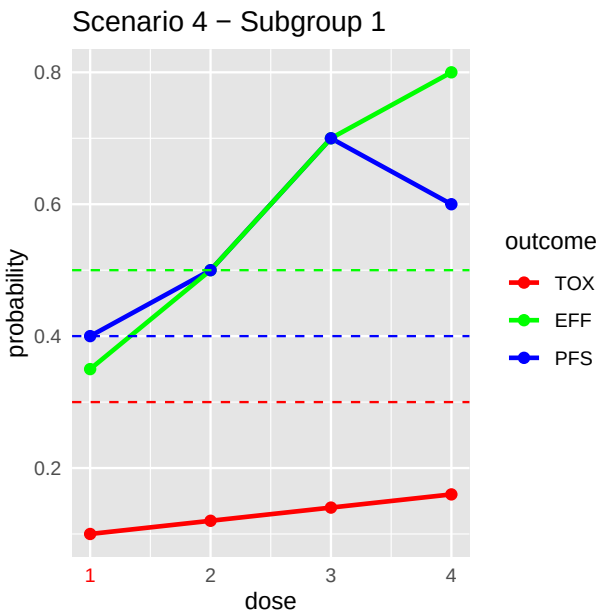


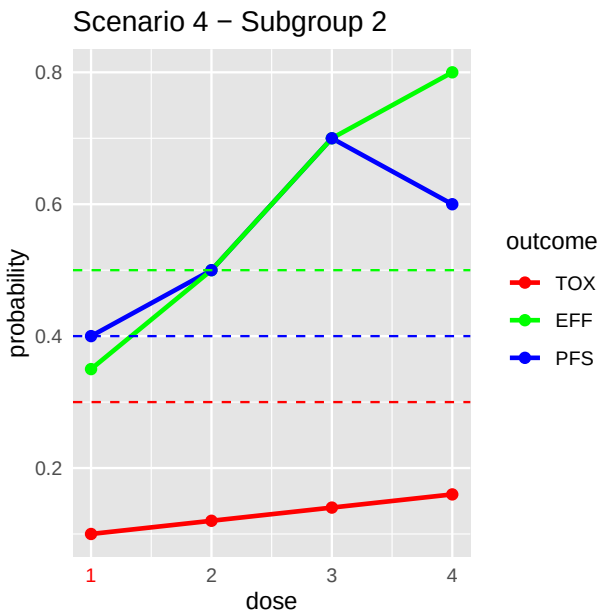
Schematic for the PGen I-II design



Section Overview

Simulation


Scenario 4 − Subgroup 1
probability
0.8
0.6
0.4
0.2
1
2
3
4
dose
outcome
TOX
EFF
PFS


Scenario 4 − Subgroup 2
probability
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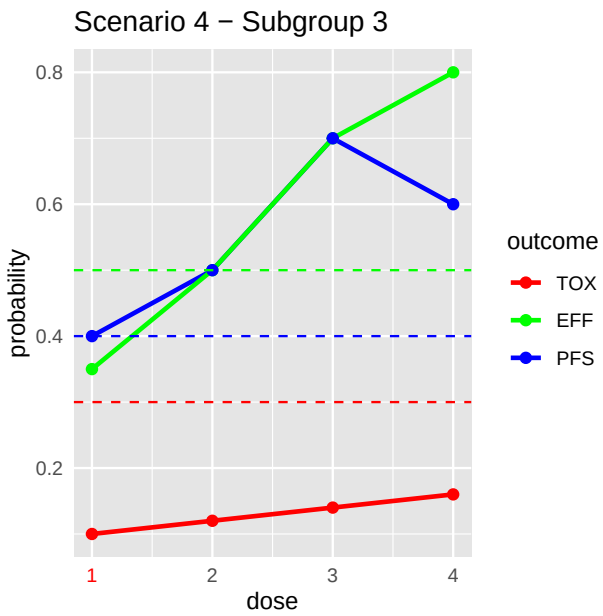
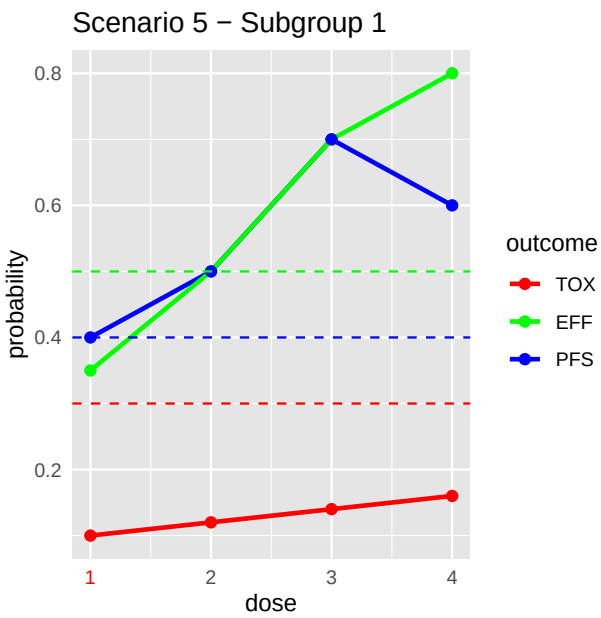
0.6
0.4
0.2
1
2
3
4
dose
outcome
TOX
EFF
PFS

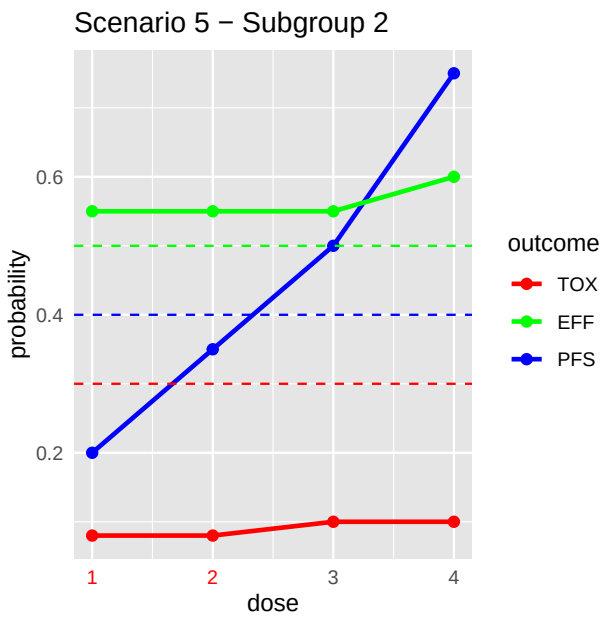

Scenario 4 − Subgroup 3
probability
0.8
0.6
0.4
0.2
1
2
3
4
dose
outcome
TOX
EFF
PFS

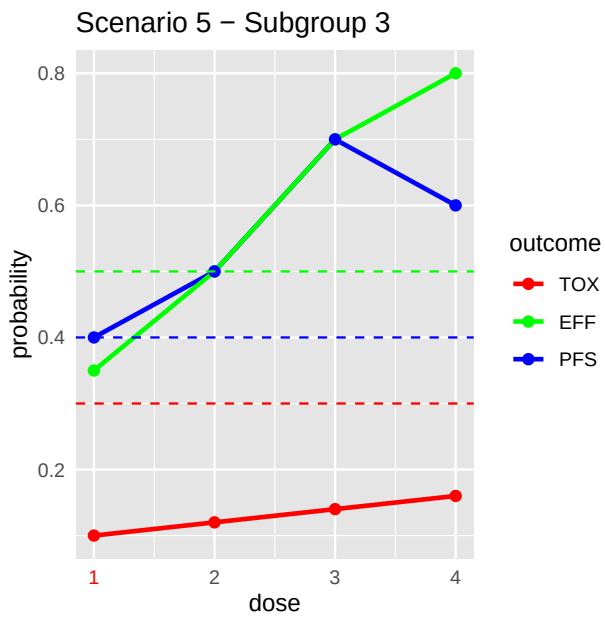
Scenario 4

	Subgroup	**g=1**					**g=2**					**g=3**				
	z_g	**1**					**1**					**1**				
	Dose(d)	$\mathbf{d_0}$	$\mathbf{d_1}$	$\mathbf{d_2}$	$\mathbf{d_3}$	$\mathbf{d_4}$	$\mathbf{d_0}$	$\mathbf{d_1}$	$\mathbf{d_2}$	$\mathbf{d_3}$	$\mathbf{d_4}$	$\mathbf{d_0}$	$\mathbf{d_1}$	$\mathbf{d_2}$	$\mathbf{d_3}$	$\mathbf{d_4}$
	$\pi_T^{\text{true}}(1 \mid d, g)$		0.10	0.12	**0.14**	0.16		0.10	0.12	**0.14**	0.16		0.10	0.12	**0.14**	0.16
	$\pi_E^{\text{true}}(1 \mid d, g)$		0.30	0.30	**0.20**	0.15		0.30	0.30	**0.20**	0.15		0.30	0.30	**0.20**	0.15
	$\pi_E^{\text{true}}(2 \mid d, g)$		0.35	0.50	**0.70**	0.80		0.35	0.50	**0.70**	0.80		0.35	0.50	**0.70**	0.80
	$\phi_{ET}^{true}(d, g)$		54.0	65.1	**76.9**	82.5		54.0	65.1	**76.9**	82.5		54.0	65.1	**76.9**	82.5
	$\phi_S^{true}(d, g)$		0.40	0.50	**0.70**	0.60		0.40	0.50	**0.70**	0.60		0.40	0.50	**0.70**	0.60
PGen I-II	Selection %	2.3	4.1	6.4	**78.8**	8.4	2.1	3.6	4.7	**81.1**	8.5	2.2	4.5	4.4	**81.4**	7.5
	Patients		8.1	11.1	**13.6**	11.5		8.5	11.1	**13.5**	11.5		11.0	14.5	**18.1**	15.2
PGen I-II-Comb	Selection %	2.2	2.2	5.5	**81.2**	8.9	2.2	2.2	5.5	**81.2**	8.9	2.2	2.2	5.5	**81.2**	8.9
	Patients		7.7	11.3	**13.7**	11.6		8.0	11.2	**13.8**	11.5		10.6	14.7	**18.3**	15.3
PGen I-II-ET	Selection %	2.0	1.2	4.5	**14.1**	78.2	2.0	1.0	4.5	**14.2**	78.3	1.9	1.6	4.2	**13.7**	78.6
	Patients		8.1	11.2	**13.5**	11.6		8.4	11.1	**13.5**	11.5		11.0	14.4	**17.9**	15.4
PGen I-II-Sep	Selection %	2.3	11.7	17.3	**58.8**	9.9	2.5	14.4	17.6	**56.3**	9.2	2.1	11.4	15.3	**61.9**	9.3
	Patients		8.3	11.1	**13.4**	11.5		8.6	11.0	**13.5**	11.3		11.2	14.6	**17.9**	15.2

Simulation Settings



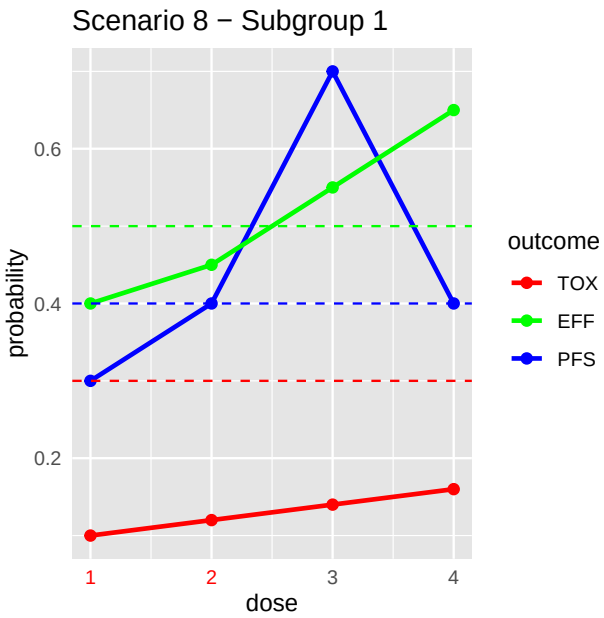


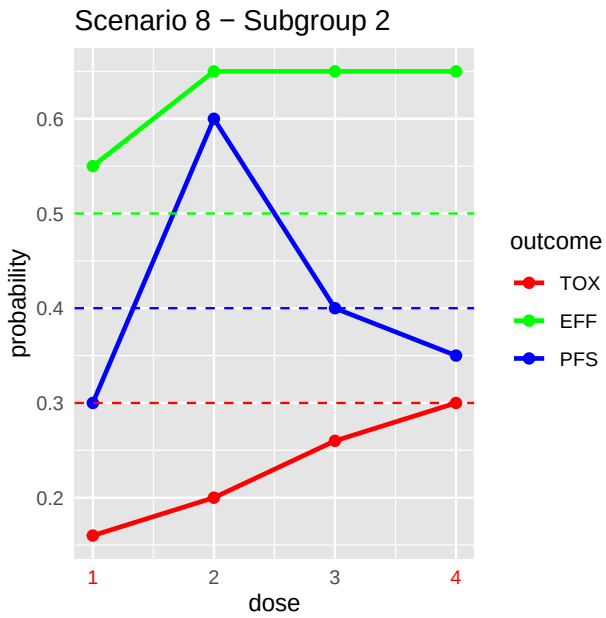


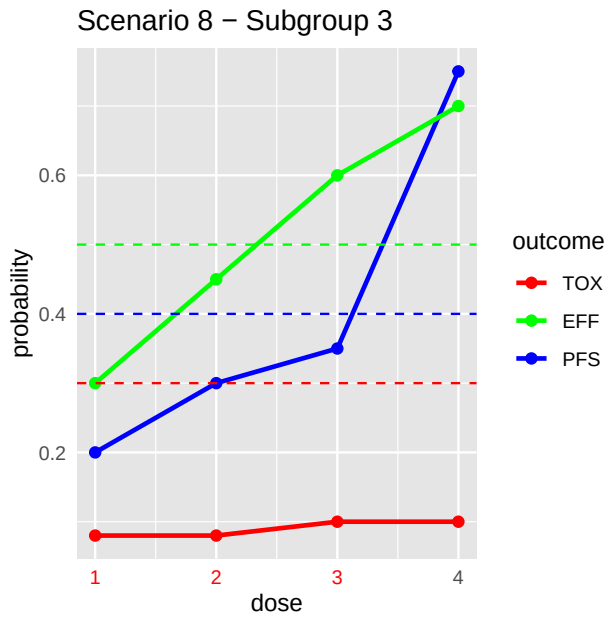
Scenario 5

	Subgroup	**g=1**					**g=2**					**g=3**				
	z_g	**1**					**2**					**1**				
	Dose(d)	$\mathbf{d_0}$	$\mathbf{d_1}$	$\mathbf{d_2}$	$\mathbf{d_3}$	$\mathbf{d_4}$	$\mathbf{d_0}$	$\mathbf{d_1}$	$\mathbf{d_2}$	$\mathbf{d_3}$	$\mathbf{d_4}$	$\mathbf{d_0}$	$\mathbf{d_1}$	$\mathbf{d_2}$	$\mathbf{d_3}$	$\mathbf{d_4}$
	$\pi_T^{\text{true}}(1 \mid d, g)$		0.10	0.12	**0.14**	0.16		0.08	0.08	0.10	**0.10**		0.10	0.12	**0.14**	0.16
	$\pi_E^{\text{true}}(1 \mid d, g)$		0.30	0.30	**0.20**	0.15		0.40	0.40	0.40	**0.35**		0.30	0.30	**0.20**	0.15
	$\pi_E^{\text{true}}(2 \mid d, g)$		0.35	0.50	**0.70**	0.80		0.55	0.55	0.55	**0.60**		0.35	0.50	**0.70**	0.80
	$\phi_{ET}^{true}(d, g)$		54.0	65.1	**76.9**	82.5		73.3	73.3	72.6	**75.0**		54.0	65.1	**76.9**	82.5
	$\phi_S^{true}(d, g)$		0.40	0.50	**0.70**	0.60		0.20	0.35	0.50	**0.75**		0.40	0.50	**0.70**	0.60
PGen I-II	Selection %	2.4	7.7	10.3	**67.3**	12.3	5.3	2.2	4.7	24.0	**63.8**	2.3	7.7	10.1	**67.1**	12.8
	Patients		9.5	11.6	**12.8**	10.6		9.5	11.4	13.1	**10.8**		12.7	15.2	**17.3**	14.1
PGen I-II-Comb	Selection %	4.0	2.0	4.0	**64.0**	26.0	4.0	2.0	4.0	64.0	**26.0**	4.0	2.0	4.0	**64.0**	26.0
	Patients		9.1	12.4	**12.2**	10.6		9.5	12.1	12.8	**10.9**		11.6	15.5	**16.7**	14.6
PGen I-II-ET	Selection %	1.7	4.3	5.4	**18.8**	69.8	1.0	10.9	8.6	18.4	**61.1**	1.5	3.8	5.8	**18.5**	70.4
	Patients		9.5	11.6	**12.8**	10.6		10.3	11.5	12.6	**10.6**		12.7	15.1	**17.3**	14.1
PGen I-II-Sep	Selection %	2.1	13.5	14.9	**59.5**	10.0	6.1	3.0	4.1	18.7	**68.1**	2.4	11.6	15.9	**61.8**	8.3
	Patients		9.6	11.6	**12.7**	10.6		9.4	11.4	13.1	**10.9**		12.8	15.1	**17.4**	14.1

Simulation Settings







Scenario 8

	Subgroup	**g=1**					**g=2**					**g=3**				
	z_g	**1**					**2**					**3**				
	Dose(d)	$\mathbf{d_0}$	$\mathbf{d_1}$	$\mathbf{d_2}$	$\mathbf{d_3}$	$\mathbf{d_4}$	$\mathbf{d_0}$	$\mathbf{d_1}$	$\mathbf{d_2}$	$\mathbf{d_3}$	$\mathbf{d_4}$	$\mathbf{d_0}$	$\mathbf{d_1}$	$\mathbf{d_2}$	$\mathbf{d_3}$	$\mathbf{d_4}$
	$\pi_T^{\text{true}}(1 \mid d, g)$		0.10	0.12	**0.14**	0.16		0.16	**0.20**	0.26	0.30		0.08	0.08	0.10	**0.10**
	$\pi_E^{\text{true}}(1 \mid d, g)$		0.20	0.20	**0.20**	0.15		0.35	**0.30**	0.30	0.30		0.30	0.30	0.25	**0.20**
	$\pi_E^{\text{true}}(2 \mid d, g)$		0.40	0.45	**0.55**	0.65		0.55	**0.65**	0.65	0.65		0.30	0.45	0.60	**0.70**
	$\phi_{ET}^{true}(d, g)$		54.9	58.2	**65.3**	70.9		69.2	**74.0**	72.0	70.6		50.7	62.4	72.0	**78.4**
	$\phi_S^{true}(d, g)$		0.30	0.40	**0.70**	0.40		0.30	**0.60**	0.40	0.35		0.20	0.30	0.35	**0.75**
PGen I-II	Selection %	12.0	2.5	9.6	**70.0**	5.9	14.4	5.0	**64.2**	11.1	5.3	18.3	0.8	2.7	5.7	**72.5**
	Patients		9.4	11.3	**12.3**	10.7		9.6	**11.8**	12.0	10.8		11.5	14.2	16.3	**16.6**
PGen I-II-Comb	Selection %	8.7	0.8	14.8	**41.8**	33.9	8.7	0.8	**14.8**	41.8	33.9	8.7	0.8	14.8	41.8	**33.9**
	Patients		8.5	11.3	**12.6**	11.1		8.6	**11.1**	12.8	11.3		11.7	15.1	16.8	**15.2**
PGen I-II-ET	Selection %	2.8	10.1	11.8	**14.3**	61.0	3.1	21.4	**15.9**	16.4	43.2	4.3	5.3	14.0	13.8	**62.6**
	Patients		9.7	11.1	**11.9**	11.0		10.0	**11.1**	12.0	10.9		12.2	14.9	16.4	**15.3**
PGen I-II-Sep	Selection %	10.5	3.2	8.8	**76.1**	1.4	12.3	4.8	**69.5**	11.1	2.3	18.4	0.9	1.5	3.7	**75.5**
	Patients		9.6	11.3	**12.3**	10.7		9.7	**11.9**	12.1	10.6		11.5	14.0	16.2	**16.7**

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Questions?

Thank you for your attention.

Please feel free to ask any questions.