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Proposal of Efficient Clinical Trials by using the Genomic Information

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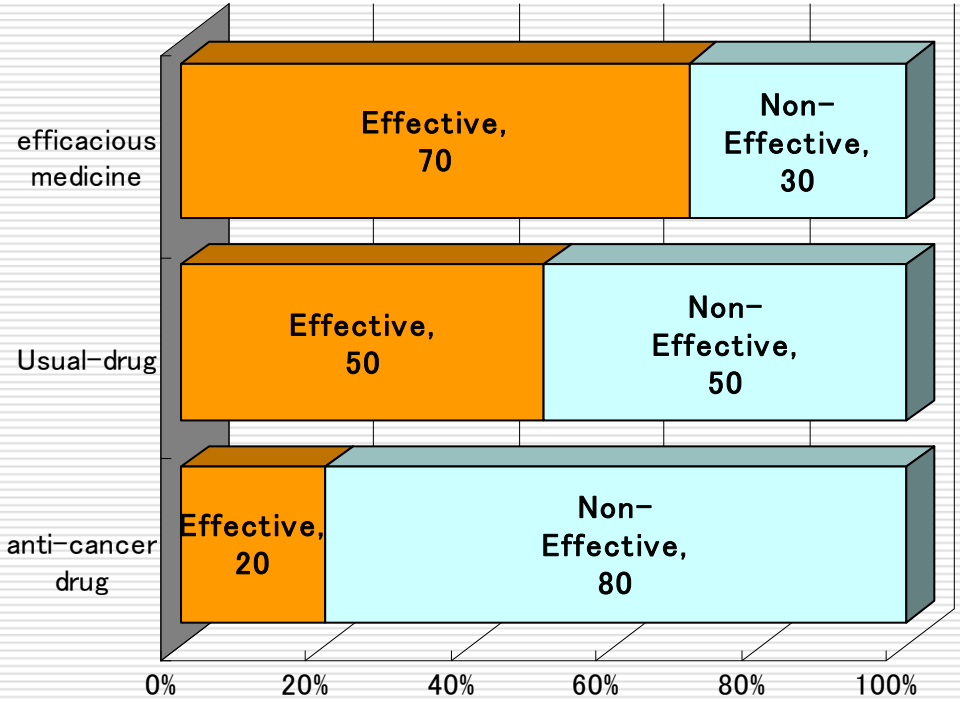
1. What does Efficacious medicine mean?



In a new drug's clinical trial, it is approved and allowed to be marketed if it can successfully show statistically significant effect compared to a placebo, a control drug (existing treatment) or a usual drug.

Even if it effects only 20% of patients like the anti-cancer drug.

The difference between responders and non-responders is often explained in terms of difference in subjects' profile. When the subjects have largely similar profiles, the difference is explained by a term called "constitution".

2. Personalized Medicine

- It is expected that the drug and dose can be determined based on the genetic information including SNPs (single nucleotide polymorphisms) of each patient.
- When personalized medicine becomes more available, unnecessary administration of drugs to non-responders can be avoided, and dose can be optimized.
- Also, medical expense in general can be reduced, and unexpected adverse effect can be avoided.

These advantages are beneficial not only to the patients concerned, but also to the society as a whole.

3.Comparison of clinical trials

Design / ***Trials***	***Determination of usage and dose***	***Determination of the number and profile of subjects to be enrolled***	***Medical expenses***	***Risk of Adverse Events***
Current	Effect and adverse effect are determined based on the average.	Determined using sample size estimation equation	Rises due to unnecessary administration to non-responders	Unknown adverse event
Personalized	Can be optimized for each patient according to the patient's capacity of drug metabolizing enzyme (e.g., CYP2C29, CYP2D6)	Can be selected and response rate can be improved based on relevant genetic information	Can be cut because unnecessary administration to non-responder can be avoided	Can be minimized based on information on causative gene and minimization of drug doze.

4.Purpose

The pharmaceutical companies are not actively engaged in the development of “personalized medicine” because ･･･

1. they are afraid of lost revenue, and other drugs would not be prescribed to non-responders.
2. the procedure for handling genetic information is not fully established yet.

The purpose of this study is to clarify the benefit and loss for the pharmaceutical companies when they adopt "personalized medicine", that is, when they take advantage of genetic information in their clinical trials. Particularly, the benefit for the pharmaceutical companies in terms of following two points will be analyzed.

1. ***Development cost of new drug and period of clinical trial can be reduced because a clinical trial needs less subjects,***
2. ***The new drug can be placed on the market earlier because the development period can be shortened***

5.Methods

Generally, the sample size of a clinical trial is calculated according to an equation as follows, for example.[1][2][3]

$$n = \frac{\left\{ Z_{\alpha}\sqrt{2\overline{P}(1-\overline{P})} + Z_{\beta}\sqrt{P_1(1-P_1)+P_2(1-P_2)} \right\}^2}{(P_1 - P_2)^2}$$

$$where \quad \overline{P} = \frac{P_1 + P_2}{2}$$

(In case of chi-square test for the difference in ratio between two groups)

N: Number of necessary samples
P_1: Response rate in investigational drug group
P_2: Response rate in control drug group
Z_{α}: Value calculated from significance level (generally 1.96 at 5%)
Z_{β}: Value calculated from power (generally 0.84 at 80%)

5.Methods(2) Power Curve

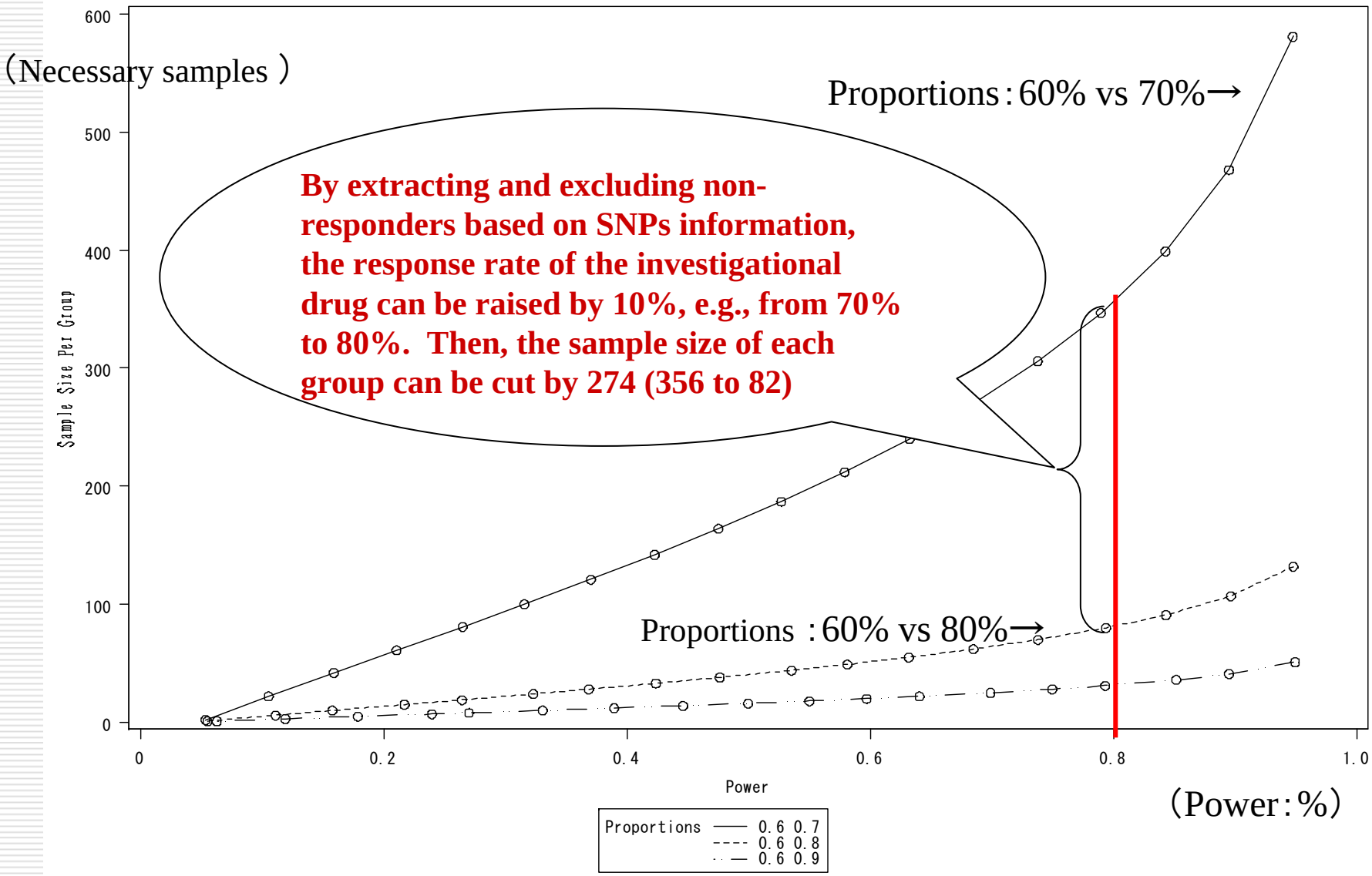


Fig. 1 Response rate and necessary sample size

6.Results

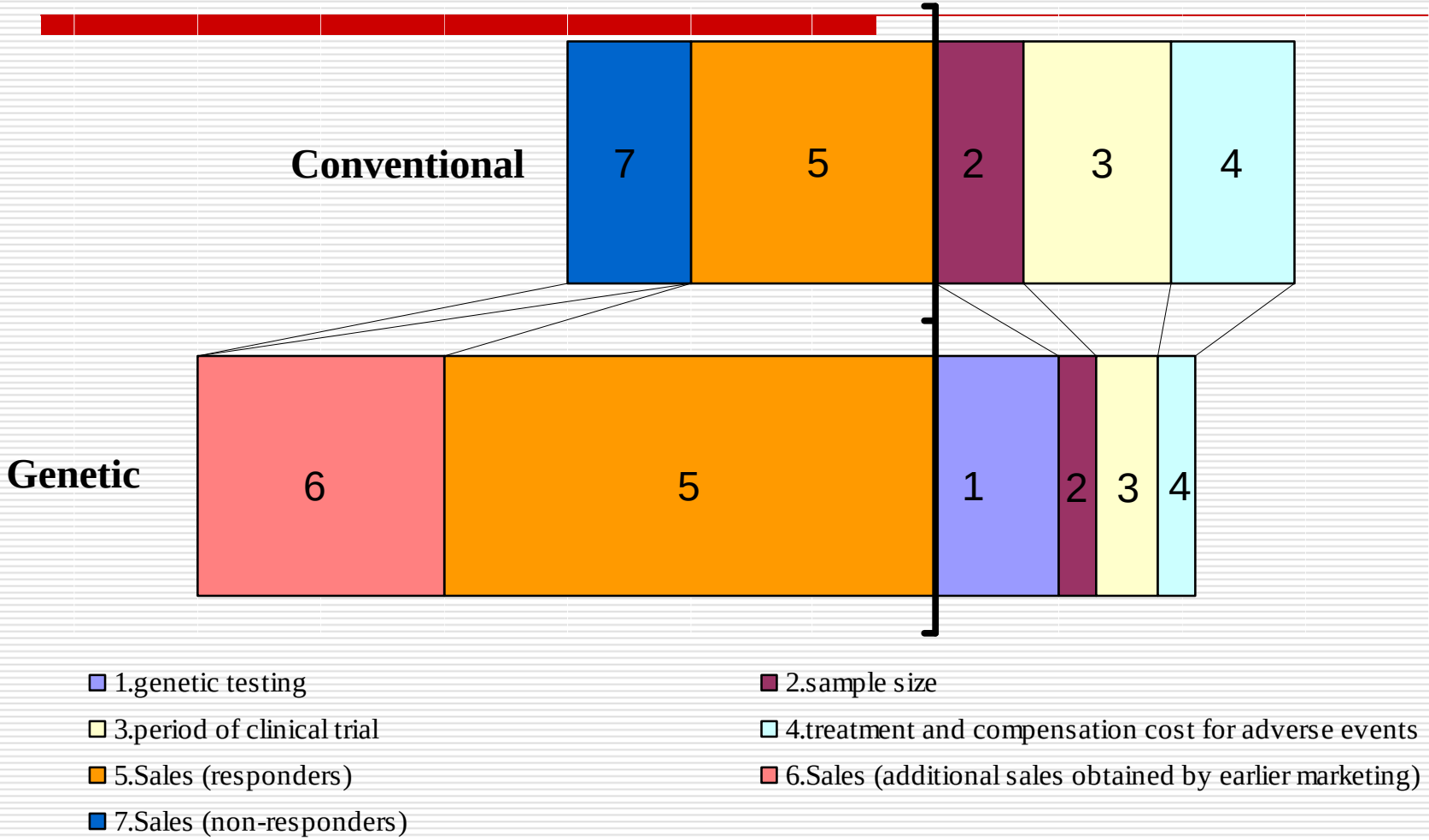
- In total, this means 548(274 per each group) cases will be unnecessary.
- This effect is more apparent when the response rate is low.
- When any known adverse event (AEs) is anticipated due to causative gene, the patients concerned can be excluded from the investigational drug group.
- Besides the safety enhanced by avoidance of an adverse event, the treatment for adverse event can be avoided.

For the society in general, medical expense can be reduced, and for the pharmaceutical companies, compensation or indemnification cost can be avoided.

(ex. In U.S, more than 2 million patients forced to be hospitalized because of the adverse effects in every year, hundred thousand people dies, and more than 70 billion health care cost wasted.)

7. Conclusion

Fig2 Profit-cost structure in conventional clinical trial and clinical trial based on genetic information



7. **Conclusion** (2)

According to our estimation, a clinical trial that takes advantage of genetic information is superior to a conventional clinical trial in terms of cost and profit.

1. **The development cost can be reduced by 5.5 million US dollar (10 thousand dollar /sample)[4].**
2. **Furthermore, the development period can be shortened by about 120 for 548 samples[4].**
3. **But, on the other hand, the sale for non-responders will be lost. However, because the drug can be marketed a120 days earlier than usual, the projected sales for the 120 days should be factored.**
4. **In addition, risk of adverse events can be mitigated by screening patients based on genetic information such as SNPs.**

7. **Conclusion** (3)

- **Reduction in compensation and indemnification cost, and reduction in medical expenses will be beneficial to the patients, the pharmaceutical companies, and the society as a whole.**
- **In a clinical trial using genetic information, temporary increase in process and cost may be inevitable. But, when genetic testing comes to be widely used, the cost will drop.**
- **Additionally, as the databases of genetic information are growing, it is apparent that the genetic testing will be simplified.**
- **We are now planning profit simulation based on a clinical trial that was actually conducted.**

Acknowledgments

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[4] In the text, the estimation is based on the average cost of a clinical trial.

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