Economic Advantage of Pharmacogenomics
- Clinical Trials with Genetic 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. Pharmaceutical Manufacturers think ⋅⋅⋅? (n=20 Companies)

- Afraid of reduced market size?
  - Yes: 70%
  - No: 30%

- PGX clinical trial is difficult?
  - Yes: 65%
  - No: 35%

Because ⋅⋅⋅
- IRB does not approve. (30%)
- MHLW has not established a guideline yet (55%)
- Not fully understood by patients and other relevant parties (85%)

But ⋅⋅⋅
- With the establishment of a guideline by regulatory authorities (95%)

PGX clinical trial is desirable?
3. 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.
3. Comparison of clinical trials

<table>
<thead>
<tr>
<th>Items</th>
<th>Current</th>
<th>Personalized</th>
</tr>
</thead>
<tbody>
<tr>
<td>Determination of usage and dose</td>
<td>Effect and ADR are determined based on the average.</td>
<td>Can be optimized for each patient according to the patient's capacity of drug metabolizing enzyme (e.g., CYP2C29, CYP2D6)</td>
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<tr>
<td>Determination of the number and profile of subjects to be enrolled</td>
<td>Determined using sample size estimation equation</td>
<td>Can be selected and response rate can be improved based on relevant genetic information</td>
</tr>
<tr>
<td>Medical expenses</td>
<td>Rises due to unnecessary administration to non-responders</td>
<td>Can be cut because unnecessary administration to non-responder can be avoided (pharmaceutical companies may lose their sales for non-responders)</td>
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<tr>
<td>Risk of Adverse Events</td>
<td>Unknown adverse event</td>
<td>Can be minimized based on information on causative gene and minimization of drug doze.</td>
</tr>
<tr>
<td>Cost of Clinical Trial</td>
<td>Usual recruiting cost</td>
<td>Temporarily increased because of the Genetic test</td>
</tr>
<tr>
<td>Difficulties of Recruiting the subject</td>
<td>Have to get consent from test subjects</td>
<td>Have to get the other consent for genomic information.</td>
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5. Methods

Generally, the sample size of a clinical trial is calculated according to an equation as follows, for example

\[
n = \left\{ \sqrt{\frac{2\bar{P}(1-\bar{P})}{P_1(1-P_1) + P_2(1-P_2)}} + Z_{\beta} \sqrt{\frac{P_1(1-P_1) + P_2(1-P_2)}{(P_1 - P_2)^2}} \right\}
\]

where \( \bar{P} = \frac{P_1 + P_2}{2} \)

(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_\alpha: Value calculated from significance level (generally 1.96 at 5%)
Z_\beta: Value calculated from power (generally 0.84 at 80%)
By extracting and excluding non-responders based on SNPs information, the response rate of the investigational drug can be raised by 10%, e.g., from 70% to 80%. Then, the sample size of each group can be cut by 274 (356 to 82).
5. Methods (3)

When any known adverse event (AEs) is anticipated due to causative gene, the patients concerned can be excluded from the investigational drug group. Thus, the risk of adverse events can be reduced.

- the extra cost for screening is 40 thousand yen $\times 712 (358\times2) = 28.48$ million yen (about 240 thousand dollars).
- However, should ADR occur, compensation about 120 million yen (1.1 million dollars) per a subject would be necessary in the case of death, and compensation about 490 million yen (4.3 million dollars) would be necessary in the case of permanent disability.

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

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

- **Conventional**
  - Benefit: 7, 5
  - Cost: 2, 3, 4

- **Genetic**
  - Benefit: 6, 5
  - Cost: 1, 2, 3, 4

Legend:
- 1. Genetic testing
- 2. Sample size
- 3. Period of clinical trial
- 4. Treatment and compensation cost for adverse events
- 5. Sales (responders)
- 6. Sales (additional sales obtained by earlier marketing)
- 7. Sales (non-responders)
7. Conclusion (2)

- **Response rate**: 70% → 80%
- **Reduction**: (356 - 82) × 2 = 548 days
- **Reduction per subject**: 548 ÷ 3.5 = 157 days
- **Additional 10 days for genetic tests**: 356 × 2 = 712, Average 3.5 days per one subject.
- **Sale for non-responders lost**: 157 - 10 = 147 days earlier placed on the market.
- **AE treatment cost**: 157 - 10 = 147 days
- **Sale for non-responders**: US350 $ × 712 = US240 thousand $
7. Conclusion (3)

- Furthermore, the screening of relevant SNP can markedly reduce the AE and ADR during a clinical trial.

- This is a great benefit for the pharmaceutical companies given that the compensation for ADR is huge (hospitalization, death), and accompanying loss of credit is heavy for the company.

- What is more, the medical cost of the society as a whole can be saved as well. Thus, it can be concluded that pgx clinical trial is highly beneficial for the patient, company and the society.
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