Discussion Paper

Evaluation policy of the companion diagnostics system using next generation sequencing (draft)

1) Evaluation of clinical performance

The efficacy and safety of drugs for which patients are selected based on the classification criteria of genetic variations that are detected by the use of next generation sequencing (NGS) must be evaluated based on the clinical trial results in those patients selected by the relevant classification criteria. Therefore, in the analysis program using NGS, the clinical utility of selecting patients based on the proposed classification criteria needs to be evaluated.

In this evaluation of clinical utility, in principle, it is required to use the clinical specimens of subjects carrying the entire range of genetic variations indicated for the corresponding drug. On the other hand, in cases where clinical utility using the clinical specimens cannot be evaluated according to the above principle because of the enormous number of types of genetic variations indicated for the corresponding drug and the difficulty to obtain the clinical specimens corresponding to all the genetic variations in a clinical study, the evaluation of analytical performance using synthetic constructs is also considered. Based on the evaluation result, it is necessary to explain in the marketing authorization application that NGS test to be applied has proper clinical utility.

Although clinical significance of genetic variations detected in NGS test should be explained based on the results of clinical confirmatory studies of the drug, there may be cases where it is difficult to collect cases necessary for evaluation of clinical significance for each genetic variation when the number of types of genetic variations indicated for the corresponding drug is enormous. In such cases, importance is attached to the evaluation of the scientific rationale for the classification criteria of genetic variants and the selection of patients to be treated based on the classification criteria (classification process).

Specifically, the following points are considered: (i) the appropriateness of the scientific findings (relation between the types of genetic variants and pathogenesis of the disease[*2], nonclinical study results, etc.) used as grounds for the classification of genetic variants[*1]; (ii) the relationship between the classification of genetic variants and the mechanism of action of the drug; and (iii) the evaluation of the process (procedures, algorithms, etc.) on which the selection of patients is based.

*1: For example, classifications such as “pathogenic variants,” “variants with unknown clinical significance,” and “clinically insignificant gene polymorphism” are conceivable.
*2: For example, classification into genetic variants that cause diseases due to gain of function, functional impairment, or defect of a particular protein and other variants is considered.

2) Evaluation of analytical performance

Also, for companion diagnosis system using NGS, it must be demonstrated that the test has

appropriate analytical performance like conventional companion diagnostics. Moreover, the test does not only confirm the presence or absence of specific generic variations, but also must correctly read sequence information and must determine whether detected generic variations are ones indicated for the corresponding drug. After taking these steps into consideration, it is necessary to evaluate analytical performance as the test system. While it is essential, as a rule, to use clinical specimens in the evaluation, the following ideas will be applied to cases where evaluation using the clinical specimens of all genetic variants is difficult due to reasons such as the presence of enormous patterns of genetic variants to be detected, provided that the scientific rationale of using the genetic variants concerned is explained. It should be noted that the concrete details of the evaluation need to be individually discussed in consideration of the characteristics of NGS used and the genetic variants to be tested.

- For genetic variants for which clinical specimens are not available, analytical performance is evaluated using synthetic constructs.
- Furthermore, analytical performance should be evaluated using multiple sequence sets from among genetic variants to be tested in terms of detection sensitivity and specificity. In this case, it is necessary to explain in the marketing authorization application why selected sequence sets are considered proper in evaluating analytical performance of the test system. When homopolymer and others that are likely to cause errors in analyzing base sequence are included in DNA domains to be tested, analytical performance for them should be also evaluated.

3) Handling of the genome database updated after approval

It is conceivable that the database of genomic information, etc. will be updated based on new scientific findings after the approval of the companion diagnosis system. In principle, by confirming the following matters at the review of the marketing authorization application, even when new scientific findings are obtained after the approval, administrative procedures (submission of partial change application) may be not necessary for update of the database and the use of the database updated after the approval as a part of the companion diagnostic system may be accepted. It should be noted that the necessity of administrative procedures for changing software used for variant classification and/or variant interpretation needs to be individually judged.

- The appropriateness[*3] of the classification criteria[*1] of genetic variants indicated for the drug
- The appropriateness[*3, 4] of the variant classification process based on the above criteria

Because the corresponding drug must be administered only to patients who are judged to be appropriate at institutions and under physicians with adequate knowledge about the efficacy and safety of the drug to be approved, sufficient information must be provided and attention drawn to it by means of package inserts and other materials referring to the latest information such as the practice guidance of related societies.

*3: The appropriateness of the classification criteria and classification process is important because these should be fixed as far as possible even when the classification of variants as outputs may be changed based on new scientific findings at the time of updating the database.
*4: The applicant for marketing authorization of the drug is required to describe the matter.

End of text