

Questions for DTC Advisory Panel Meeting

Clinical (medical) genetic tests that provide clinical or health information such as for diagnosis, prevention or treatment of a disease are considered to be medical devices under the Federal Food Drug and Cosmetic Act. Tests that do not provide such information are not considered medical devices; examples of tests not used for medical purpose include ancestry tests, forensic tests, and tests for non-medical phenotypes such as hair curliness.

Here, we consider questions related to clinical genetic tests that are offered directly to consumers (DTC). The questions below address the risks and benefits of DTC genetic tests, how risks may be mitigated, and the level of evidence that is needed to support clinical DTC genetic test claims.

1. What are the risks and benefits of making clinical genetic tests available for direct access by a consumer without the involvement of a clinician?

- a) DTC genetic tests are offered to a mixed population consisting of symptomatic and asymptomatic individuals, with or without known family history of disease, with varying demographic features, and with varying access to medical expertise. Please provide your assessment of the following questions, using the specific categories of tests listed below as examples
- Is there value, considering likely benefits and risks, in offering clinical genetic tests directly to consumers (DTC) rather than through more traditional means?
 - Should any of the categories or specific genetic tests listed below, or other genetic categories/tests, be offered solely upon prescription?
 - For those that can be DTC, are there results for certain genetic tests that should be routed through a clinician / specialist, even if the test is offered DTC?

An extensive list of tests that are being offered is available in Appendix 2. Categories and some examples to consider are:

| Category | Description | Examples |
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| Carrier tests | Tests intended to show that a person is a genetic carrier of a condition, so that although they are not themselves affected, there is a risk they may have affected children | Cystic fibrosis, Gaucher Disease, Fanconi Anemia, Tay-Sachs Disease, muscular dystrophies |
| Pre-symptomatic | Tests intended to predict that an asymptomatic person has a high probability of developing a condition | BRCA test for breast cancer, mutation testing in autosomal dominant single gene disorders such as Huntington Disease |
| Susceptibility/pre-dispositional tests (risk assessment) | Tests that estimate the risk (relative or absolute) that an individual will develop a condition | APOE for Alzheimer's disease, age related macular degeneration, rheumatoid |

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| | | arthritis, bladder cancer, melanoma, lung cancer, heart attack, type 1 diabetes, obesity, venous thromboembolism, Parkinson's disease |
| Pharmacogenetic | Tests that predict drug effect | Response to warfarin, Abacavir, clopidogrel, irinotecan, statins, Tamoxifen, fluorouracil, hepatitis C virus treatment |
| Nutrigenetic | Tests that estimate an individual's responsiveness to a particular food/diet | How the food affects metabolism, health status and risk of disease |

- b) Should personal utility be incorporated in considerations of “clinically significant results”?
 - There may be a proportion of test users who express anxiety about reported test results. Should this be considered in assessment of safety and effectiveness?

2. What are possible mitigations against incorrect, misinterpreted, miscommunicated, or misunderstood test results for clinical genetic tests offered through DTC testing, without live counseling?

- a) Some tests lack established performance characteristics for certain populations. Should some DTC tests be offered only to certain consumers (e.g., certain ethnic or geographically-defined groups)?
- b) When might provision of information about the risks, benefits, and limitations of clinical DTC genetic tests be sufficient to:
 - Enable informed decisions by consumers on whether to order these tests (pre-test information)?
 - Mitigate the risk that consumers will be misled by or incur harm from acting on test results (post-test information)?
- c) Are there other essential risk mitigation tools for providing DTC test results?
- d) In testing general populations for rare conditions/markers, the false positive rate (the proportion of positive results that are false) can be significant.
 - Should DTC test reports recommend confirmatory or supplemental testing when positive results are obtained for a rare condition/marker?
 - Should the test be offered only to populations with higher prevalence of condition/marker?
- e) Should medically actionable results for certain DTC tests be always routed through a clinician / specialist?
- f) What should be the involvement of a genetic counselor when ordering the test or providing DTC genetic test results?

- g) Many companies currently marketing DTC genetic tests report genetic test results for risk as relative measures (relative risks, odds ratios, etc) based on currently available publications. The way in which risk information is communicated may affect the individual's perception of the magnitude of that risk.
 - Are some measures of risk more easily understood by consumers, e.g., relative risk, absolute risk, or descriptive categories such as low-average-high risk?
 - Should test reports include warnings/information about additional factors (beyond the reported genetic markers) that may refine the individual's specific risks?

3. FDA requires valid scientific evidence (typically with both analytical and clinical validation) in order to determine that medical devices, including home-use and over-the-counter (OTC) tests, are safe and effective. Results of clinical DTC tests may be used in many ways including for patient management, for health improvement, or for “personal interest.” Do these different uses suggest different evidence requirements for supporting DTC genetic test claims?

- a) Should analytical and clinical performance characteristics for clinical DTC genetic tests be different than those for genetic tests offered through physicians?
 - Given the possibility of fewer risk mitigation options in DTC testing than when the testing is offered through a physician, should DTC tests have more stringent performance characteristics, e.g., greater test accuracy?
 - What are appropriate evidence levels to support DTC test performance characteristics?
- b) What may be advantages and disadvantages of providing a number of genetic tests together (e.g., for certain categories listed in question 1a), vs. separately for specific indications?
- c) There is a need to develop efficient approaches for analytical validation of highly multiplexed genetic tests. One suggested approach (i.e., for cytogenetic arrays that query the entire genome) is to select and validate an appropriate subset of genetic markers, with an inference that the platform as a whole is analytically valid. Another approach is to explicitly validate each marker that is used in generating a test result.
 - Please discuss the advantages and disadvantages of these (or other suitable) approaches to validation of highly multiplexed DTC tests.
 - If the first suggested approach were adopted, for DTC tests reporting on a number of different disorders, what strategy should be used to select the representative subset of markers.
 - Should the subset be enriched with markers that pose an analytical challenge?
 - Should the subset of markers include markers from each of the relevant disorders?
 - Would adoption of the first suggested approach make it advisable to perform confirmatory testing of the results of highly multiplexed clinical DTC genetic tests?

- d) Should a contribution of the test result beyond the current risk factors (e.g., family history) be demonstrated?
- e) DTC companies may validate tests using results and information from current customers. Important characteristics of this population may differ from the characteristics of the general population to whom the test is offered. What considerations are necessary concerning these differences?
- f) Usually, case-control studies in published literature provide information about particular markers and corresponding odds ratios. Differences in selection of publications, in approaches for summarizing the information about odds ratios, and in stratifying odds ratios into risk categories can yield different test results, e.g., one approach may report high risk while another reports moderate risk. Is it important to avoid inconsistencies in how the information in the published papers is used?
 - Should there be a separate group of experts formed who can summarize information from existing literature?
- g) What is an appropriate study design for a DTC test that reports absolute risk (relative risks)? What is an appropriate study design for a DTC test that reports likelihood ratios (odds ratio), or categories such as low, average, or high risk?
 - When are prospective studies in the intended use population necessary?
 - When using web-based studies, what considerations are needed about possible biases?