

Evidence of Compliance:

- ✓ Records confirming intended target

CYG.44666 PGD Report**Phase I**

If in situ hybridization (ISH) testing is performed on cells obtained from embryo biopsy for the purposes of preimplantation genetic diagnosis (PGD), the final report includes an interpretation with information on the limitations of single cell diagnosis in preimplantation embryos.

NOTE: Because only one or two cells may be collected for ISH chromosome analysis using blastomere biopsy, testing that can be conducted is limited and does not allow analysis of all chromosomes for abnormalities. Mosaicism can affect the results of PGD when blastomere biopsy is performed. Also, signal overlap, diffuse hybridization, poor hybridization or poor specimen quality can affect ISH results. Because of the inherent risk of inaccuracy of results, it is important to make patients aware of prenatal follow-up and testing options. The interpretation must be written to facilitate understanding by a non-geneticist.

REFERENCES

- 1) Munné S and Cohen J (1998) Chromosome abnormalities in human embryos. Hum Reprod Update 4, 842-855. [\[Abstract/Free Full Text\]](#)
- 2) Ruangvutilert P, Delhanty JDA, Serhal P, Simopoulou M, Rodeck CH and Harper JC. FISH analysis on day 5 post-insemination of human arrested and blastocyst stage embryos. *Prenat Diagn.* 2000; 20(7):552-60.
- 3) Ruangvutilert P, Delhanty JD, Rodeck CH and Harper JC. Relative efficiency of FISH on metaphase and interphase nuclei from non-mosaic trisomic or triploid fibroblast cultures. *Prenat Diagn.* 2000; 20(2):159-162.
- 4) Malmgren H, Sahlen S, Inzunza J, Aho M, Rosenlund B, Fridstrom M, Hovatta O, Ahrlund-Richter L, Nordenskjöld M, Blennow E. Single cell CGH analysis reveals a high degree of mosaicism in human embryos from patients with balanced structural chromosome aberrations. *Mol Hum Reprod.* 2002 May;8(5):502-10

CYG.46799 Modified FDA-Cleared/Approved Assay**Phase II**

If the laboratory modifies an FDA-cleared/approved assay, the modified procedure has been validated to yield equivalent or superior performance.

Evidence of Compliance:

- ✓ Records of validation studies for modified FDA-cleared/approved assays

REFERENCES

- 1) American College of Medical Genetics, Standards and Guidelines for Clinical Genetics Laboratories, 2021 edition.

CYG.47866 ISH Interpretation**Phase II**

If an in situ hybridization (ISH) study requires consultation with a qualified pathologist and/or a cytogeneticist for accurate interpretation, the appropriate expert is consulted and their involvement is recorded.

PREDICTIVE MARKERS

The term predictive marker as used in this section refers to in situ hybridization (ISH) biomarkers used independent of histologic findings to identify individuals who are more likely to experience a favorable or unfavorable effect from a specific (targeted) therapy, compared to individuals with the same diagnosis lacking the biomarker. Rather than confirming a specific diagnosis, these biomarkers predict responsiveness to a specific treatment among cases of the same diagnosis.

The current CAP guidelines ([CAP Guidelines](#)) relating to predictive marker testing (eg, ASCO/CAP HER2 in breast cancer) may be found at [cap.org](#) in the Protocols and Guidelines section. The guidelines are periodically updated based on new evidence. Laboratories should review updated predictive marker guidelines and promptly implement changes for items relating to requirements in the checklists (eg, validation, fixation, scoring criteria).

If digital image analysis is used, additional requirements in the Digital Image Analysis section also apply.

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CYG.47880 Report Elements

Phase I

For in situ hybridization (ISH) tests that provide independent predictive information, the patient report includes information on specimen processing, the probe, and the scoring method used.

NOTE: The following information must be included in the patient report:

1. The type of specimen fixation and processing (eg, formalin-fixed paraffin-embedded sections, air-dried imprints)
2. The probe and, if applicable, the detection system used (ie, LSAB, polymer, proprietary kit, vendor name, etc.; information on the type of equipment used is not necessary)
3. Criteria used to determine a positive vs. negative result and scoring system (eg, manual or automated)
4. Laboratory interpretation of predictive marker testing (ISH) is reported according to the manufacturer's instructions, or when available, following the structure, format, and criteria set forth in the current [CAP guidelines](#) relating to predictive marker testing (eg, ASCO/CAP HER2 testing in breast cancer and CAP/ASCP/ASCO HER2 in gastroesophageal carcinoma).
5. Limitations relating to suboptimal preanalytical factors that may impact results, such as prolonged cold ischemia time, unknown ischemia time, or over- or under-fixation.

Evidence of Compliance:

- ✓ Report template containing all required elements **AND**
- ✓ Copies of patient reports confirming inclusion of the required elements **AND**
- ✓ Established guidelines used by the laboratory

REFERENCES

- 1) Wolff AC, Somerfield MR, Dowsett M, et al. Human Epidermal Growth Factor Receptor 2 Testing in Breast Cancer: American Society of Clinical Oncology/College of American Pathologists Guideline Update. *Arch Pathol Lab Med*. Published online June 7, 2023. doi: 10.5858/arpa.2023-0905-SA.
- 2) Bartley AN, Washington MK, Ventura CB, et al. HER2 Testing and Clinical Decision Making in Gastroesophageal Adenocarcinoma: Guideline from the College of American Pathologists, American Society for Clinical Pathology, and American Society of Clinical Oncology. *Arch Pathol Lab Med*. 2016;140(12):1345-1363.

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CYG.48399 Validation/Verification - Predictive Marker Testing

Phase II



Predictive marker testing by in situ hybridization is validated/verified and records of validation/verification are retained.

*NOTE: For validation of **laboratory-developed and modified FDA-cleared/approved HER2 (ERBB2) breast predictive assays**, the validation must be performed on a minimum of 40 cases (20 positive and 20 negative samples).*

*For verification of **unmodified FDA-cleared/approved HER2 (ERBB2) breast predictive assays**, the laboratory must follow the instructions provided by the manufacturer. If the instructions do not list a minimum number of samples for assay verification, the verification must be performed on a minimum of 20 positive and 20 negative tissues.*

*For **other predictive marker assays**, the laboratory director must determine the appropriate number of positive and negative samples to be used to adequately validate/verify the test. In general, laboratories should consider using higher numbers of test cases when assessing laboratory-developed tests or modified FDA-cleared/approved tests than is necessary for unmodified FDA-cleared/approved tests for the same analyte. For genetic abnormalities where positive cases are rare, the laboratory director may determine that fewer validation cases are necessary. However, the rationale for using fewer cases must be recorded.*