

Corporate Medical Policy

DNA Ploidy Cell Cycle Analysis AHS – M2136

File Name: dna_ploidy_cell_cycle_analysis
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Description of Procedure or Service

DNA ploidy refers to the number of sets of chromosomes present in an organism or cell (Raby, 2017). DNA ploidy has been suggested as a predictor of biological behavior and risk of malignant transformation (Alaizari, Sperandio, Odell, Peruzzo, & Al-Maweri, 2018).

DNA ploidy testing measures the DNA content within cells using either image analysis microscopy or flow cytometry to detect aneuploidy, abnormalities in DNA content (Vago, 1995).

*****Note: This Medical Policy is complex and technical. For questions concerning the technical language and/or specific clinical indications for its use, please consult your physician.**

Policy

DNA ploidy cell cycle analysis is not covered. BCBSNC will not reimburse for non-covered services or procedures.

Benefits Application

This medical policy relates only to the services or supplies described herein. Please refer to the Member's Benefit Booklet for availability of benefits. Member's benefits may vary according to benefit design; therefore member benefit language should be reviewed before applying the terms of this medical policy.

When DNA Ploidy Cell Cycle Analysis is covered

Not Applicable.

When DNA Ploidy Cell Cycle Analysis is not covered

Reimbursement is not allowed for the measurement of flow cytometry-derived DNA content (DNA index) or cell proliferative activity (S-phase fraction or % S-phase) for prognostic or therapeutic purposes in the routine clinical management of cancers.

Policy Guidelines

Aneuploidy Testing in Cancer

Cancer is the uncontrolled growth and spread of abnormal cells and is increasingly shown to be initiated, propagated, and maintained by somatic genetic events (Johnson et al., 2014). About 1,688,780 new cancer cases are expected to be diagnosed in 2017 with about 600,920 Americans expected to die of cancer (~1650 people per day)(Siegel, Miller, & Jemal, 2017).

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Cancer cells differ from normal healthy cells in multiple aspects ranging from altered cellular signaling through metabolic changes to aberrant chromosome content (Durrbaum & Storchova, 2015; Gordon, Resio, & Pellman, 2012). Chromosomal instability of tumors leads to cell clones and to numerical and structural chromosome abnormalities. These changes in the number of whole chromosomes (aneuploidy) can stimulate oncogenes and cause amplification and over-expression (Gordon et al., 2012; Tembhare et al., 2016). Sporadic solid cancers are aneuploid in about 90% of cases ("Mitelman Database of Chromosome Aberrations and Gene Fusions in Cancer," 2017) However, defining the role of aneuploidy in the pathogenesis and prognosis of cancer is particularly difficult since the associated chromosomal aberrations in the different tumors are often different (Alaizari et al., 2018).

Ploidy status and S-phase fraction (SPF) cell cycle analysis have been established as useful indicators for the biologic aggressiveness of various neoplasms. Either abnormal ploidy or elevated proliferative activity predict a worsened disease-free or overall survival in breast, non-small cell lung, and colorectal cancers, and in all stages of ovarian cancer, kidney, bladder, prostate, and endometrial cancers (Bagwell et al., 2001; Gawrychowski, Lackowska, & Gabriel, 2003; Kenney, Zieske, Rinder, & Smith, 2008; Mangili et al., 2008; Pinto et al., 2011; Ross, 1996).

Clinical Validity and Utility in Cancer

However, flow based assays have not been found to have significant validity or utility. Dabic et al (2008) examined clinical, histological, and flow cytometric parameters as predictors of survival in cervical adenocarcinoma and concluded that flow cytometric parameters did not predict patient survival. Wolfson et al (2008) studied possible associations between measurements of DNA index (DI), S-phase fraction (SPF), and tumor heterogeneity (TH) using flow cytometry and overall survival for patients with invasive cervical carcinoma treated with definitive irradiation. The authors concluded that there were no statistically significant associations among DI, SPF, or TH and patient outcome. They stated that additional studies are needed to identify tumor biomarkers that could predict patients at risk for disseminated disease.

A study of the 25-year experience of the Portuguese Institute of Oncology of Lisbon to assess the clinical relevance and application of DNA flow cytometry for the prognosis of breast cancer (Pinto, Pereira, Silva, & Andre, 2017) found that: "Overall, data from Portuguese Institute of Oncology of Lisbon indicate that DNA flow cytometry provides significant prognostic information that is biologically relevant and clinically useful for the management of patients with breast cancer. Furthermore, this data has demonstrated the independent value of DNA aneuploidy as a prognostic indicator of poor clinical outcome in various subgroups of patients with early or locally advanced breast cancer at short- and long-term follow-up. Notably, aneuploidy identifies subsets of patients with grade (G)1 or G2 tumors who exhibit a poor clinical outcome. These patients may benefit from adjuvant chemotherapy, particularly those with luminal A and luminal B/human epidermal growth factor-2-negative endocrine-responsive breast cancer. In conclusion, data from Portuguese Institute of Oncology of Lisbon reinforces the clinical importance and utility of DNA flow cytometric analysis, particularly DNA ploidy, in the prognostic assessment and therapeutic planning for patients with breast cancer.

Carloni et al (2017) in a study of 53 patients with peritoneal carcinomatosis from ovarian cancer found that "SPF differed significantly among ploidy categories ($P=0.01$), and high SPF was associated with short-term survival ($P=0.48$). Patients with multiploid tumors were the most resistant to platinum-based chemotherapy, whereas those with hyperdiploid tumors were the most responsive. In vitro multiploid tumors were the least sensitive, while hypodiploid samples showed the highest sensitivity to the tested drugs. Sensitivity to adriamycin was significantly correlated with ploidy ($P=0.03$), whereas sensitivity to taxol was correlated with SPF ($P=0.04$)." They concluded that "ploidy and SPF could facilitate the choice of therapy for patients with peritoneal carcinomatosis."

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Suzuki et al (2018) found that “DNA ploidy assessed with intraoperative flow cytometry may be effectively used as prognostic indicator in cases of low grade gliomas, especially of diffuse astrocytomas. Aneuploid tumors demonstrate more aggressive clinical course translated into shorter overall survival of patients. Thus, their detection during surgery may be helpful for decision on the optimal EOR, and for choice of the most appropriate postoperative adjuvant therapy”.

Alaizari et al (2018) analyzed five studies assessing aneuploidy as a risk marker of malignant change in oral potentially malignant disorders. “Aneuploidy was found to be associated with a 3.12 -fold increased risk to progress into cancer (RR = 3.12, 95% CI 1.86 -5.24). Based on the 5 studies meta -analyzed, “no malignant progression” was more likely to occur in DNA diploid OPMD by 82% when compared to aneuploidy (RR = 0.18, 95% CI 0.08 – 0.41). In conclusion, aneuploidy is a useful marker of malignant transformation in oral potentially malignant disorders, though a diploid result should be interpreted with caution.”

Aneuploidy Testing in Evaluating Products of Conception

Products of conception can be sent for histological examination, mainly to exclude a gestational trophoblastic disorder (Jauniaux, Farquharson, Christiansen, & Exalto, 2006). Distinction of hydatidiform moles from nonmolar specimens (NMs) and subclassification of hydatidiform moles as complete hydatidiform mole (CHM) and partial hydatidiform mole (PHM) are important not only for clinical management but also for accurate ascertainment of the risk of persistent gestational trophoblastic disease (GTD)(Gupta et al., 2012). However, histologic classification of POC specimens can be difficult, and ancillary testing (flow cytometry, digital image analysis, fluorescence in situ hybridization, p57 immunostaining, molecular genotyping) is often required for a definitive diagnosis (Kipp et al., 2010).

Additionally, many referral centers for recurrent pregnancy loss currently start their evaluation of a couple with recurrent pregnancy loss with a products of conception karyotype (El Hachem et al., 2017; Kutteh, 2015). Ploidy status of the miscarriage tissue or products of conception can help in determining prognosis for subsequent pregnancy outcome (Kutteh, 2015). Numeric chromosome errors, account for 50%–70% of miscarriages of less than 10 weeks' gestation (Bernardi, Plunkett, & Stephenson, 2012; Ohno, Maeda, & Matsunobu, 1991). If euploid, a full workup is ordered. If an unbalanced chromosomal translocation or inversion is found, a parental karyotype is ordered and PGD offered for future attempts. Finally, an aneuploidy in the POC confirms the diagnosis and no further tests are necessary (El Hachem et al., 2017). A 2012 study from Binati found this strategy to be cost-saving.

Clinical Validity and Utility in Evaluating Products of Conception

Kipp et al (2010) “evaluated 66 POC specimens by flow cytometry, digital image analysis, p57 immunohistochemical analysis, and fluorescence in situ hybridization (FISH). The final diagnosis, based on the combined analysis of all test results, included 33 HAs, 24 PMs, and 9 CMs. The p57 immunostain identified 9 CMs that were evaluated as nontriploid by all other techniques. FISH seems to have the best accuracy (100%) for determining whether a specimen contains a triploid chromosome complement. These data suggest that the combination of p57 and FISH seems to be the best ancillary testing strategy.”

Vang et al (2012) also found that “Sensitivity of a diagnosis of CHM ranged from 59% to 100% for individual pathologists and from 70% to 81% by consensus; specificity ranged from 91% to 96% for individuals and from 94% to 98% by consensus. Sensitivity of a diagnosis of PHM ranged from 56% to 93% for individual pathologists and from 70% to 78% by consensus; specificity ranged from 58% to 92% for individuals and from 74% to 85% by consensus. The percentage of correct classification of all cases by morphology ranged from 55% to 75% for individual pathologists and from 70% to 75% by consensus. The κ values for interobserver

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agreement ranged from 0.59 to 0.73 (moderate to good) for a diagnosis of CHM, from 0.15 to 0.43 (poor to moderate) for PHM, and from 0.13 to 0.42 (poor to moderate) for NM. The κ values for intraobserver agreement ranged from 0.44 to 0.67 (moderate to good). Addition of the p57 immunostain improved sensitivity of a diagnosis of CHM to a range of 93% to 96% for individual pathologists and 96% by consensus; specificity was improved from a range of 96% to 98% for individual pathologists and 96% by consensus; there was no substantial impact on diagnosis of PHMs and NMs. Interobserver agreement for interpretation of the p57 immunostain was 0.96 (almost perfect).” However, “even at the hands of experienced gynecologic pathologists, diagnosis of HMs and their distinction from NMs is imperfect. Ancillary techniques can substantially improve the diagnosis of HMs, with p57 enabling recognition of virtually all CHMs and molecular genotyping providing a definitive diagnosis for the ~20% to 30% of specimens that are misclassified by morphology.”

Recently (Moussa et al., 2018), “differential expression of Twist1, Ki-67, and E-cadherin was analyzed in gestational products from 55 cases of CHM, PHM, and HA using immunohistochemistry and diagnosis was confirmed by flow cytometric assessment of DNA ploidy and p57 immunostaining.” They found that “Twist1 expression is a highly reliable marker for the diagnosis of CHM, where combined Ki-67 and E-cadherin immunoreactivity can distinguish PHM from nonmolar pregnancies.” “These findings add additional support and strength for an algorithm that combines p57 immunohistochemistry and molecular genotyping for the differential diagnosis of molar and nonmolar gestations”.

Applicable Federal Regulations

This test is considered a laboratory developed test (LDT); developed, validated and performed by individual laboratories.

LDTs are regulated by the Centers for Medicare and Medicaid (CMS) as high-complexity tests under the Clinical Laboratory Improvement Amendments of 1988 (CLIA’88).

As an LDT, the U. S. Food and Drug Administration has not approved or cleared this test; however, FDA clearance or approval is not currently required for clinical use.

Practice Guidelines and Position Statements

American Society of Clinical Oncology (ASCO)

In 2000, ASCO released evidence-based guidelines on the use of tumor markers in breast cancer and colorectal cancer (Bast et al., 2001). Regarding DNA ploidy or flow cytometric proliferation analysis as a marker for colorectal cancer, ASCO concluded that “present data are insufficient to recommend DNA flow cytometrically-derived ploidy (DNA index) for the management of colorectal cancer.” Regarding the use of DNA flow cytometrically-derived parameters as markers for breast cancer, ASCO concluded that “present data are insufficient to recommend obtaining flow cytometric or immunohistochemical measures of DNA content and/or S phase fraction (proliferation) in breast tissue to determine prognosis or treatment in the adjuvant or metastatic setting.” ASCO further stated that “present data are insufficient to recommend obtaining flow cytometric or immunohistochemical measures of DNA content and/or S phase fraction (proliferation) in breast tissue to determine prognosis or treatment for carcinoma-in-situ of the breast”(Bast et al., 2001).

ASCO's updated recommendations on the use of tumor markers in colorectal cancer state that “neither flow-cytometrically derived DNA ploidy nor DNA flow cytometric proliferation analysis (% S phase) should be used to determine prognosis of early-stage colorectal cancer” (Locker et al., 2006). It further states that “as such, flow cytometric determination of DNA ploidy or proliferation should, at best, be considered an experimental tool” (Locker et al., 2006).

In 2007, ASCO updated the guidelines for the use of tumor markers in breast cancer which noted that there is “insufficient evidence to support routine use in clinical practice of DNA/ploidy by flow cytometry”(Harris et al., 2007).

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National Comprehensive Cancer Network (NCCN)

NCCN clinical practice guidelines (NCCN, 2018) on diagnosis and/or management of Breast Cancer (Version 1.2018), Cervical Cancer (Version 1.2018), Colon Cancer (Version 2.2018), Small Cell Lung Cancer (Version 2.2018), and Non-Small Cell Lung Cancer (Version 3.2018) do not mention flow cytometrically-derived DNA content (ploidy) and or cell proliferation activity (S-phase fraction or % S-phase) as a management tool.

There are no NCCN Guidelines on the management of gestational trophoblastic disease.

American Society for Reproductive Medicine

The ASRM (2012) recommends that “Karyotypic analysis of products of conception may be useful in the setting of ongoing therapy for RPL”. However, it does not specifically recommend evaluation of DNA ploidy status using flow cytometry.

American College of Obstetrics and Gynecology

ACOG (2015) guidelines on early pregnancy loss state that “Maternal or fetal chromosomal analyses ... are not recommended routinely after one early pregnancy loss.” “No workup generally is recommended until after the second consecutive clinical early pregnancy loss” ACOG (Soper, Mutch, & Schink, 2004) guidelines on diagnosis and treatment of gestational trophoblastic disease state that “Despite the cytogenetic, pathologic, and clinical differences between the two diagnoses, the management of patients with complete and partial moles is similar.” And that “Ultrasonography has replaced all other noninvasive means of establishing the diagnosis”.

European Society for Medical Oncology

Contrastingly, ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up of gestational trophoblastic disease (Seckl et al., 2013) state that “All products of conception from non-viable pregnancies must undergo histological examination regardless of ultrasound findings” and that “The morphological distinction between non-molar miscarriage, especially when associated with chromosomal abnormality, and PHM can sometimes be difficult, and ancillary techniques may be required including immunostaining with p57KIP2 (negative in CHM), ploidy analysis by in situ hybridisation or flow cytometry or molecular genotyping.”

Billing/Coding/Physician Documentation Information

This policy may apply to the following codes. Inclusion of a code in this section does not guarantee that it will be reimbursed. For further information on reimbursement guidelines, please see Administrative Policies on the Blue Cross Blue Shield of North Carolina web site at www.bcbssc.com. They are listed in the Category Search on the Medical Policy search page.

Applicable service codes: 88182

BCBSNC may request medical records for determination of medical necessity. When medical records are requested, letters of support and/or explanation are often useful, but are not sufficient documentation unless all specific information needed to make a medical necessity determination is included.

Scientific Background and Reference Sources

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Medical Director review 3/2020

Medical Director review 7/2020

Policy Implementation/Update Information

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| 1/1/19 | New policy developed. DNA ploidy cell cycle analysis/measurement of flow cytometry-derived DNA content (ploidy) or cell proliferative activity (S-phase fraction or % S-phase) for prognostic or therapeutic purposes in the routine clinical management of cancers is considered investigational. Medical Director review 1/1/2019. Policy noticed 1/1/2019 for effective date 4/1/2019. (lpr) |
| 9/10/19 | Reviewed by Avalon 2 nd Quarter 2019 CAB. Under “When Covered” section: deleted term “ploidy” and replaced with “DNA index” for clarity. No change to policy intent. Deleted coding table from Billing/Coding section. Deleted CPT codes 86356, 88358, 88361 and added CPT code 88182. Medical Director review 8/2019. (lpr) |
| 10/29/19 | Wording in the Policy, When Covered, and/or Not Covered section(s) changed from Medical Necessity to Reimbursement language, where needed. (gm) |
| 4/14/20 | Specialty Matched Consultant Advisory Panel review 3/18/2020. No change to policy statement. Reference added. (lpr) |
| 7/28/20 | Reviewed by Avalon 2 nd Quarter 2020 CAB. Medical Director review 7/2020. (lpr) |

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