



BlueCross BlueShield
of Alabama

Name of Policy:

Laboratory Tests of Sperm Maturity, Function and DNA Integrity

Policy #: 219
Category: Laboratory

Latest Review Date: January 2009
Policy Grade: **Active Policy but no
longer scheduled for
regular literature
reviews and updates.**

Background/Definitions:

As a general rule, benefits are payable under Blue Cross and Blue Shield of Alabama health plans only in cases of medical necessity and only if services or supplies are not investigational, provided the customer group contracts have such coverage.

The following Association Technology Evaluation Criteria must be met for a service/supply to be considered for coverage:

- 1. The technology must have final approval from the appropriate government regulatory bodies;*
- 2. The scientific evidence must permit conclusions concerning the effect of the technology on health outcomes;*
- 3. The technology must improve the net health outcome;*
- 4. The technology must be as beneficial as any established alternatives;*
- 5. The improvement must be attainable outside the investigational setting.*

Medical Necessity means that health care services (e.g., procedures, treatments, supplies, devices, equipment, facilities or drugs) that a physician, exercising prudent clinical judgment, would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury or disease or its symptoms, and that are:

- 1. In accordance with generally accepted standards of medical practice; and*
- 2. Clinically appropriate in terms of type, frequency, extent, site and duration and considered effective for the patient's illness, injury or disease; and*
- 3. Not primarily for the convenience of the patient, physician or other health care provider; and*
- 4. Not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of that patient's illness, injury or disease.*

Description of Procedure or Service:

This policy addresses 2 laboratory tests of sperm maturity and function: the sperm penetration assay and hyaluronan-binding assay.

Sperm Penetration Assay (SPA)

The SPA is a multistep laboratory test that offers a biological assessment of human sperm fertilizing ability. Specifically, 4 distinct processes must occur for sperm-oocyte fertilization: capacitation, acrosome reaction, penetration of the ooplasm, and chromatin decondensation within the ooplasm. The SPA uses a zona-free hamster egg as an in vitro model for sperm-oocyte interaction. (The zona pellucida is a thick, glassy membrane surrounding the oocyte that maintains species specificity for fertilization. Removal of the zona pellucida from hamster ova permits their use as a model for sperm oocyte interaction.) The test is performed by incubating a number of zona-free hamster eggs with human sperm for several hours. According to the percentage of ova penetrated, the semen sample is rated as being in a potentially “fertile” or “infertile” range. Aspects of sperm function not assessed by the SPA include the capacity of sperm to penetrate the cervical barrier or their ability to bind to the zona pellucida of human ova. The sperm penetration assay, alternatively referred to as the hamster oocyte penetration test or the zona-free hamster egg test, was initially developed in 1976. Although it has been used as a test for male infertility, the test has been controversial due to variability in procedures used by different laboratories, poor reproducibility of test outcomes, and uncertainty regarding the range of normal values.

Hyaluronan Binding Assay (HBA)

The HBA is a qualitative assay for the maturity of sperm in a fresh semen sample. The assay is based on the ability of mature, but not immature, sperm to bind hyaluronan, the main mucopolysaccharide of the cumulus oophorus matrix and a component of human follicular fluid. Research has shown that hyaluronan-binding capacity is acquired late in the sperm maturation process; immature sperm lack this ability. Therefore, a low level of sperm binding to hyaluronan suggests that there is a low proportion of mature sperm in the sample. Similar to the sperm penetration assay, it has been suggested that the HBA assay may be used to determine the need for an intracytoplasmic sperm injection procedure (ICSI) as part of an assisted reproductive technique. The HBA is a laboratory test that has received U.S. Food and Drug Administration (FDA) clearance through the 510(k) approval process. The FDA-labeled indications are as follows:

- As a component of the standard analysis of semen in the diagnosis of suspected male infertility.
- As a component of analyses for determining the proper course of in vitro fertilization treatment of infertility.

Note: Both of the tests are laboratory tests that are frequently performed as part of an assisted reproductive technique (ART).

DNA Integrity and Fragmentation

In addition to the conventional parameters of sperm quality, such as concentration, motility, and morphology, sperm DNA integrity has emerged as a potential cause of idiopathic male infertility. For example, while sperm with fragmented DNA may be able to fertilize oocytes, subsequent embryo and fetal development may be impaired. Oocytes and embryos may be able to repair fragmented DNA, but there may be a point beyond which repair is possible. In addition, the ability of oocytes to repair DNA damage may decrease with age, while DNA fragmentation in sperm increases with age. Therefore, impaired DNA integrity may be an increasing infertility factor among older couples. A variety of etiologies have been proposed for impaired DNA integrity, including protamine deficiency, apoptosis, drugs, chemotherapy or radiation therapy, cigarette smoking, and varicoceles. It is estimated that up to 8% of infertile men will have abnormal DNA integrity despite normal semen parameters.

One measure of sperm DNA integrity is the sperm chromatin structure assay (SCSA). Sperm DNA is exposed to an acid pH of 1.2, which will not affect normal DNA, but will denature fragmented DNA. Then the treated DNA is stained with acridine orange, which emits green fluorescence in the presence of double-stranded, intact, DNA, and red fluorescence with single-stranded DNA. These patterns can be detected by flow cytometry, a procedure that can analyze thousands of sperm. Flow cytometry tests of DNA integrity that are commercially available include the sperm chromatin structure assay test (SCSA®) and the sperm DNA fragmentation assay (SDFATM) test, available at specialized reference laboratories. Another assay of sperm DNA integrity measures sperm chromatin dispersion (SCD) following acid-induced decondensation (denaturation). A kit to measure SCD is commercially available in Europe (Halosperm® kit, INDAS Laboratories). In the United States, Repromedix® is marketing an “advanced sperm panel” that includes a sperm DNA condensation test and a sperm DNA fragmentation assay. Other laboratory tests for sperm integrity, such as the TUNEL and COMET assays require microscopic analysis, and thus can only assess a limited number of sperm. These latter tests are not widely used clinically.

It has been proposed that sperm DNA testing may help to determine the most effective method of assisted reproduction [i.e., intrauterine insemination (IUI), in vitro fertilization (IVF), or intracytoplasmic sperm injection (ICSI)].

Other proposed clinical uses for tests of DNA integrity include:

- Evaluation of failed pregnancy or spontaneous abortions, in unassisted pregnancy, and after failed IVF attempts.
- Men with high levels of fragmented DNA could be advised that natural attempts at pregnancy or IVF attempts are unlikely to succeed or that donor sperm should be used.
- Selection of sperm sample for cryopreservation.

The level of DNA fragmentation from a given patient may vary. Therefore, multiple sperm samples could be tested over time, and the sample with the lowest level of fragmentation could be selected for storage.

Policy:

Sperm penetration assay meets Blue Cross and Blue Shield of Alabama's medical criteria for coverage as a technique to determine whether intracytoplasmic sperm injection should be offered as part of an in vitro fertilization technique **and is subject to contract benefits.**

Sperm hyaluronan binding assay does not meet Blue Cross and Blue Shield of Alabama's medical criteria for coverage and is considered **investigational.**

Tests of sperm DNA integrity do not meet Blue Cross and Blue Shield of Alabama's medical criteria for coverage and are considered **investigational.**

Blue Cross and Blue Shield of Alabama does not approve or deny procedures, services, testing, or equipment for our members. Our decisions concern coverage only. The decision of whether or not to have a certain test, treatment or procedure is one made between the physician and his/her patient. Blue Cross and Blue Shield of Alabama administers benefits based on the members' contract and corporate medical policies. Physicians should always exercise their best medical judgment in providing the care they feel is most appropriate for their patients. Needed care should not be delayed or refused because of a coverage determination.

Key Points:

Sperm Penetration Assay

Originally, the SPA was used primarily as a diagnostic technique for male infertility. More recently, the advent of sperm micromanipulation techniques, specifically intracytoplasmic sperm injection (ICSI), has changed the role of in vitro fertilization (IVF) and changed the role of SPA. IVF was originally developed as a treatment option for women with irreversible tubal damage, but the development of sperm micromanipulation techniques as an adjunct to IVF has now expanded the indications for IVF to those with severe male factor infertility. Thus, SPA can be used to identify those normospermic patients who would benefit from ICSI or other adjuncts to IVF. In 2001, Freeman and colleagues reported on the diagnostic accuracy of sperm penetration assay in predicting success of in vitro fertilization. Among 216 couples, the sperm penetration assay predicted IVF with high negative (84%) and positive (98%) predictive value, with correct prediction in 88% of cycles. While there is still concern regarding standardization of the procedure, these results suggest that the results of the sperm penetration assay can be used to select patients for ICSI.

Hyaluronan Binding Assay (HBA)

The HBA has been proposed as a component of the standard analysis of semen in the diagnosis of suspected male infertility. In addition, it potentially represents a more convenient and reproducible laboratory test for identifying candidates for ICSI. However, published scientific data were inadequate to permit conclusions regarding either of these indications. A literature search identified 2 published articles that discussed the biologic basis of the HBA, but no articles were identified that established the diagnostic performance of the test (i.e., establishment of positive and negative cut-off values, sensitivity, specificity, positive and negative predictive

values) or examined the clinical role of the test. The package insert also does not provide adequate data to evaluate the diagnostic performance of the test.

Tests of Sperm DNA Integrity and Fragmentation (i.e., SCSA® and SDFATM)

Tests of DNA integrity and fragmentation have been an important research tool to further explore the etiologies of infertility. For example, as reviewed by O'Brien and Zini, several studies have reported that poor sperm DNA integrity is an independent risk factor for male infertility. A threshold of 30% of abnormal DNA (referred to as the DNA fragmentation index or DFI) is frequently suggested as a cutoff to distinguish between a potentially fertile versus infertile semen sample. However, this cutoff point has not been evaluated in large scale studies, and studies have reported variable results regarding the relation between DFI and reproductive outcomes. Payne et al have published the largest case series, comparing the results of the SCSA test to outcomes of assisted reproductive techniques. In the 100 couples included in the series, 19 had a DFI of >27%, suggesting a poor IVF outcome. However, 9 of these couples achieved a clinical pregnancy. In contrast, in 22 couples the DFI was less than 9%, suggesting a favorable outcome. Only 1 of these patients achieved a clinical pregnancy. These results are consistent with other reports and contrast with favorable results reported from smaller case series.

In summary, there are inadequate published data to permit scientific conclusions about tests of DNA integrity of sperm as a diagnostic test used in the management of infertile couples.

Selection of mature sperm for ICSI using hyaluronan has been proposed as a promising method to reduce the risk of DNA abnormalities. No studies were identified that assessed clinical outcomes following sperm selection with hyaluronic acid. This procedure is at an early stage of research and is considered investigational.

A meta-analysis of observational studies assessed the risk ratio (RR) for sperm DNA damage (assessed with either the TUNEL or SCSA assay) and fertilization or clinical pregnancy rates for IVF and ICSI. The analysis found that sperm DNA damage as assessed by the SCSA assay was not predictive of fertilization or pregnancy rate after IVF or ICSI. Sperm DNA damage as assessed by the TUNEL assay was associated only with a decrease in clinical pregnancy for the IVF procedure (RR = 0.68). The impact of this information on clinical decision making is unknown.

The Practice Committee of the American Society for Reproductive Medicine concludes in their recent guidelines that although sperm DNA damage is more common in infertile men, there is no proven role for routine DNA integrity testing in the evaluation of infertility. In the absence of any evidence that DNA integrity testing improves clinical outcomes, the policy statement remains unchanged.

January 2009 Update

As indicated, the Practice Committee of the American Society for Reproductive Medicine concluded in 2006 that the clinical utility of sperm DNA testing was unknown. At issue was the limited data on the relationship between abnormal DNA integrity and reproductive

outcomes. In particular, studies had indicated that “the results of sperm DNA integrity testing alone do not predict pregnancy rates achieved with intercourse, IUI, or IVF and ICSI.”

Recent studies indicate that DNA integrity does not affect pregnancy rates for IVF and ICSI, although it may alter fertilization rate, embryo quality, and miscarriage rate. A prospective study with 322 couples (88 IVF cycles and 234 ICSI cycles) found that a DNA fragmentation index (DFI) of 15% or greater was associated with lower fertilization rate and embryo quality (ICSI only), but pregnancy rates (either ICSI or IVF) were not altered. Miscarriage rates were found to be higher (38% vs. 9%) when the DFI was 15% or greater. DFI was weakly correlated ($r = -0.2$) with standard sperm parameters (count, motility, morphology). Similar results were obtained in 2 additional studies with a combined total of 850 couples. Lin et al note that, “The selection of morphologically normal sperm for ICSI and good quality embryos for transfer at IVF/ICSI may reduce the potential adverse effects of sperm DNA damage on outcome of ART.”

Another multicenter study from Europe examined the relation between sperm DNA integrity and pregnancy outcomes in 637 consecutive couples with either unexplained infertility (387 IUI cycles), female factor infertility (388 IVF cycles), or male infertility factor (223 ICSI cycles). A high DFI (>30% by SCSA) was observed in 17% of IUI, 16% of IVF, and 32% of ICSI cases. Pregnancy rates were not affected by the percentage of DNA fragmentation in IVF and ICSI groups, and early pregnancy loss was not significantly different in these groups. For the group referred to IUI due to unexplained infertility, the pregnancy rate for a DFI >30% was 2/66 (3%) compared to 76/321 (24%) cycles when the DFI was 30% or less. In another study, sperm DNA integrity (measured by SCD) was assessed in 100 couples undergoing IUI; female infertility was unexplained in 79 (79%) of the couples. There were 23 (23%) pregnancies with 25 newborns from the first cycle. Weak correlations ($r = -0.22$ to -0.29) were observed between DNA dispersion and standard sperm parameters; no differences in SCD were found between couples that did or did not achieve a pregnancy.

Reports from the Practice Committee of the American Society for Reproductive Medicine indicate that up to 30% of couples who are unable to conceive are determined to have unexplained infertility, and up to 8% of infertile men will have abnormal DNA integrity despite normal semen parameters. Current literature indicates that sperm DNA integrity does not affect pregnancy rates in couples who undergo IVF or ICSI. One study suggests that sperm DNA integrity testing with a chromatin structure assay may improve decision making for couples with infertility unexplained by standard panels; however, another study indicates no relation between sperm chromatin dispersion and pregnancy outcomes following IUI. The evidence is insufficient to permit conclusions concerning the effect of sperm DNA integrity tests on health outcomes. Therefore, the policy statements are unchanged.

Key Words:

Hamster Egg Penetration Test, Sperm Hyaluronan Binding Assay (HBA), Sperm Penetration Assay (SPA), Zona-Free Hamster Egg Test, intracytoplasmic sperm injection procedure (ICSI), assisted reproductive technique (ART), in vitro fertilization (IVF).

Approved by Governing Bodies:

The HBA is a laboratory test that has received U.S. Food and Drug Administration (FDA) clearance through the 510(k) approval process on September 21, 2001.

Benefit Application:

Coverage is subject to member’s specific benefits. Group specific policy will supersede this policy when applicable.

ITS: Home Policy provisions apply

FEP contracts: FEP does not consider investigational if FDA approved. Will be reviewed for medical necessity. Special benefit consideration may apply. Refer to member’s benefit plan.

Pre-certification/Pre-determination requirements: Not applicable

CURRENT Coding:

In 2005, a category III CPT code is available that explicitly identifies the hyaluronan binding assay.

CPT codes:

89329 Sperm evaluation; hamster penetration test

Effective for dates of service on or after January 1, 2010:

89398 Unlisted reproductive medicine laboratory procedure

PREVIOUS Coding:

0087T Sperm evaluation, hyaluronan binding assay **(Code deletes effective January 1, 2010)**

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in vitro fertilization and intracytoplasmic sperm injection cycles. Fertil Steril, May 2004; 81(5): 1289-1295.

Policy History:

Medical Policy Group, January 2007 **(4)**

Medical Policy Administration Committee, January 2007

Available for comment January 11-February 24, 2007

Medical Policy Group, January 2009 **(1)**

Medical Policy Administration Committee, February 2009

Available for comment February 6-March 23, 2009

Medical Policy Group, June 2011; Effective June 14, 2011 this policy is still active but is no longer scheduled for regular literature reviews and updates.

This medical policy is not an authorization, certification, explanation of benefits, or a contract. Eligibility and benefits are determined on a case-by-case basis according to the terms of the member's plan in effect as of the date services are rendered. All medical policies are based on (i) research of current medical literature and (ii) review of common medical practices in the treatment and diagnosis of disease as of the date hereof. Physicians and other providers are solely responsible for all aspects of medical care and treatment, including the type, quality, and levels of care and treatment.

This policy is intended to be used for adjudication of claims (including pre-admission certification, pre-determinations, and pre-procedure review) in Blue Cross and Blue Shield's administration of plan contracts.