CLINICAL LABORATORY IMPROVEMENT ADVISORY COMMITTEE MEETING

NOVEMBER 6-7, 2019

TAMMIE K. SCHALUE, Ph.D, HCLD(ABB)

DIRECTOR OF LABORATORIES

HEARTLAND CENTER FOR REPRODUCTIVE MEDICINE, OMAHA, NE.

ASSOCIATE DIRECTOR AMERICAN BOARD OF BIOANALYSIS

PRESENTED ON BEHALF OF THE AMERICAN BOARD OF BIOANALYSIS

The American Board of Bioanalysis (ABB) is one of the four original certifying boards recognized in CLIA to certify high complexity clinical laboratory directors. The ABB believes that the application of mandatory quality standards under CLIA can provide meaningful assurance to patients that the laboratory testing crucial to the ART process is performed under high quality conditions and rigorous safety and specimen handling requirements.

The ABB first petitioned this committee to specifically include ART laboratory testing as CLIA covered testing in May 1998. Interestingly, also included on the agenda for that CLIAC meeting was a discussion about the inclusion of genetic testing. At the May 1998 meeting the members of the CLIAC recommended "that embryology laboratory procedures should be under the purview of CLIA, and that appropriate CLIA coverage should be defined." To date, this has not occurred. Today, with the advent of genetic testing of gametes and embryos and the increase in highly complex processes in the laboratory, e.g., the use of testicular sperm for intracytoplasmic injection (ICSI), it is more important than ever that these laboratories be under the purview of CLIA.

The primary purpose of this document is to provide this committee with our position regarding the applicability of CLIA to laboratory testing performed in ART laboratories. We firmly believe that ART laboratories provide critical diagnostic information used in the determination of the causes and the treatment of male and female infertility. We further believe that in order to ensure patients that all ART laboratories provide at least a minimal and consistent degree of quality testing performed by competent laboratories and qualified personnel, federally mandated oversite of the ART laboratory and its personnel is necessary.

CLIA defines a clinical laboratory as a "facility for the …examination of materials derived from the human body for the purpose of providing information for the diagnosis, prevention or treatment of any disease or

impairment of, or the assessment of the health of, human beings." The laboratory analysis conducted in ART laboratories clearly fall within this definition. The analysis performed (examples described below) in these laboratories are highly complex, require substantial clinical laboratory training and expertise, and are an integral part of correctly diagnosing and treating individuals suffering from infertility. The language and intent of CLIA is plain, unambiguous, and encompassing. ABB strongly believes that failure to include ART laboratories under the purview of CLIA places patients at risk and is in direct contradiction to the mandates of the CLIA statue.

The laboratory professionals and technologists working in ART laboratories examine, using microscopes and other laboratory tools, oocytes, sperm and the embryos that result from their mixing. At every stage of the process the ART laboratory personnel perform tests that are reported to the physician and that are then used to diagnose and assess the infertile individual(s), and ultimately to treat them in this and subsequent ART cycles. Excellent personnel competency as well as quality control, quality assurance, and quality improvement procedures are essential for the successful diagnosis and subsequent treatment by the physician of these patients.

Prior to the start of an ART cycle the female is given hormones to stimulate follicle growth and oocyte maturation. Once mature, the oocytes are retrieved by surgical aspiration of the follicle(s). The follicular aspirate is transferred to the laboratory where a reproductive biologist microscopically evaluates the aspirate and then identifies, isolates, and grades the oocytes(s) (if any). If no oocytes are found, it may indicate "empty follicle syndrome", and in subsequent cycles an oocyte donor would be required. In addition, the laboratorian may further analyze the aspirate to determine its makeup (is it clear, bloody, or contaminated from endometriosis). If the number of oocytes is lower than expected this, along with examination of the aspirate, can be used to diagnose a "low responder." This information is then used by the physician in subsequent ART cycles to alter the stimulation hormone protocol or to recommend oocyte donation in extreme cases. Manual assessment of the follicular aspirate to include the number of oocytes is substantially more complicated and demanding than counting sperm, which is already categorized as highly complex, and the consequence of error is at least as great.

Each oocyte retrieved is analyzed microscopically by a laboratorian to determine maturity and morphology. This analysis involves the oocyte as well as the surrounding zona pellucida, corona radiate, and cumulus oophorous. In addition, the oocyte is analyzed for abnormal size, gross vacuolation, dysmorphic cytoplasmic inclusions, and fractured or damaged zona pellucida. Determination of any of these abnormalities can impact the success of this ART cycle and provide information to the physician for further treatment of the patient. The factors analyzed by these evaluations directly affect fertilization and embryonic development. Only mature and morphologically normal oocytes should be inseminated. Again, the analysis of sperm morphology is considered to be a highly complex diagnostic test. We argue that the diagnostic assessment of oocytes requires as much, if not more, expertise and training than the assessment of sperm.

Normal oocytes are fertilized either conventionally (mixing of sperm and oocytes in media) or by injection of individual sperm into the ooplasm (ICSI). The selection of sperm (either ejaculated, or of epididymal, or testicular origin) requires skill in sperm selection (assessment of sperm quality) as well as skill in the placement and injection of the oocyte. Improper ICSI technique can cause the destruction of the oocyte. After insemination, the fertilized oocyte is assessed for fertilization. Binding and penetration of the oocyte by sperm is one factor the laboratorian will document. Failure of sperm to bind or penetrate the oocyte(s) may be used by the physician to diagnose a male-factor infertility. In addition, the laboratorian will microscopically evaluate the oocyte for abnormal fertilization such as polyspermy and other genetic/fertilization abnormalities. These evaluations are time sensitive and require a highly skilled laboratorian to differentiate between a normally fertilized oocyte and abnormal fertilization. Only normally fertilized oocytes/embryos should be used for transfer. Transferring abnormally fertilized embryos can result in serious health issues.

Microscopic analysis of the resultant embryo(s) will continue over the next 4-5 days. The morphological development of the embryo will be documented at several time points, for cleavage number; the shape and size of the cleavages; intercellular adhesion and geometric pattern appropriate to the length of culture; the timing and formation of the blastocele; and the size, cell number and morphology of the intercell mass. All of these parameters will be use to morphologically grade the embryo and to determine which embryos to transfer to the uterus. In addition, this information is used by the physician to assess issues such as “egg factor infertility” and to make determinations regarding future ART cycles or the use of donor oocytes.

Genetic analysis of the oocyte (polor body analysis) and the embryo (PGD, PGS, PGT-A) are analyses that can be utilized to inform the clinical team which embryos are most likely to achieve a successful pregnancy. In many ART laboratories, this stage of testing involves collection of the specimen and processing, while the genetic testing is performed elsewhere. Even so, the micromanipulation procedure used to obtain the sample (biopsy) is critical to the outcome of a successful test result. In addition, precise documentation of the sample identity is imperative to the outcome. Pre-analytic errors are some of the most prevalent in clinical laboratories. We believe that due to the complex nature of this collection process, and the critical importance of the proper preparation of the sample to the outcome of the test, the procedures involving the preparation of this sample should be covered by CLIA.

All analyses described above, from the analysis of the follicular aspirate to the grading of blastocysts (a span of 5-6 days), are performed by highly trained ART laboratory professionals. It is rare for a physician to perform any of these analyses. Until it is determined that the embryos are healthy and suitable for implantation, the oocytes, sperm, and embryos remain in the ART laboratory under the control of laboratorians, who continue to analyze and evaluate them until the embryos are released to the physician for implantation. The analyses performed in the ART laboratory are highly complex, require substantial

clinical laboratory training and expertise, and are an integral part of correctly diagnosing and treating individuals suffering from infertility.

We acknowledge that others have suggested that there are better oversite mechanisms for ART laboratories than CLIA. It has been stated that ART is a therapeutic process and is not a diagnostic test performed in order to gather information; that the CAP/ASRM Reproductive Laboratory Accreditation Program (RLAP) is the only mechanism needed to assure quality care; and that the Fertility Clinic Success Rate and Certification Act (FCSRCA) is a better oversite mechanism. On behalf of the AAB and ABB, which represents thousands of clinical laboratorians across the country, many of whom work in these ART laboratories, we wish to provide the CLIAC with our position supporting the recommendation that ART laboratories should be under the purview of CLIA...a position overwhelmingly supported by this committee in 1998.

We acknowledge that there are many aspects of the ART clinic that are therapeutic. The ART laboratory, like all clinical laboratories, is just one part of a large team that cares for patients within these clinics. The physicians, nurses, and laboratory staff work together for the benefit of their patients. This does not mean that the work done in the ART laboratory is any less diagnostic that that performed in an andrology laboratory (which is CLIA covered). In fact, in most ART laboratories oocyte and embryo testing is housed in the same physical space and is performed by the same staff as sperm testing. We feel the information written above indicates that complex diagnostic information is obtained during the analysis of oocytes and embryos in the ART laboratory. This diagnostic information is commonly used in altering subsequent treatment cycles. The information obtained in an unsuccessful cycle (i.e., when pregnancy does not occur) is used to diagnose heretofore unobserved problems with the couple that aids in altering the next treatment cycle. The procedures, equipment and techniques to analyze oocytes and embryos are virtually identical to that used to analyze sperm, which is covered by CLIA as a highly complex test. However, the morphological analysis of oocytes and embryos arguably requires even greater care and expertise than the analysis of sperm. There is no justification for classifying the analysis of sperm as a highly complex test by CLIA while the analysis of oocytes and embryos goes unregulated by CLIA.

The current ART laboratory accreditation programs offered by CAP and Joint Commission are very good programs, and are grounded in the CLIA regulations. However, they are voluntary for ART laboratories. There is no regulatory requirement to participate and little ramification for ART laboratory noncompliance. The only criticism we have regarding these programs is that they are not mandatory.

When the FCSRCA was enacted in 1992 the expectation was that individual states would adopt ART laboratory requirements requiring quality procedures as does CLIA. However, this has not occurred. The FCSRCA does require the reporting of clinic success data to the CDC, but there is little consequence for laboratories who choose not to do so. In other words, FCSRCA is a very good attempt to regulate ART

laboratories, but has no mandatory or enforcement component. CLIA provides the mandatory framework needed for oversite of the ART laboratory.

In summary, ART laboratories perform diagnostic testing that contributes both to the diagnosis and therapy of infertility. ART laboratories are an integral part of patient care, just as are all clinical laboratories. The morphological analysis of human oocytes and embryos deserves the same mandatory oversight as the analysis of sperm, which is covered by CLIA. In addition, having the analysis of sperm covered by CLIA but no other aspects of the ART laboratory, has created unnecessary confusion in the field. Although ART laboratories are not "expressly included" by CLIA, this does not mean that ART laboratories are "expressly excluded" either. The CDC model plan for ART laboratory oversight implemented by FCSRCA, while addressing important aspects of ART laboratories, has not been implement by individual states and is completely voluntary. Nothing in the FCSRCA supersedes or serves to repeal CLIA. CLIA provides the mandatory framework upon which the CDC model plan can be built. The CLIA statute and the FCSRCA are completely compatible. The mechanisms are now in place for accreditation and inspection of ART laboratories under CLIA. CLIA coverage of ART laboratories will not increase costs, and will not limit patient access to quality care. CLIA coverage of ART laboratories will, however, ensure a minimal and consistent degree of quality testing performed by competent laboratories and qualified personnel. The American Board of Bioanalysis (ABB) strongly believes that patients who seek treatment for their infertility deserve this minimal mandatory assurance. Recent headlines support the need for mandatory regulation of these laboratories. We urge CLIAC to recommend…once again…that the CMS exercise its authority and recognize that ART laboratories fall within the regulatory purview of CLIA.