



COLLEGE of AMERICAN
PATHOLOGISTS

Inspecting Reproductive Laboratory Accreditation Program (RLAP) Laboratories

Tips for the Clinical Inspector

Have you ever been on an inspection and felt like a fish out of water?

- **Stepping from a traditional clinical laboratory into a specialty laboratory such as a reproductive laboratory (embryology and/or andrology) can certainly be daunting.**
- **Luckily, the CAP checklists are designed to fit all types of clinical facilities.**

The CAP can help!

- **This activity will illustrate how you may have to shift your mindset when inspecting a Reproductive Laboratory Accreditation Program (RLAP) laboratory (if this is outside your own experience and comfort level).**
- **It will also address some key differences between the specialized reproductive laboratory environment and the traditional clinical laboratory environment.**

Objectives

- **Describe reproductive labs, their purpose, and organization.**
- **Identify key differences between clinical and reproductive laboratories regarding:**
 - **Lab director requirements**
 - **Competency Assessment**
 - **PT**
 - **Safety**
 - **QM**

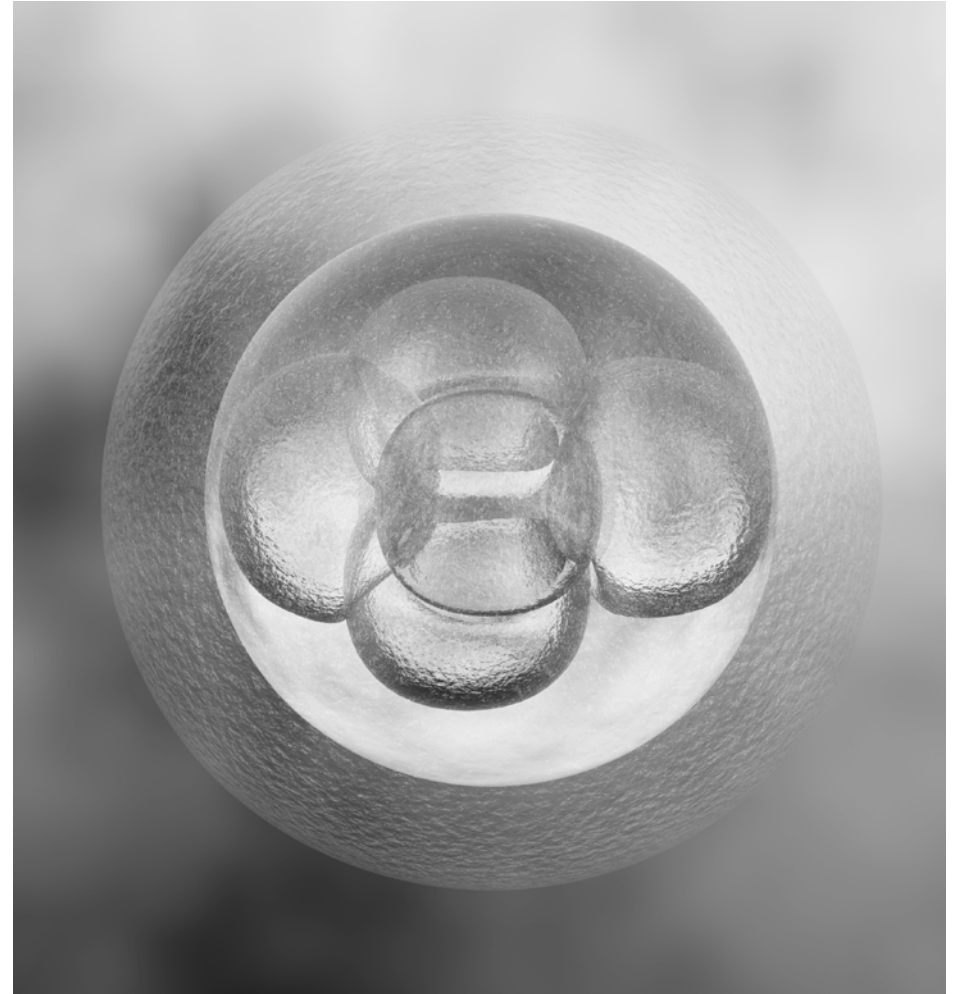
Reproductive Laboratory Accreditation Program (RLAP)

- **Created in 1993 to meet the needs of reproductive laboratories with:**
 - The inclusion of the activities of andrology and endocrine lab sections under CLIA-88.
 - Oversight needs for embryology (embryology was not included under CLIA-88).
- **The CAP also developed:**
 - Proficiency testing for RLAP labs
 - Inspector training for RLAP inspectors

Function of Reproductive Laboratories

Reproductive laboratories have a dual focus. They are designed for both the:

- **Diagnosis and**
- **Treatment of infertility**



Organization of Reproductive Laboratories

- **Reproductive laboratories are not uniform in their organization and may have as many as three disciplines in one facility.**
 - 1. Andrology (male fertility testing)**
 - 2. Endocrinology (hormone assays)**
 - 3. Embryology (activities of in vitro fertilization (IVF))**
- **Alternately, some (or all) of these disciplines may exist as a stand-alone laboratory with its own accreditation.**
- **Most commonly, reproductive laboratories accredited by the CAP RLAP are a combination of andrology and embryology functions.**

Organization of Reproductive Laboratories

In addition, a typical RLAP facility may also have:

- 4. Cryopreservation and cryo-storage activities (gametes and/or embryos – not subject to CLIA-88).**
- 5. Donor gamete/embryo collection, processing, storage, and transfer (subject to specific FDA regulations).**
- 6. *These activities may be part of a patient/couple's treatment or be part of a commercial sperm or oocyte bank.***

RLAP Inspection

- **RLAP endocrine laboratory activities mirror those of traditional clinical chemistry laboratories; therefore, inspection of endocrinology will not be discussed.**
- **Andrology and embryology laboratory activities are the areas that may be the most foreign to the clinical inspector, and the areas most reviewed in an RLAP inspection.**

Andrology

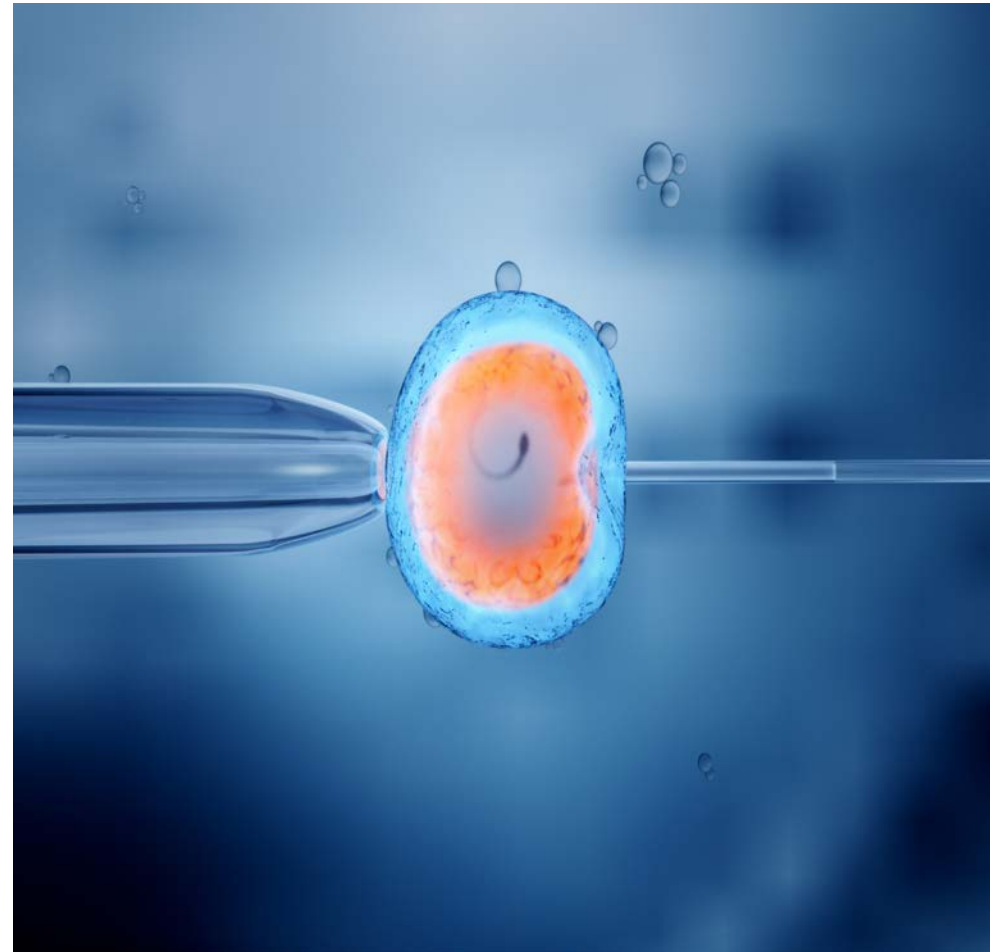
Andrology laboratories perform some (or all) of the following.

Tests:

- Semen analysis
- Semen biochemical tests
- Tests for sperm survival
- Sperm viability and sperm membrane integrity
- Sperm antibody testing
- Sperm penetration assays
- Sperm DNA fragmentation assays

Procedures:

- Sperm cryopreservation
- Sperm preparation for intrauterine insemination (IUI) or IVF treatments



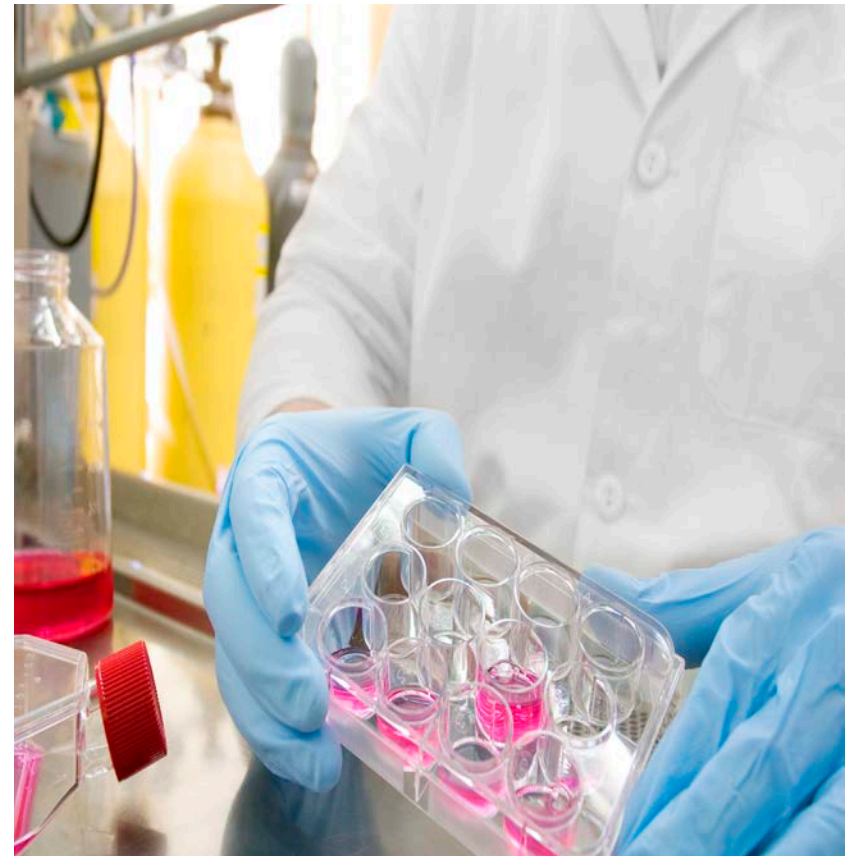
Embryology

- **Embryology laboratories are responsible for treatment procedures that manipulate both the human male and female gametes in vitro.**
- **Collectively these procedures are known as assisted reproductive technologies (ART).**
- **The most common ART procedure is IVF.**
- **Other treatment variations may also be part of the laboratory's menu:**
 - **Gamete intrafallopian transfer (GIFT)**
 - **Tubal embryo transfer (TET)**
 - **Zygote intrafallopian transfer (ZIFT)**

Embryology

Embryology laboratories perform any combination of the following:

- **Culture medium preparation**
- **Examination of follicular aspirates with oocyte identification**
- **Assessment of oocyte quality and maturity**
- **Sperm preparation**
- **Insemination of oocytes (standard or intracytoplasmic sperm injection)**



Embryology

Embryology laboratories perform any combination of the following (cont.):

- **Assessment of fertilization**
- **Embryo culture (contingent on blastocyst stage development)**
- **Embryo assessment**
- **Embryo transfer**
- **Oocyte/embryo/sperm cryopreservation**
- **Micromanipulation of human oocytes and/or embryos**



Shift Your Mindset

- In the traditional clinical laboratory the focus is on a ***diagnosis***.
 - This is also true of the endocrine and *most* functions of the andrology sections of a reproductive laboratory.
- However, in the embryology section, the focus is on a ***treatment*** (*development of a pregnancy and subsequent live birth of one or more offspring*).

Shift Your Mindset, cont'd

Clinical laboratories treat a single patient and reproductive laboratories most commonly treat a “patient couple.”

- **This complicates sample identification protocols due to the critical nature of matching the egg, sperm, and/or embryos from the proper partners when performing these procedures.**

Shift Your Mindset, cont'd

Because of the nature of the treatment (creation of a pregnancy/live birth), other aspects of the inspection may be a little different.

- **Example, the required retention of laboratory records is 10 years for treatment cycles involving human donor cells which is longer than what is usual in a traditional clinical laboratory**

The next few slides will examine some of the major differences with the RLAP facilities.

Let's Look at Some Director Requirements . . .

CAP checklist:

- **RLM.10166 and DRA.10100 address qualifications for laboratory directors.**
 - **RLM.10166 is specific for embryology directors.**
 - **DRA.10100 contains a table of laboratory director qualifications based on complexity of testing.**

RLM.10166 Embryology Laboratory Director Qualifications

The embryology laboratory director has proper qualifications through education and experience to provide direction and administration of the laboratory.

Note: The embryology laboratory director must have at least two years of experience in a laboratory performing in vitro fertilization or assisted reproductive technologies-related procedures and meet the following requirements:

- MD or DO licensed (if required) in the jurisdiction where the laboratory is located; or
- Doctoral degree in a chemical, physical, biological, or clinical laboratory science from an accredited institution; or
- Individual functioning as an embryology director on or before July 20, 1999.

RLM.10166 Embryology Laboratory Director Qualifications, cont'd

In addition, effective January 1, 2006, all new laboratory directors in laboratories located in the US and its territories must hold a current:

- **HCLD board certification (high complexity laboratory director), or**
- **ELD certification (American Board of Bioanalysis – embryology lab director), or**
- **Equivalent certification.**

RLM.10166 Embryology Laboratory Director Qualifications, cont'd

**For laboratories located outside of the US,
embryology laboratory directors must:**

- **Be an MD or DO licensed (if required) in the jurisdiction where the laboratory is located, or**
- **Have a doctoral degree in a chemical, physical, biological, or clinical laboratory science, and have at least two years of appropriate laboratory training and experience. Board certification is strongly encouraged (*but not required*).**

RLM.10166 Embryology Laboratory Director Qualifications, cont'd

- **“If the laboratory is also performing testing for the purpose of diagnosis, the laboratory director must meet the personnel requirements defined in the Director Assessment Checklist.”**
 - *In other words, if the lab performs even one CLIA-88 regulated test or procedure (eg, semen analysis, hormone assays), then the lab director must meet the CLIA requirements for that position.*
- **“If more stringent state or local regulations are in place for supervisory qualifications, including requirements for state licensure, they must be followed.”**

DRA.10100 Laboratory Director Qualifications

The CAP DRA checklist indicates:

- **“The laboratory director satisfies the personnel requirements of the College of American Pathologists.”**
 - **“Note: The qualifications required by the CAP for the position of laboratory director depend on the testing performed in the laboratory. The qualifications are also dependent upon whether the laboratory is subject to US regulations.”**

DRA.10100 Laboratory Director Qualifications, cont'd

It then indicates that:

- ***“For laboratories participating in the Reproductive Laboratory Accreditation Program, directors of laboratories performing andrology testing must meet the requirements described for high complexity testing and have at least two years of experience in a laboratory performing andrology procedures. This experience must include quality management, quality control, inspection, accreditation, and licensing procedures, as well as andrology procedures.*”**

Laboratory Director Differences

Clinical Laboratory	Reproductive Laboratory
Medical director is typically also the laboratory director	Medical director and laboratory director are generally two <i>different</i> people (the medical director runs the affiliated clinic and usually appoints the laboratory director (who runs the lab))
Laboratory directors are usually MDs or DOs	Laboratory directors are usually PhDs, most directors are HCLDs; An ELD certification is also acceptable (for embryology labs only)
Laboratories must follow CLIA guidelines for director qualifications	Embryology is not under CLIA and does not have to follow CLIA guidelines; however, it must follow the CAP requirements for lab director qualifications
Laboratory director typically does not do benchwork	Not uncommon for laboratory director to perform procedures

Laboratory General Checklist

In the reproductive laboratory there is no “GEN” person. These roles are filled by embryologists, endocrinologists, and andrologists.

Let’s review some unique GEN differences you may encounter in an RLAP laboratory...

Competency

When assessing competency, consider the following:

- **Many reproductive laboratories are very small. Therefore, it is common for staff to be cross-trained in other areas of the laboratory.**
- **The laboratory director in some labs performs some of the benchwork.**
 - **It is important to determine if competency is being properly assessed for all activities of each lab employee, including laboratory directors who are performing tests or procedures.**

Competency, cont'd

Competency for **embryology** has only **five** (not six) elements:

1. Direct observations of routine embryology procedures, including, as applicable, patient identification, specimen collection, handling, and processing
2. Monitoring the recording and reporting of embryology cycle events
3. Review of intermediate test results or worksheets quality control records, proficiency testing results, and preventive maintenance records
4. Direct observation of performance of equipment maintenance and function checks
5. Evaluation of problem-solving skills

Assessment of test performance through testing previously-analyzed specimens, internal blind testing samples, or external proficiency testing samples is not required.

Physical Environment

- **When active, embryology areas are kept under sterile conditions.**
- **If you are inspecting an embryology area, you may need to change into appropriate attire (shoe covers, cap, scrubs, or paper coveralls).**

Physical Environment, cont'd

- **The creation and/or culture of human embryos in an embryology laboratory may require maintenance of incubator function for as long as seven continuous days. Likewise, the cryopreservation function of these labs involves the long-term maintenance of patient's gametes and embryos in cryo-storage.**
- **It is essential that the laboratory has contingency plans for both internal and external disasters in order to preserve this special patient's material. This would include but not be limited to:**
 - **Back-ups for all critical equipment**
 - **Back-up power source**
 - **Adequate back-up inventory of supplies**
 - **Adequate supply of LN2**
 - **Training of staff in emergency procedures**

Safety

- **Reproductive labs will frequently have liquid nitrogen (LN2). An inspector coming from a clinical laboratory may not have experience with LN2.**



Safety, cont'd

- **Liquid nitrogen storage in the cryo-lab requires addressing safety issues upfront:**
 - **Lab must be able to show that adequate ventilation is present in the room.**
 - **Oxygen sensors must be present at breathing height.**
 - **Appropriate personal protective equipment (PPE) to prevent frostbite must be available and used as the lab's written policy indicates.**
 - **Safety data sheet (SDS) sheets must be available.**
- **Inspectors should ask probing questions (eg, what would you do in the event of an LN2 spill).**

Safety, cont'd

- **GEN.77550 Liquid Nitrogen Safety**

The laboratory has identified all areas where liquid nitrogen (LN2) is used and/or stored, and there are appropriately mounted oxygen sensors with a low oxygen alarm in all areas where there is an asphyxiation risk.

- **GEN.77500 Liquid Nitrogen and Dry Ice**

Adequate policies, procedures, and practices are in place for the use of liquid nitrogen (LN2) and dry ice.

Quality Management (QM)

To refresh, a good QM plan:

- **Is a documented system**
- **Defines improvement goals**
- **Focuses on clinical issues**
- **Is consistent with scope of services**
- **Considers all customers**

Quality Management (QM), cont'd

For reproductive labs, you may see these discipline specific indicators:

- **Andrology**
 - IUI prep quality
- **Embryology**
 - Cryo-survival rate
 - Intracytoplasmic sperm injection (ICSI)
- **Cryopreservation**
 - Quality of post-thaw specimens
 - Outcomes of insemination/implantation

GEN Checklist Differences

Clinical Laboratory	Reproductive Laboratory
Competency Assessment	
<ul style="list-style-type: none"> • Six elements must be met; • Staff are generally specialized; • Director usually does not do benchwork 	<ul style="list-style-type: none"> • Five elements for embryology • Staff are generally cross-trained in all areas of laboratory • Director often does benchwork (requires applicable competency assessment)
Safety	
<p>Usually will not see long-term specimen storage or liquid nitrogen in a clinical laboratory</p>	<p>Liquid nitrogen is universally used for cryo-storage. Check:</p> <ul style="list-style-type: none"> • Back-up storage procedures • Oxygen sensor placement • Level/temperature monitoring procedures
Quality Management	
<p>Monitors are frequently associated with improving diagnostic outcomes</p>	<p>Monitors are frequently associated with treatment outcomes</p>

All Common Checklist

Now let's look at some unique COM differences you may encounter in a reproductive laboratory...



Proficiency Testing (PT)

- While commercial PT is *offered* for embryology testing, CAP Accreditation does not require laboratories to enroll.
- Alternative performance assessment (APA) is required.
- Ensure you inspect the laboratory's APA and that the laboratory follows **COM.01500**.

Proficiency Testing (PT), cont'd

COM.01500 Alternative Performance Assessment

For tests for which the CAP does not require proficiency testing (PT), the laboratory at least semiannually exercises an alternative performance assessment system for determining the reliability of analytic testing.

Performing commercial PT is one way to meet this requirement.

Specimens

- **Because of the special nature of the gametes and embryos and the difficulty in obtaining these specimens, rejection criteria for reproductive specimens is not as stringent as what you may see in the clinical laboratory.**
- **Ensure you read the rejection criteria policy and that the laboratory follows its own policy.**

Specimens, cont'd

COM.06300 Specimen Rejection Criteria

There are written criteria for the rejection of unacceptable specimens, instructions for the special handling of suboptimal specimens, and records of disposition of all unacceptable specimens in the patient/client report and/or quality management records.

Specimens, cont'd

Specimen identification is multipronged, required at all critical steps:

- **At the collection of the gametes**
- **At fertilization (proper sperm and oocytes are used)**
- **During embryo culture**
- **During biopsy of embryos**
- **During cryopreservation**
- **During thaw of cryopreserved samples**
- **Before transfer to the uterus**



Specimens, cont'd

- **Again the specimen identification process is unique because in the case of reproductive laboratories, the specimens are usually from a “patient couple,” rather than an individual.**
- **Improperly-labeled specimens in a reproductive laboratory is a life-changing error that effects more than just the “patient couple.” It may also impact another individual or couple as well as any resulting child. It becomes an ongoing human tragedy. Strict policies for specimen identification must be in place.**

Specimens, cont'd

RLM.09400 Chain-of-Custody

The identity of the patient specimen (sperm or embryos) is checked against the identity of the patient prior to transfer or insemination and this identification is recorded.

Donor Specimens

Reproductive labs, must comply with the FDA regulations regarding infectious disease testing/screening of donor cell/tissue transplantation, that use:

- Donor sperm
- Donor oocytes
- Donor embryos
- Gestational surrogates



Donor Specimens, cont'd

RLM.12455 FDA Registration

Laboratory is registered with the FDA for all appropriate human cells, tissues, and cellular- and tissue-based products (HCT/P).

RLM.12499 Donor Cells/Tissue Tracking

Each donor cell/tissue product is assigned a unique identification code that relates to the donor and to all records pertaining to that product, with maintenance and tracking of this identifier throughout receipt, storage, issuing of the product, and disposition.

COM Checklist Differences

Clinical Laboratory	Reproductive Laboratory
Proficiency Testing	
<ul style="list-style-type: none">• Enrollment in CAP-accepted PT is required for many analytes• PT evaluations will be readily available for inspector review	<ul style="list-style-type: none">• Not as many PT requirements• APA is required; many acceptable ways to meet APA requirements
Specimens	
<ul style="list-style-type: none">• Most specimens are easily recollected; rejection criteria may be stringent• Labeling errors may be life-changing in certain areas (eg, transfusion medicine) but often labeling errors can be caught with delta checks or patient history; specimens are not stored/tracked long-term	<ul style="list-style-type: none">• Specimens are more difficult/sensitive to collect, rejection criteria may be more lax• Labeling errors are life-changing; specimens must be carefully labeled throughout the treatment process; policies/procedures must address labeling/tracking for all phases and types of specimens

One Final Thought

We hope this presentation has both enlightened and reassured you about the RLAP inspection process.

Although there are unique aspects to reproductive laboratories, the goals of the RLAP program remain the same as any other type of CAP-accredited lab:

- Maintain accuracy of test or procedure outcomes to ensure quality patient care and safety.**
- Meet required regulatory standards.**
- Exchange ideas and best practices among laboratory peers.**
- Offer professional development and learning opportunities for laboratory staff.**

References

- 1. College of American Pathologists; Hoeltge GA, ed. *Laboratory Accreditation Manual*. Northfield, IL: College of American Pathologists; 2019.**
- 2. College of American Pathologists. *CAP Accreditation Program Checklists*. Northfield, IL; College of American Pathologists; 2019.**
- 3. College of American Pathologists. *Standards for Reproductive Laboratory Accreditation*. Northfield, IL; College of American Pathologists; 2017.**



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