Request for Proposals: National PHL Drug Susceptibility Testing (DST) Reference Center for *Mycobacterium tuberculosis* (MTBC)

Application Due date: November 15, 2019

Submit to: Anne Gaynor, Manager of HIV, Viral Hepatitis, STD and TB (Anne.Gaynor@aphl.org)

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Summary

The Association of Public Health Laboratories (APHL), in cooperation with the US Centers for Disease Control and Prevention (CDC) Division of Tuberculosis Elimination (DTBE), is seeking to recompete the National Public Health Laboratory (PHL) Drug Susceptibility Testing (DST) Reference Center for *Mycobacterium tuberculosis* (MTBC) for PHLs with low to moderate incidences of TB. APHL is seeking to identify one (1) state or local public health laboratory to serve as the Reference center. This Reference center will serve as an extension of the CDC DTBE Laboratory Branch and provide services that are complementary to those at CDC. Services provided by the Reference center for PHLs with lower volumes of drug susceptibility testing (DST) (<50 isolates per year) will include:

1) first-line DST;
2) second-line DST;
3) molecular detection of drug resistance.

Background

Performing DST is technically demanding and maintaining proficiency in performing testing and interpreting results is critical to ensuring accuracy. Historic data from the National TB Laboratory Services Survey[1] revealed that 60/96 (63%) of responding laboratories performing first-line DST were PHLs. However, 42% of these responding laboratories performed testing for five or fewer MTBC isolates per month. In more recent data from CDC's Model Performance Evaluation Program for DST of MTBC, 69% (50/72) of participants were PHLs.[2] Thirty-five percent (25/72)of the particpating laboratories reported performing fewer than or equal to 50 DST per year.[2] CDC currently recommends referring testing if a laboratory is performing DST for fewer than 50 isolates per year.[3] These data indicate that PHLs are an essential provider of first-line DST for MTBC in the United States. Nevertheless, many of these laboratories have low testing volumes.

Second-line DST is critical when isolates are resistant to rifampin (RMP) or any two first-line drugs as well as situations where additional information to design an effective regimen is needed (e.g., drug intolerance). Methods for second-line DST are not standardized and currently, there are no FDA-cleared assays for this purpose. Therefore, laboratories may choose to follow established consensus guidelines (e.g. CLSI or WHO) or evaluate their own test concentrations and interpretive criteria. As a result, discordance among laboratories and methods is common for some second-line drugs. In the National TB Laboratory Services Survey, 79% (23/29) of respondents performing second-line DST were PHL. Each of the 22 PHL performing fewer than 50 first-line DST per year currently refer for second-line DST.[1]

Molecular detection of mutations associated with drug resistance can provide rapid results within hours or days versus the weeks required for growth-based DST. CDC offers the molecular detection of drug resistance (MDDR) service for concurrent molecular and phenotypic testing of isolates and nucleic acid amplification test (NAAT) positive sediments meeting submission criteria. With the wide-spread

availability of the FDA market authorized Cepheid Xpert MTB/RIF assay, rapid confirmation of drug resistance by molecular methods takes on increasing importance as more clinical laboratories adopt these technologies. Performing molecular testing (primarily sequencing) requires technical expertise and extensive experience in interpreting test results. Laboratories performing molecular testing must be competent in providing consultative services and must continually adapt to advancements in the field. These requirements may limit the number of laboratories that should be providing molecular testing for drug resistance. However, advancements in the predictive value of genetic determinants are rapidly progressing with some laboratories choosing to provide molecular testing as a primary methodology.

In addition to performing quality assured testing, it is imperative that testing and reporting of results is performed in a timely manner to ensure the greatest impact on clinical management. The goal of the reference center is to offer molecular detection of drug resistance within two days, first-line DST within 17 days, and second-line DST results within 21 days of receipt at the reference center. To meet the stated turn-around-time requirements for DST testing and reporting, extensible laboratory information systems (LIMS) and infrastructure must be available or adopted to support DST testing and resulting workflows. In addition to a Laboratory Information Management System (LIMS) to support analytical data capture during testing, careful consideration must be placed on the ability to electronically capture and share pre and post analytical data with external submitters. This functionality, known as Electronic Test Order and Result (ETOR) is an important, yet still maturing, technical capability for public health laboratories.[4] ETOR allows a public health laboratory to offer a higher level of service to its submitters, reduces the impact of manual data entry and reporting methods, and increases communication efficiencies across a network of clinical and public health partners.

To address the gap in access to quality assured and cost-effective DST, APHL and CDC established the National PHL DST Reference Center for in March 2015. As of June 2019, there were 17 enrolled submitters. From 2016–2018, the National PHL DST Reference Center for MTBC received a total of 518 samples (462 isolates and 56 specimens) for DST.[5] In 2016–2017 this changed to 247 samples and in 2017–2018 a total of 271 samples were received. Between 2016 and 2018, molecular DST was performed on 200 samples, first-line DST was performed on 441 samples and second-line DST was performed on 85 samples.[5] During this timeframe, testing in the Reference center identified 68 isolates with drug resistance

Eligibility

Eligible laboratories include all public health laboratories with the following capabilities, resources and facilities in place. Specific expectations regarding the methodologies to be used by the reference center are outlined in Appendix A: *Expectations for National PHL DST Reference Center for MTBC*. All applicants are required to agree to the following minimum requirements (as outlined in Appendix B: Minimum Requirements for National PHL DST Reference Center for MTBC):

1. Availability of necessary equipment (e.g., MGIT) or ability to purchase additional equipment if necessary, anticipating no more than 300 additional first-line DSTs;
2. Availability of adequate laboratory space (including infrastructure for unidirectional workflow for molecular testing) or accommodate additional equipment if necessary, anticipating no more than 300 additional first-line DSTs;
3. Sufficient workforce capacity for expanded testing volume or the ability to hire additional qualified staff;
4. Established capacity for MTBC culture and to perform first and second-line DST phenotypic methods to detect drug resistance in MTBC;
5. Established capacity to perform molecular detection of drug resistance for MTBC
    a. Applications that include molecular testing as the primary method will be considered;
6. Participation in CDC's Model Performance Evaluation Program (MPEP);
7. Willingness to alter or amend existing testing protocols;
8. Willingness to increase frequency of performing certain methods (if required) to meet expected turnaround times;
9. Willingness to amend specimen submission form(s) to include additional variables;
10. Willingness to alter existing reporting language to a standardized reporting language with input from APHL/CDC;
11. Willingness to share copies of QA or biosafety documentation associated with relevant procedures to APHL and CDC upon request;
12. Informatics capabilities:
    a. **Laboratory Information Management System** in place and able to be enhanced or modified to meet DST test algorithms, workflows, submission requirements and reporting language and

       Electronic Test Order and Results (ETOR)
    b. Proven capability to support ETOR, either through an existing web portal or through standardized messaging

       OR

    c. The ability to adopt APHL's LabWeb Portal Solution, hosted on the APHL Informatics Services platform (AIMS) using LIMSConnect

13. Ability to perform and report results from laboratory developed tests or research use only assays

Anticipated RFP Schedule

September 30, 2019	–	RFP Issued
October 10, 2019	–	Informational Teleconference (Q&A)
October 18, 2019	**–**	**Letter of Intent Due to APHL (see below)**

Submit the Letter of Intent (Due 10/18/19) and completed application (Due 11/15/19) to Anne Gaynor, anne.gaynor@aphl.org

November 15, 2019	–	**RFP Responses Due**
December 6, 2019	–	Proposal review completed
December 9-13, 2019	–	If needed, follow-up interviews and updated proposals due
December 20, 2019	–	Final review completed and awardees selected
Spring 2020	–	Harmonization, Validations and other Pre-Planning (as needed)
July 1, 2020	–	First year contract awarded

APHL will communicate any modification to this anticipated schedule on APHL's procurement website (www.aphl.org/rfp) and via an email blast to the public health laboratories (PHLs).

Response Submittal

Confirmation of Intent to Respond

APHL requires that prospective applicants submit a brief email statement indicating an intent to submit a proposal. APHL must receive this email by no later than **5:00pm EST on October 18, 2019.** To allow for appropriate review process planning, **a letter of intent is required** for consideration.

Final Response

APHL must receive complete responses by **5:00 pm EST on November 15, 2019**. Please see Proposal-Required Submissions section for items that must be included in the completed proposal. Applicants may send proposals via email to Anne.Gaynor@aphl.org

APHL will send an email acknowledging the receipt of your application; if you do not receive an acknowledgement within 48 hours, please email the RFP point of contact above to confirm receipt.

Award

One laboratory will be selected. The amount of the award will be based on submitted budgets and may vary year to year based on testing performed and volume of specimens submitted. Anticipated specimen volume is approximately 250-300 specimens per year, although not all test methods will be performed on all specimens. The maximum compensation is estimated at $350,000, to be distributed based on per specimen rates. Funding is distributed through an annual contract with APHL. By accepting this award, the laboratory agrees to the agreed upon rate for up to a five (5) year time span barring substantive changes in scope or material expenses at APHL's discretion.

Use of funds: The awarded laboratory should use the funding for testing of referred specimens (including retesting due to laboratory/personnel error), reagents and consumables and personnel time required to conduct these activities and may be used for necessary equipment upgrades or expansions, equipment maintenance and service agreements or validation of new testing services.

Submit the Letter of Intent (Due 10/18/19) and completed application (Due 11/15/19) to Anne Gaynor, anne.gaynor@aphl.org

Term of Project

The project term will be from July 1, 2020 through June 30, 2021. Additional activities may precede this start term if needed to establish testing capacity, data transmissions and proficiency demonstrations to ensure operational expectations are in place for the contracted period.

The potential for annual renewals (with each additional funding year running from July 1 to June 30) may be considered by APHL based on availability of funds and performance of the awardee for a maximum of four additional years (to end June 30, 2025). Each of the potential renewals may involve some adjustment to the scope of work in order to address any change in the funding received by APHL and to accommodate CDC programmatic needs in that funding year. The awardee will be notified in advance of any modification to the anticipated scope of work in a future funding year.

Evaluation Team

APHL staff, led by the HIV, Viral Hepatitis, STD and TB (HHST) Program Manager, will conduct an initial review of all proposals for completeness. Any application that is incomplete as of the proposal due date specified in the Anticipated RFP Schedule section above will not be considered and will not receive a formal evaluation.

Complete proposals will be reviewed by a team of three subject matter experts (SMEs) from CDC's Division of Tuberculosis Elimination and a panel of three APHL members selected from non-applicant public health laboratories. SMEs from CDC will be identified and selected by the DTBE Laboratory Branch Chief based on their familiarity with laboratory techniques and project requirements. APHL member experts will be identified from among the non-applicant laboratories by the APHL HHST Program Manager and will have expertise in the laboratory testing methods described in this RFP and familiarity with APHL reference center structure. Once potential reviewers have been identified, APHL's Director of Infectious Disease Programs will have final approval over the review team's composition.

Conflict of Interest

APHL will ask potential reviewers to complete and sign APHL's **Conflict of Interest Disclosure Statement** in order to disclose any real or perceived conflict of interest prior to the start of the evaluation process. Reviewers will have to affirm that they have no conflict of interest that would preclude an unbiased and objective review of the proposals received. A copy of the disclosure statement and the related Fiduciary Responsibility and Conflict of Interest Policy is attached as **Appendix D**: Conflict of Interest Disclosure Statement and Policy. APHL will not select reviewers with a perceived or potential conflict of interest. This Conflict of Interest Disclosure Statement is provided in the RFP for Applicant review only. **Applicants should not complete the Conflict of Interest Disclosure Statement unless instructed by APHL.**

Evaluation Criteria

The evaluation team will evaluate proposals based on responses to the questions in the Proposal – Required Submissions section and will give a numeric score of up to 100 maximum points based on the scorecard template in Appendix C.

Laboratories meeting the following criteria have preference in the evaluation:

1. Extensive experience with the test methods;
2. Ability to handle increased volume;
3. Existing in-house subject matter expertise;
4. Experience and past performance serving as a reference center;
5. Current usage of APHL's LabWeb Portal Solution;
5. Ability to comply with expectations laid out in Appendix A; and
6. Ability to meet the minimum expectations outlined in Appendix B.

Evaluation Process

The evaluation team will conduct the review via a combination of email communication between APHL's HHST Program Manager and the members of the evaluation team, or among the evaluation team members and teleconference and/or webinar evaluation sessions. APHL's HHST Program Manager will coordinate the review process and the evaluation sessions.

The reviewers may request follow-up interviews with all or some of the applicant laboratories and, following these interviews, may request supplemental information on an applicant's proposal. The evaluation team will use these interviews and any supplemental information to clarify a laboratory's capacity or experience in one or more of the evaluation criteria, or to explain other information contained in an applicant's proposal.

There will be no formal evaluation performed by a member of APHL staff. In cases where all other evaluation criteria are substantially similar, APHL will have the ability to advise the evaluation team on selections that would provide geographical spread or otherwise diversify APHL's funding allocations. In addition, the evaluation team may receive documentation from APHL staff on an applicant's past performance in other capacities as part of the evaluation criteria.

Post-Evaluation Procedures

APHL staff will notify the selected laboratories within ten business days of the completion of the evaluation and will post the names of the recipient(s) to APHL's procurement website, www.aphl.org/rfp, within three (3) business days of the laboratory's acceptance of the award. Unsuccessful applicants will receive notification of these results by e-mail within 30 days after the name of the selected awardee is posted.

All applicant laboratories will be entitled to utilize APHL's RFP Appeals Process to formulate a protest regarding alleged irregularities or improprieties during the procurement process. Specific details of this policy are located on the procurement website.

Conditions of Award Acceptance

The eligible laboratory must be able to contract directly with APHL or have an existing relationship with a third-party organization that can contract directly with APHL on behalf of the laboratory. Laboratories must agree to comply with expectations outlined in Appendix A. Acceptance of the award means agreement to the compensation structure and amounts agreed upon with the awardee and APHL.

Prior to making the official award, a group of individuals from CDC and APHL will be entitled to elect to tour the facilities to assess compliance with requirements for testing and/or have a teleconference with applicant laboratories. Post award, monitoring site visits may be conducted to include an assessment of continued compliance.

Following selection and prior to making the official award, APHL will require finalists to submit a letter of support from the LIMS vendor confirming the following items as applicable: Confirming the respondents capability to modify and maintain the DST specific test algorithms, and reporting language within the LIMS, confirming the ability of the respondent to connect the LIMS to APHL's instance of the LabWeb Portal using the LIMSConnect Solution on the AIMS cloud-based platform and confirming the applicants ability and willingness to extend any current ETOR capability to support the requirements of this project.

Proposal – Required Submissions

An interested laboratory must submit both a letter of intent to apply (due October 18, 2019) and a proposal (due November 15, 2019). Applications must comply with submission requirements set out in the Additional Information and Deadlines for Application Submission below. A complete proposal will include the following items:

- **A completed and signed copy of Appendix B,**

  Note: If your laboratory cannot respond "yes" to each of the minimum requirements, your laboratory does not meet the minimum qualifications required to apply for this award.

- **A letter of support from your institution's IT department:**
  a. **Current Reference Center Only:** Confirming your commitment to maintain connectivity to the AIMS LabWeb Portal environment using the LIMSConnect solution (see reference documents: ETOR-LWP-LIMSConnect Slides, LWP.v8 Architecture General Information and LIMS Connect Overview) with the support of a designated IT staff member **OR**

  b. Confirming your ability to establish connectivity to the AIMS LabWeb Portal environment using the LIMSConnect solution (see reference documents: ETOR-LWP-LIMSConnect Slides, LWP.v8 Architecture General Information and LIMS Connect Overview) **OR**

c. Confirming your current ETOR capability using an existing web portal or through standardized messaging and that there is the capacity to onboard all submitting laboratories (current submitter list available upon request) to the system including any costs associated with such onboarding **AND**

Confirming that the applicant will have the support of a designated IT staff member to support this work.

- **Responses to Questions (below)**
  - Responses should be limited to no more than ten (10) single spaced pages (font size ≥ 11pt, 1 inch margins)
  - The proposal should include responses to the questions below, including each aspect of the question. The proposal should indicate what question is being answered.

Response to Questions

Physical Environment

1. Describe your laboratory's ability to absorb increased workload in performing growth-based and molecular testing for drug resistance at current staffing levels by defining the additional monthly volume your laboratory would be able to undertake for growth-based DST (first and second-line) as well as molecular-based testing.
   a. Does the facility have laboratory space available for additional instrumentation or staff that may be needed to accommodate increased workload? Please describe the existing space, equipment and staff to handle the testing volume(s) for all three aspects of testing as well as ability to expand?
   b. Does the laboratory have the ability to hire additional staff to accommodate the workload if necessary? If yes, please describe approximate timelines associated with posting and hiring new positions.

Workforce

2. Does your laboratory have staff with the subject matter expertise to provide guidance to submitting laboratories and interpretation of growth-based and molecular test results including discordant results?
   a. Please describe the qualifications and experience staff have in providing consultative services.

Growth-Based DST Methods

3. Please describe the current methodology used in your laboratory for growth-based first-line DST for MTBC. Include information on:
    a. how long the methodology has been in use
    b. how often it is performed
    c. Information on testing algorithm(s) and reflexes associated with FL-DST
    d. annual volume (2017 and 2018 Calendar Year)
    e. average turnaround time (from diagnostic specimens and reference isolates)
    f. number of laboratory staff and their experience with the method(s) including the years of experience of each trained staff member
    g. any training your staff has received

4. Please describe the current methodology used in your laboratory for growth-based second-line DST for MTBC. Include information on:
    a. how long the methodology has been in use
    b. how often it is performed
    c. information on testing algorithm(s) and reflexes associated with SL-DST
    d. annual volume (2017 and 2018 Calendar Year)
    e. average turnaround time (from diagnostic specimens and reference isolates)
    f. number of laboratory staff and their experience with the method(s) including the years of experience of each trained staff member
    g. any training your staff has received

Molecular DST Methods

5. Please describe the current methodology and algorithms used in your laboratory for molecular detection of drug resistance for MTBC. Include information on:
    a. the method/platform(s) used
    b. how often it is performed
    c. how long the methodology has been used
    d. information on algorithm(s) and reflex testing associated with molecular DST
    e. which genetic loci are evaluated
    f. how interpretations are determined
    g. specimen types tested
    h. your annual volume (2017 and 2018 Calendar Year if available)
    i. average turnaround time (primary specimen or isolate)
    j. number of laboratory staff and their experience with the method(s) including the years of experience of each trained staff member
    k. Any training your staff has received.

Reporting Results/Information Technology

6. Please describe all LIMS, tools, and infrastructure available to support the work outlined in Appendix A including ordering, testing and resulting workflows (e.g. LIMS, ETOR HL7 or ETOR web portal, secure fax, etc.) Respondents must identify any ETOR capability available to support the reporting requirements of the TB DST Reference Center including ability to modify LIMS to agreed upon reporting language (current reporting language available at www.aphl.org/tbdst) and capacity to onboard submitting sites to the ETOR solution and any/all back-up reporting mechanisms. Please also include the process and estimated timeline to onboard current submitting public health laboratory's (roster of submitting sites is available upon request).

   *If no current ETOR system is in place or the system is unable to be used for this work, the laboratory will be expected to adopt APHL ETOR Lab Web Portal solution. Respondents should review the referenced Lab Web Portal reference documents (*ETOR-LWP-LIMSConnect Slides, LWP.v8 Architecture General Information and LIMS Connect Overview*) and evaluate their capability to connect to the Lab Web Portal Solution hosted on APHLs Informatics Messaging Service platform*

Reference Center Testing

7. Briefly describe your laboratory's experience, if any, in providing reference testing for other public health laboratories in a shared service model including but not limited to coverage for a limited period of time to assure continuity of operations.

New Technology and/or Laboratory Developed Tests

8. If selected, would your laboratory be willing to evaluate and incorporate additional new technologies and/or testing algorithms as they become available?
   a. Please briefly describe your experience in participating in method or platform evaluation(s).
   b. Briefly describe your procedures for validating laboratory developed tests including but not limited to adding new drugs to susceptibility panels and/or new molecular targets. Please also describe estimated sample size and general approach.

Budget

9. Provide a 1 year budget outlining at least the following line items: equipment purchase or upgrade based on the methods requirements outlined in Appendix A (if needed); staff time; charge per specimen/isolate tested by each method; and anticipated overhead charges if any.

Additional Information and Deadlines for Application Submission

Applicants must direct all questions to Anne Gaynor (anne.gaynor@aphl.org). APHL will post questions received from interested PHLs, together with the answers provided by APHL or CDC staff to APHL's procurement website associated with the specific RFP (www.aphl.org/rfp).

To allow for appropriate review process planning, a **letter of intent is required for consideration**. Applicants should submit letters by email to Anne Gaynor at APHL (anne.gaynor@aphl.org) no later than **5:00 pm EST on Friday, October 18, 2019.**

Applications are due to Anne Gaynor at APHL (anne.gaynor@aphl.org) **by close of business (5:00pm ET) November 15, 2019.** APHL will send an email acknowledging the receipt of your application. If you do not receive an acknowledgement within two (2) business days, call 240-485-2739 to confirm receipt.

APHL will hold an optional teleconference on Thursday October 10, 2019 at 2:00pm ET. The purpose of this call will be to provide a brief overview of the project and to allow potential applicants to ask CDC and APHL questions. Please come with questions prepared.

Teleconference Call-in Information is below, or please contact anne.gaynor@aphl.org or infectious.diseases@aphl.org no later than 8:00am ET on October 10, 2019 to receive the calendar invitation.

Join Zoom Meeting
https://aphl.zoom.us/j/130625862

Call-in Information
1-646-876-9923 OR 1-669-900-6833
Meeting ID: 130 625 862

References:

1. Association of Public Health Laboratories. (2012). National TB Laboratory Services Survey Report. Silver Spring, MD. Available at: http://www.aphl.org/AboutAPHL/publications/Documents/NationalTBReport_June2012.pdf
2. Centers for Disease Control and Prevention. (2019). Mycobacterium tuberculosis Complex Drug Susceptibility Testing Program-Model Performance Evaluation Program, Report of Results. Atlanta, GA. Available at: https://www.cdc.gov/tb/topic/laboratory/mpep/pdf/MPEP-March-2019.pdf
3. Association of Public Health Laboratories. (2007). TB Drug Susceptibility Testing Expert Panel Meeting Summary Report. Silver Spring, MD. Available at: http://www.aphl.org/aphlprograms/infectious/tuberculosis/Documents/ID_2007Dec_TB-DST-Report.pdf
4. Dudik I, Dennis M, Higginbotham K, Johnson S, Sankrithi N, Shepard R, Weding M. The public health need for ETOR, presented at APHL 2019, St. Louis, MO, June 2019. Available at: https://www.aphl.org/rfp/Documents/ID_TB-DST-RC-ETOR%20Poster_2019%20AM.pdf
5. Ancona N, Yu S, Lin G, Desmond E, Dalton T, Johnston S, Starks A, Wroblewski K, Gaynor A. An evaluation of testing activities undertaken by the National Public Health Laboratory Drug Susceptibility Testing (DST) Reference Center, 2016-2018, presented at the 11th National

Conference on Laboratory Aspects of Tuberculosis, Atlanta, GA, April 2019. Available at: https://www.aphl.org/conferences/proceedings/Documents/2019/1.Ancona.TBDSTRC.pdf

Appendix A: Expectations for National PHL DST Reference Center for MTBC

Methods and Test Algorithms

Molecular Testing

- Molecular detection of drug resistance testing needs to be performed as needed to provide an expeditious turnaround time from sample receipt. This turnaround time may vary depending on methodology (e.g., conventional vs. NGS) employed.
- The minimum panel for testing will include the following targets:
    - Rifampin
        - RRDR of *rpoB*
        - codon 170 (previously 176) in *rpoB*
        - codon 491 (previously 572) in *rpoB*
    - Isoniazid
        - the promoter region of *inhA*
        - *katG*
        - *fabG*
        - *ahpC*
    - Results should be reported using MTBC codon numbering rather than the historic (*E. coli*) numbering schemes but may include the previous numbering for reference as well during the transition.
- Laboratory must have a validated heat inactivation protocol and provide documentation of verification upon request.
- The reference center will accept NAAT positive **sediments** for testing with one exception. Sediments submitted for confirmation of an Xpert MTB/RIF result "rifampin resistance detected", may be referred directly to CDC's MDDR from the submitting laboratory for confirmation and the expanded molecular panel available at CDC.
    - Cultures will be set up from sediments for growth-based first-line DST.
    - When rifampin resistance is detected, an aliquot of the residual sediment (if available), heat-kill, or isolate may be referred to CDC's MDDR as soon as possible for additional molecular testing and concurrent second-line DST. Second-line DST will also be performed at the reference
    - A system will be established (e.g., trigger in LIMS) for identifying problematic samples requiring extensive time for growth (>2 weeks) whereby an isolate can be requested from the submitting laboratory for first-line DST.
    - If rifampin resistance is detected by molecular testing, an aliquot may be referred to CDC's MDDR as soon as possible for additional molecular testing and concurrent

second-line DST. If the volume of the remnant aliquot is not sufficient, DNA extract from molecular testing can be submitted, or the reference center may request that the submitting lab submit another sample directly to CDC. First and second-line DST will also be performed at the reference center.

First-line DST (FL-DST)

- Testing will be performed as needed to meet the turnaround time goal of 17 days from date of receipt at the reference center.
- FL-DST will be performed with a panel of rifampin (RIF), isoniazid (INH) (0.1 µg/mL), pyrazinamide (PZA), and ethambutol (EMB).
    - Reflex to higher concentration of INH as needed
    - Submitting laboratories will be asked to refer an aliquot of positive growth (optimally from broth) as soon as the culture becomes positive and identification of MTBC is confirmed.
    - A purity plate will be set up as well.
- If resistance to any first-line drug is detected, reflex testing to confirm resistance and for second-line drugs will be performed.
- If growth-based testing reveals resistance to rifampin, isolate may be referred to CDC's MDDR as soon as possible for additional molecular testing and concurrent second-line DST. Second-line DST will also be performed at the reference center.

Second-line DST (SL-DST)

- Testing will be performed as often as needed and with a goal turnaround time of 21 days from date of receipt at the reference center to result when ordered by the submitter
- At a minimum, the testing panel mustinclude the following:
    - Second-line injectables (amikacin and kanamycin)
    - Ethionamide
    - Rifabutin
    - Fluoroquinolones
        - Moxifloxacin should be included
- SL-DST methods may include agar proportion, automated liquid broth systems (i.e. MGIT) or minimum inhibitory concentration (MIC)
- SL- DST will be performed on reflex when resistance is detected to any first-line drug (including rifampin)
- SL-DST will be performed when requested due to clinical need (e.g., drug intolerance).
- It is expected that second-line testing will be performed as soon as possible when needed.
- DTBE/LB Reference Laboratory will provide access to isolates needed for validation.
- DTBE/LB can assist with training if needed/as applicable.

Electronic Test Order and Resulting

- Laboratory Information Management System in place and able to be enhanced or modified to meet DST test algorithms, workflows, submission requirements and reporting language.
    - Current reporting language for molecular detection of drug resistance is available at: www.aphl.org/tbdst
- Proven Electronic Test Order and Results (ETOR) capability:
    - Ideally: Established connectivity to the AIMS LabWeb Portal environment
    - Alternatively: Through an existing web portal or through standardized messaging
- The capacity and capability to adopt APHL's ETOR LabWeb Portal Solution, hosted on the APHL Informatics Services platform (AIMS) using LIMSConnect. (See supplemental Lab Web Portal documentation for more details: LIMS Connect Overview, ETOR-LWP-LIMSConnect Slides and LWPv8 architecture general).
- Capacity to engage and onboard all submitting sites to the ETOR solution within the first two-three months of contracted work.

Back-up reporting mechanisms in place to meet reporting requirements outside of ETOR/LIMS (such as secure fax).

Performance Management and Evaluation

APHL in collaboration with CDC/ DTBE Laboratory Branch will monitor workload, reasons for submission to reference center, data quality, transport times, turnaround times, data anomalies and outliers, discordant results, level of drug resistance, types of mutations detected, appropriate use of reporting language, appropriate use of reflex testing algorithms, effective consultative services, customer satisfaction, referrals to CDC, and service costs on a monthly basis through the following mechanisms:

Data Review

- On a monthly basis as defined in the contract, a complete report including elements similar to those outlined below, will be provided to APHL and CDC.
    - Monthly Report
        - Aggregate data including: turnaround times, number of RIF resistant and INH resistant specimens detected by pyrosequencing
        - Line Listed Specimens and Isolates including fields agreed upon by APHL, CDC and the reference center. Fields may include but are not limited to: accession number, submitting state, test(s) requested, test(s) performed, comments on condition and reflex testing, date of specimen collection, date of receipt at the reference center, specimen type, date testing performed (molecular) or setup (DST), submission criteria (if applicable), date results reported, date and reason for referral to CDC (if applicable), final result for sample (Susceptible, or noting which Resistance was detected) and date of referral of isolate to genotyping laboratory.
        - Test results will include genotypic data (e.g. locus, nucleotide sequence, amino acid substitution [when applicable] and interpretive comments) and associated phenotypic data (to include contaminated and no growth when applicable) for each sample tested.

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        - Listing of nonconforming events, complaints, and QC failures related to the project.
            - If a non-conforming event, complaint or QC failure has the potential to have significant repercussions the reference center should perform an investigation and determine appropriate remediation and prevention strategies. The reference center will also complete and submit an incident tracking form (provided by APHL) to APHL and CDC within one week of the request by CDC or APHL unless otherwise specified. If additional time is needed for appropriate investigation, APHL and CDC should be notified.
    - The reference center may develop additional QA monitors, in conjunction with CDC, for their own performance and that of submitting laboratories.
- Pending phenotypic data will be matched with genotypic data during the subsequent collection period. Data will be provided with any personal identifying information (PII) removed prior to submitting to APHL and CDC.
    - If matching of patient results between CDC and the DST Reference Center is needed, a representative from the DTBE Reference Laboratory Team will coordinate communication to protect PII.
- Data will be analyzed by a team at APHL and CDC with feedback provided to the reference center within 1 month of receipt either by email or during a teleconference, if appropriate timing.
- Genotypic and correlated phenotypic data will be added to the DTBE Reference Laboratory database.

Site visits and teleconferences

- APHL in collaboration with CDC will perform site visits as needed. Additional monitoring visits may be needed based on data review and any ongoing challenges mutually identified. Site visits could include data review, review of laboratory workflow, procedural observation, QC information, worksheets for DST, and review of sequencing data.
- APHL, CDC and the reference center will participate in teleconferences every other month to review reports, assess successes and challenges and discuss potential resolutions.

Customer satisfaction

APHL may perform customer satisfaction surveys that may include key informant interviews with select submitters to assess satisfaction with service, turnaround time, reporting format, expert consultation, and continued use of reference laboratory.

Performance Assessment

- The DST Reference Center is required to participate in the CDC sponsored Model Performance Evaluation Program (MPEP) and test the panel against all funded methods. In addition to MPEP, APHL may collaborate with CDC to provide no more than two challenges of isolates each year to specifically assess genotypic and phenotypic testing, if needed. Blinded testing will be performed by CDC staff concurrently if a panel separate from MPEP is provided.
- Quality of consultations will be assessed through outreach to participating PHL and TB Programs

Submit the Letter of Intent (Due 10/18/19) and completed application (Due 11/15/19)
to Anne Gaynor, anne.gaynor@aphl.org

Reporting Language

- Reporting language and disclaimers harmonized with the DTBE Reference Laboratory must be used by the TB DST Reference Center. Genotypic results must be provided in an interim report with phenotypic results to follow.
- Annual Review of Reporting Language (including a catalog of interpretative comments for wild-type, novel mutations, and common mutations) and Sensitivity/Specificity document to ensure they are up to date. The document will be updated as necessary per discussions by all partners on teleconferences.
  The final report should include a categorical result of 'R' or 'S' for each drug, as applicable. Perceived discordance between genotypic and phenotypic testing should be clearly indicated and additional interpretative comments provided. CDC can assist with language around discordant results.

Consultation

- Subject matter expertise within the TB DST Reference Center should be available for consultation by phone or dedicated email address
- CDC DTBE Reference Laboratory may be consulted when discordant results are seen.
- The TB DST Reference Center will maintain dedicated lines of communication for submitters (i.e. phone number, email, website)
- APHL will host a dedicated website available to submitting laboratories to include appropriate contact information and TB DST Reference Center Documents.

Submission of isolates to genotyping laboratory

- Within 7 days of a positive culture from sediment or subculture of a referred isolate, the reference laboratory will package and ship isolates to the CDC supported genotyping laboratory.
  - The submitting laboratory will be notified that the isolate was submitted for genotyping.
- Prior to shipping the isolates, isolate information will be entered into the Tuberculosis Genotyping Information Management System (TB GIMS) by the reference laboratory.
- If submitting laboratory sends directly to CDC MDDR service based on sediment submitted for confirmation of an Xpert MTB/RIF result "RMP resistance detected", CDC will be responsible for isolate submission to the genotyping laboratory.

Archiving isolates

- Isolates will be stored frozen by the TB DST Reference Center for a period of 2 years.
- Isolates will be archived at the genotyping laboratory and eventually shipped to CDC for long-term storage.

Continuity of Operations Assurance

- In the event that CDC is unable to provide TB testing due to extenuating circumstances (e.g. laboratory shutdown), the TB DST Reference Center may be requested to perform testing for additional specimens on an as needed basis on behalf of CDC.

Appendix B: Minimum Requirements for National PHL DST Reference Center for MTBC

Please review and respond to each of the minimum requirements below. By signing this agreement you are affirming that your laboratory can meet each of the minimum requirements described.

YES	NO	MINIMUM REQUIREMENT
		Does your laboratory have the necessary equipment or ability to purchase additional equipment if necessary?
		Does your laboratory have adequate laboratory space (including infrastructure for unidirectional workflow for molecular testing) and to accommodate additional equipment if necessary?
		Does your laboratory have sufficient workforce capacity for expanded testing volume or the ability to hire additional qualified staff?
		Does your laboratory have established capacity for MTBC culture and to perform phenotypic first-line DST and second-line DST methods to detect drug resistance in MTBC?
		Does your laboratory have established capacity for molecular detection of drug resistance for MTBC?
		Does your laboratory participate in the Model Performance Evaluation Program (MPEP)?
		Is your laboratory willing to alter or amend existing testing protocols at the request of APHL and CDC?
		Is your laboratory willing to increase the frequency of performing certain methods (if required to meet expected turnaround times?
		Is your laboratory willing to amend specimen submission form(s) to include additional variables?
		Is your laboratory willing to alter existing reporting language to a standardized reporting language with input from APHL and CDC?
		Is your laboratory willing to provide copies of QA or biosafety documentation to APHL and CDC upon request?
		Does your laboratory have the necessary informatics capabilities including a LIMS and either proven capability to support ETOR or ability to adopt APHL's LabWeb Portal Solution?
		Is your laboratory able to perform and report results from LDT or RUO assays?

On behalf of the applicant laboratory, I agree that the applicant laboratory is able to meet the minimum requirements necessary to apply for this award as outlined above.

Signature: _____ Date: _____

Printed Name: _____

Submit the Letter of Intent (Due 10/18/19) and completed application (Due 11/15/19) to Anne Gaynor, anne.gaynor@aphl.org

Appendix C: Score Card

The following table is a copy of the score card that will be used to evaluate RFP responses.

Category/Question	Maximum Value	Score	Comments (REQUIRED)
Physical Environment 1. Does the applicant demonstrate the ability to handle the testing volume for all required methods? Consider the availability of existing staff, equipment and space and the ability of the laboratory to purchase additional equipment or hire additional staff. **Ideal** (11-15 points): Describes ability to handle testing volume for all activities; describes appropriate staffing, equipment and space or ability to obtain additional equipment or staffing in a timely manner. **Adequate** (6-10 points): Describes ability to meet most testing volume requirements but may have to adjust workflow and/or staffing to accommodate work; has some deficiencies in their staffing, equipment or ability to obtain additional resources. **Limited** (1-5 points): Applicant describes limited ability to meet testing volume requirements; has Many deficiencies in their staffing, equipment or ability to obtain additional resources. **Inadequate** (0 points): Applicant does not demonstrate the ability to handle the testing volume for all methods and neither has the current staffing or equipment or ability to obtain the unmet needs and/or does not demonstrate a clear understanding of the requirements.	15		Type comments here. (REQUIRED)
2. Does the applicant describe in-house subject matter expertise that is sufficient to provide consultation to submitting jurisdictions on discordant results or other issues? **High** (8-10 points): Applicant has a strong history of relevant experience, subject matter expertise: at least 1.0 FTE with > 5 years or 2.0 FTEs with > 3 years of experience providing consultation to submitters on interpretation of results including discordant results. **Moderate** (4-7 points): Applicant has some relevant experience but will require additional training, guidance or technical assistance in others, subject matter expertise: >1.0 FTE with ≥ 3 years of experience providing consultation to submitters on interpretation of results including discordant results. **Low** (1-3 points): Deficiencies in staffing in this area, subject matter expertise: ≤ 1 FTE with <3 years of experience	10		Type comments here. (REQUIRED)

providing consultation to submitters on interpretation of results including discordant results. **No Experience** (0 points): Applicant does not demonstrate internal subject matter expertise is this area.			
First-Line DST Methods 3. Does the applicant have sufficient capacity and experience performing first-line DST for MTBC? Consider experience with described method(s), experience of existing staff? **High** (11-15 points): Describes extensive experience performing method, sufficient capacity and staff experience to handle additional volume, describes appropriate staffing and equipment, and regularly meets target turnaround times as recommended in the CDC Tuberculosis Elimination and Laboratory Cooperative Agreement. **Moderate** (6-10 points): Describes sufficient experience performing method, some concerns appropriate capacity to handle additional volume and/or does not regularly meet target turnaround times as recommended in the CDC Tuberculosis Elimination and Laboratory Cooperative. **Low** (1-6 points): Describes experience performing method, deficiencies in workforce experience and/or ability to meet target turnaround times and/or handle additional volume. **No Experience** (0 points): Applicant does not demonstrate internal subject matter expertise is this area.	15		Type comments here. (REQUIRED)
Second Line DST Methods 4. Does the applicant have sufficient capacity and experience performing second line DST? Consider experience with described method(s), experience of existing staff? **High** (11-15 points): Describes extensive experience performing method, sufficient capacity and staff experience to handle additional volume, describes appropriate staffing and equipment, and regularly meets target turnaround times as recommended in the CDC Tuberculosis Elimination and Laboratory Cooperative. **Moderate** (6-10 points): Describes sufficient experience performing method, some concerns appropriate capacity to handle additional volume and/or does not regularly meet target turnaround times as recommended in the CDC Tuberculosis Elimination and Laboratory Cooperative. **Low** (1-6 points): Describes experience performing method, deficiencies in workforce experience and/or ability to meet target turnaround times and/or handle additional volume. **No /Unclear** (0 points): Applicant does not demonstrate internal subject matter expertise is this area.	15		Type comments here. (REQUIRED

Molecular DST Methods 5. Does the applicant have sufficient capacity and experience performing molecular detection of drug resistance for TB? Consider experience with described method(s), experience of existing staff? **High** (11-15 points): Describes extensive experience performing method, sufficient capacity and staff experience to handle additional volume, describes appropriate staffing and Equipment, and regularly meets target turnaround times as recommended in the CDC Tuberculosis Elimination and Laboratory Cooperative. **Moderate** (6-10 points): Describes sufficient experience performing method, some concerns about appropriate capacity to handle additional volume and/or does not regularly meet target turnaround times as recommended in the CDC Tuberculosis Elimination and Laboratory Cooperative. **Low** (1-6 points): Describes experience performing method, deficiencies in workforce experience and/or ability to meet target turnaround times and/or handle additional volume. **No /Unclear** (0 points): Applicant does not demonstrate internal subject matter expertise is this area.	15		Type comments here. (REQUIRED)
Reporting 6. What is the applicants' ability to offer electronic test ordering and reporting? **Ideal** (10 points): Applicant already has a connection to AIMS/LWP for electronic ordering and reporting **Adequate** (5 points): Applicant has an ETOR system in place and/or the ability to connect to AIMS/LWP for electronic ordering and reporting **Inadequate** (0 points): Applicant does not have an ETOR system or ability to connect to AIMS/LWP	10		Type comments here. (REQUIRED)
Reference Center Testing 7. Rate the applicant's level of experience in providing reference testing services for other public health laboratories in a shared service model. **Rate on a scale of 0-5 points** (5= Applicant has served as a reference center for other PHL on an ongoing basis with submissions from and reporting to multiple out-of-jurisdiction submitters; 0=applicant has no experience serving as a reference center for other PHLs)	5		Type comments here. (REQUIRED)

New Technology and/or Laboratory Developed Tests 8. How well does the laboratory demonstrate a willingness to evaluate and incorporate additional new technologies and or alter algorithms to address changing needs? **High** (6-10 points); Applicant has experience with bringing on new test technology, adding new drugs to growth-based susceptibility panels or adding targets to panels for molecular detection of drug resistance, procedures for validation are appropriate including general approach and sample size. **Moderate** (1-5 points); Applicant has limited experience with bringing on new test technology, adding new drugs to growth-based susceptibility panels or adding targets to panels for molecular detection of drug resistance, or some concerns about appropriateness of validation procedures. **No experience** (0 points); Applicant does not demonstrate expertise is this area.	10		Type comments here. (REQUIRED)
Budget 10. Rate the appropriateness of the applicants budget **Rate on a scale of 0-5 points** (5=most cost-effective budget; 0=budget is inappropriate)	5		Type comments here. (REQUIRED)
TOTAL SCORE	**100**	**____**	

Appendix D: Conflict of Interest Disclosure Statement and Policy

Association of Public Health Laboratories
Conflict of Interest Disclosure Statement

Applicability: Disclosure of the following information is required of all Officers, Directors, committee members, staff members and other volunteers who have been designated and who have accepted responsibility to act on behalf of APHL ("APHL Personnel"). Please answer the following questions and, where indicated, include the same information for your immediate family members (your parents, your spouse or partner, your children and your spouse/partner's parents).

APHL will keep your completed disclosure statement in the corporate records of the association.

1. Please list the name, address, phone number, email address and type of business of your current employer. If you are self-employed, please note that below and provide us with the address, phone number, email address and type of business you operate.

_____

_____

_____

2. Do you, or does any family member, currently serve as an officer, director, committee member, or other volunteer (or work as an employee of or a paid consultant to) any organization serving the interest of laboratory science or public health laboratories other than APHL or your state or local laboratory?

☐ **Yes** ☐ **No**

If yes, please list the organization(s) and provide detail on your or your family member's interest or position in the organization(s).

_____

_____

_____

3. Do you, or any family member, have an existing or potential interest in, or compensation arrangement with, any third party providing goods or services to APHL, or with which APHL is currently negotiating?

☐ **Yes** ☐ **No**

If the answer is yes, please provide the name of the organization below and describe in detail the nature of the position held.

4. Please note any other financial or business interest you may have with any organization serving the interests of public health laboratories.

If you have none, please check this box: ☐

5. Do you, or does any family member, have any other interest or affiliation that is likely to compromise your ability to provide unbiased and undivided loyalty to APHL, or that could come in conflict with your official duties as an Officer, Director, committee member, staff member or other volunteer who has been designated and who has accepted responsibility to act on behalf of APHL?

☐ **Yes** ☐ **No**

If you answered yes, please describe in detail below the nature of each such interest or affiliation.

6. If you are currently aware of any actual or possible conflict of interest that might otherwise hamper your ability to serve APHL to your best ability and with the highest degree of care, loyalty and obedience – ***including any potential conflict you or a family member may have with one or more of the RFP applicants*** – please describe them in detail below.

_____

_____

_____

_____

_____

7. Do you agree that so long as you are an Officer, Director, committee member, staff member or other volunteer who has been designated and who has accepted responsibility to act on behalf of APHL you will immediately disclose to the other Directors and/or Officers or, for staff members, the Executive Director and/or General Counsel the nature of any interest or affiliation which you may hereafter acquire, which is in or is likely to become in conflict with your official duties with APHL?

☐ **Yes** ☐ **No**

YOU MUST READ THIS SECTION AND THEN SIGN BELOW

I acknowledge that I have received and read APHL's Fiduciary Responsibility and Conflict of Interest Policy (the Policy). I have listed all my relevant fiduciary responsibilities and affiliations, and I have identified any actual or potential conflict of interest on this Disclosure Statement and I agree to abide by the Policy. I understand that it is my responsibility to inform APHL in writing of any change in circumstances relating to the Policy and this Disclosure Statement.

Signature: _____ Date: _____

Printed Name: _____

APHL Fiduciary Responsibility and
Conflict of Interest Policy

1. Policy Statement and Purpose

The members of the APHL Board of Directors understand the importance of serving APHL to the best of their ability and with the highest degree of obedience, loyalty and care. Accordingly, the Board adopts the following policy for APHL Officers and Directors, all staff, committee members, and other volunteers who have been designated and who have accepted responsibility to act on behalf of APHL ("APHL Personnel").

2. Individual Duty and Annual Disclosure

APHL Personnel will avoid any conflict of interest with APHL. APHL Personnel will not profit personally from their affiliation with APHL, or favor the interests of themselves, relatives, friends or other affiliated organizations over the interests of APHL. As used in this Policy, "Conflict of interest" includes any actual, apparent, and potential conflict of interest.

Upon commencing service with APHL, each APHL Personnel will file with the Board an annual statement disclosing all material business, financial, and organizational interests and affiliations they or persons close to them have which could be construed as related to the interests of APHL or the profession of public health laboratory science. Each APHL Personnel has an obligation to make an additional disclosure if a conflict of interest arises in the course of the individual's service to APHL, whether arising out of his/her employment, consulting, investments, or any other activity. These disclosures will be documented promptly in writing and recorded in the Board minutes and corporate records.

3. Procedure

Whenever APHL considers a matter, which presents an actual, apparent, or potential conflict of interest for APHL Personnel, the interested individual will fully disclose his/her interest in the matter, including the nature, type, and extent of the transaction or situation and the interest of the individual or that individual's relatives, friends or other affiliated organizations. The Board, after consultation with counsel as appropriate, will determine whether an actual and material conflict exists and, if so, what is the appropriate course of action under this policy and the Board vote will be recorded in the minutes.

Any Board member having a conflict of interest must either (i) voluntarily abstain from and be disqualified from participation in all deliberation and voting on all Board actions relating to the situation or matter that gives rise to the conflict of interest, or (ii) ask the Board to determine whether an apparent or potential conflict of interest is considered by the Board to be an actual and material conflict. In the event that the Board member in question requests that the Board evaluate the apparent or potential conflict, that Board member will abstain and be disqualified from participating in (and voting on) the determination of whether the issue presents an actual and material conflict. If the Board determines that an actual and material conflict exists, the Board member in question will abstain from all voting on, and will be disqualified from participation in all deliberation concerning all Board actions relating to the conflict of interest. The vote will be recorded in the minutes.

These procedures will neither prevent the interested individual from briefly stating his/her position on the matter, nor preclude him/her from answering pertinent questions of Board members, since his/her knowledge may be of assistance to the Board's deliberations.

APHL Personnel must be cautious and protective of the assets of APHL and insure that they are used in the pursuit of the mission of APHL. The association's policy requires APHL Personnel to avoid transactions in which APHL personnel may have a significant financial interest in any property which

APHL purchases, or a direct or indirect interest in a supplier, contractor, consultant, or other entity with which APHL does business. The Board, after consultation with counsel as appropriate, will determine whether an actual and material conflict exists and, if so, determine whether the transaction is nonetheless favorable to APHL before considering whether to approve it.

4. Other Duties and Obligations

Whenever any APHL Personnel discovers an opportunity for business advantage which is relevant to the activities of APHL, the opportunity belongs to APHL and the individual must present this opportunity to the Board. Only once the Board determines not to pursue the matter and relinquishes the opportunity may the individual consider it a matter of possible personal benefit.

APHL Personnel may not accept favors or gifts exceeding $75.00 from anyone who does business with APHL.

All APHL Personnel will keep confidential those APHL matters designated confidential. APHL Personnel are prohibited from disclosing information about APHL to those who do not have a need to know or whose interest may be adverse to APHL, either inside or outside APHL, and are prohibited from using in any way such information for personal advantage to the detriment of APHL.

All APHL Personnel who participate in APHL activities, including committee activities and international consultation activities, must be adequately prepared to fully participate as their position descriptions require and will do so in accordance with the applicable laws and regulations of their respective state or territory and APHL's Articles of Incorporation, Bylaws, and corporate policies. The APHL Board will read and understand the association's Articles of Incorporation, Bylaws, corporate policies and financial statements, and routinely verify that all state, federal, and local tax payments, registrations and reports have been filed in a timely and accurate manner.

Board members will never exercise authority on behalf of APHL except when acting in meetings with the full Board or the Executive Committee or as authorized by the Board. If any member of the Board has significant doubts about a course of action of the Board, he or she must clearly raise the concern with the Executive Director and the Board and, when appropriate, seek independent expert advice.