Council on Dairy Cattle Breeding

Quality Certification Requirements for Genotyping Laboratories

Latest review: 09/24/2019
Effective: 09/01/2017

Contents

Revision History

20180501 – Update on the "Performance Metrics for Genotyping Laboratories" section, to standardize the documentation with the Genomic Nominator Guidelines.

20180518 – Final version of "Performance Metrics for Genotyping Laboratories" section, merging all sources of information and after receiving input from Laboratories representatives at the 2018 Genotyping Laboratories Workshop.

20190206 – Time limitation introduced for the approval process.

20190924 – Time standards included related to genotyping lab submissions.

Purpose

These requirements serve to ensure the accuracy and uniformity of all records included in the national genomic evaluation program so that the impact of contributed resources and efficiency of the system are maximized.

Background

Genomic tests combined with phenotypic information on individual animals and their relatives have been shown to be a powerful resource for predicting future performance in dairy cattle at an early age. Obtaining these highly accurate predictions is dependent upon confirming that the entry of data into the national database is completed with a minimum of errors (for example, sampling the wrong animal, mislabeling samples, swapping samples within the laboratory, etc.). Core requirements and performance metrics that are supported by available monitoring and quality reporting systems such as the CDCB Laboratory Report Card are needed to help minimize the introduction of such errors to the national genetic evaluation program.

Adherence to Quality Certification standards for laboratory processes and *management* systems is considered essential for all laboratories for data production. CDCB will monitor and conduct periodic reviews of the performance of genomic laboratories for data submission and interaction with the U.S. genomic evaluation process.

A CDCB Quality Certification is required for each genotyping technology used (e.g. Genotyping Labs using Affymetrix and Illumina will require one certification for each technology).

Core Requirements for Genotyping Laboratories

When applying to become a CDCB Certified Genotyping Laboratory[1]

The genotyping laboratory has to be able to perform the tasks required for submission of genotypes to the CDCB database and agree to comply with all the following requirements:

1. Pay the CDCB Genotyping Laboratory Certification fee ($1000). The CDCB Genotyping Laboratory Certification fee is due at the beginning of each certification process. A fee is required for each certification: laboratories applying for multiple certifications are required to pay one fee for each application.
2. Provide the CDCB Quality Certification for Genotyping Laboratories completed application form (https://redmine.uscdcb.com/documents/72)
3. Provide a copy of an up-to-date accreditation in a Quality Certification program (e.g. ISO17025 or similar). The scope of the certification must include the whole process involved in creating the genomic data submitted to CDCB.
4. Appoint the laboratory personnel who will be granted access to the CDCB file submission tools and web queries and receive the initial training from CDCB staff.
5. Provide a completed CDCB laboratory Standard Operating Procedures (SOPs) form (https://redmine.uscdcb.com/documents/73)
6. Provide test files for verification by the CDCB staff (samples and proficiency test will be distributed and managed separately by CDCB). CDCB Genotyping Laboratory Certification fee entitles Genotyping Laboratories up to five (5) file review processes within 2 months from the application date. The inability of a Genotyping Laboratory to fully comply with CDCB requirements within the time period or the number of review processes will result in the termination of the process. In such an event, the Genotyping Lab will be required to start the process again (including the payment of the CDCB Genotyping Laboratory Certification fee).
7. Sign a Material License Agreement (MLA) proposed by the CDCB which describes the respective rights and obligations regarding how data are provided to CDCB and how CDCB is allowed to use the data (https://redmine.uscdcb.com/documents/74)

After certification is granted

1. Maintain a valid Quality Certification of standard laboratory processes. Laboratories already approved by CDCB by 09/01/2017 but without ISO certification (or equivalent), will have 2 years of time to become certified. Any genomic laboratory not ISO certified (or equivalent) by 09/01/2019 will be decertified, consequently loosing its permission to submit genotypes to the CDCB collaborator's database.

[1] All materials should be submitted to Kaori Tokuhisa (kaori.tokuhisa@uscdcb.com).

2. Submit genotypes periodically to allow an assessment of the genotyping laboratory performance. The minimum requirement is at least one submission per month in at least 7 months per year, with no more than a 3 months gap between submissions.
3. Verify the nomination of samples before submission to CDCB.

4. Be able to submit genotypes in the format required by the CDCB (https://redmine.uscdcb.com/projects/cdcb-customer-service/wiki/CDCB_Accepted_genotype_file_formats) and provide the related sample sheet to CDCB.
5. Be able to check submissions using the CDCB online system prior to submitting them for upload.
6. Be able to eliminate low-call-rate samples (<90%) prior to upload.
7. Be able to investigate and resolve issues involving SNP genotypes with low call rate, abnormal portion of heterozygous genotypes, or high number of parent-progeny with a target of no more than 10 SNP outside the acceptance range.
8. Be able to coordinate with the genomic nominator(s) of the genotyped animals to ensure that submitted genotypes can be reliably associated with a valid animal identification, fee code and pedigree.
9. Comply with the Performance Metrics for Genotyping Laboratories defined in these guidelines.

Performance Metrics for Genotyping Laboratories

The CDCB provides a Laboratory Report Card on a monthly basis with statistics on the observed performance regarding the quality of the submitted data. Based on the monthly Laboratory Report Card, the CDCB has established the following performance metrics for genotyping laboratories:

- **Submissions** with fewer than 10 animal genotypes
- **Submissions** failing on SNP call rate
- **Submissions** failing on SNP parent-progeny conflicts
- **Submissions** failing on HWE
- Percentage of **animal genotypes** with No Nomination
- **Submissions** failing on excessive conflicts per chip
- Percentage of **animal genotype** reassigned

Full QC metrics information can be found in
https://redmine.uscdcb.com/projects/cdcb-customer-service/wiki/QC_Metrics_for_submitted_genotypes

Certification Process

Laboratories can apply for genotyping certification at any time throughout the year. Upon demonstration, through review, of the capability to provide data meeting the standards outlined in the *Quality Certification Requirements for Genotyping Laboratories*, they will initially achieve conditional certification status. Further, the CDCB Staff is responsible for identifying both the conditions or deficiencies to be

addressed and the timeframe for action so that the laboratory may achieve full certification.
Genotyping laboratories that receive conditional certification status will be authorized to start providing data to the CDCB database.
Laboratories will remain certified unless the CDCB Staff renders them decertified or provisional because of the deterioration of their submissions (failure to meet core requirements).

Certification Status

Conditional
Conditional certification status may be assigned to both new and existing genotyping laboratories. A new laboratory may be assigned conditional status if the Genotyping Laboratory has met the requirements of the Quality Certification Requirements for Genotyping Laboratories, but has not undergone a comprehensive review.
An existing provisional genotyping laboratory may be assigned conditional status if the Genotyping Laboratory has met all conditions or eliminated deficiencies outlined as part of a previous review but has not undergone a subsequent review.

Provisional
A previously certified genotyping laboratory that fails repeatedly in meeting one or more aspects of the CDCB guidelines in a period of six months will be deemed as having provisional status. Upon further action and review by CDCB, the genotyping laboratory may be:

- Restored to full certification;
- Designated conditional until an annual review is conducted;
- Designated provisional for an additional period of review; or
- Decertified.

Certified
A certified genotyping laboratory meets or exceeds the Quality Certification Requirements for Genotyping Laboratories.

Decertified
A genotyping laboratory that fails to meet the Quality Certification Requirements for Genotyping Laboratories, even after a period of provisional certification and review, will be decertified by the CDCB. A decertified laboratory will not be allowed to submit data to the Cooperator database. Notification of the decertification will be sent via email and via mail by CDCB to the decertified Genomic Laboratory.
Decertification will only be considered when:

- The performance of the genotyping laboratory has fallen below the minimum standards established by CDCB; and
- The genotyping laboratory does not take prompt action to return to compliance within the time period specified by CDCB.

Decertification Appeals

Any provisional genotyping laboratory that fails to obtain certification from the CDCB Staff will have the right to appeal that decision to CDCB within 10 business days of receipt of the first notification received. The appeal will consist of a written report that must be submitted to the CDCB Chair by the genotyping laboratory and must explain why the decision of the reviewer was incorrect.

The matter will be reviewed by CDCB within 30 calendar days of receipt of the report, and CDCB's decision will be final. If CDCB upholds the findings of the CDCB Staff, no more data will be accepted from the genotyping laboratory after 30 calendar days from the time that CDCB notifies the appealing entity of its decision.

If no appeal is forthcoming, no more data will be accepted from that laboratory after the deadline for the appeal. Genotyping laboratories that are no longer certified but wish to reapply for certification must meet the same costs and conditions as a new entity wishing to offer certified services.

Review of Genotyping Laboratories

Performance of genotyping laboratory will be monitored continuously to assure that the quality of data provided by the laboratory continues to meet the standards outlined in the Quality Certification Requirements for Genotyping Laboratories.

The CDCB Staff may request submission of electronic or hard copy data to determine if the genotyping laboratory is fulfilling the requirements. The material submitted will be evaluated using pass/fail criteria.

Review Classes

Reviews of genotyping laboratories are classified as either mandatory or discretionary:

1. A mandatory review is defined as a regularly scheduled review of the laboratory. CDCB staff will schedule these reviews towards the end of the year to determine if the laboratory is eligible to continue to submit data to the cooperator database.
2. A discretionary review is defined as a review deemed necessary by either the CDCB staff or the genotyping laboratory and will be scheduled on an as needed basis when:
    2.1. Changes in facilities, procedures, or staffing have occurred;
    2.2. Certain aspects of the laboratory's performance are out of compliance with Quality Certification Requirements for Genotyping Laboratories;
    2.3. The laboratory wishes to attain full certification from a conditional status;
    2.4. The laboratory wishes to regain full certification from a provisional status; or
    2.5. The laboratory wishes to regain provisional certification from a decertified status.

CDCB Staff Responsibilities

The CDCB Staff has the responsibility to ensure that all certified laboratories are meeting the CDCB Quality Certification Requirements for Genotyping Laboratories. Specific responsibilities are to:

1. Assure trained staff is available to perform the review.
2. Perform review of laboratories according to the specifications documented in the Quality Certification Requirements for Genotyping Laboratories.
3. Designate a certification status for each laboratory reviewed.
4. Post certification status of certified laboratories on CDCB website.
5. Submit a printed report within 30 days of a review to the genotyping laboratory and to the CDCB Chair that will identify missing or deficient data and options for addressing the deficiencies prior to expiration of certification.