Use of Public Human Genetic Variant Databases to Support Clinical Validity for Next Generation Sequencing (NGS)-Based In Vitro Diagnostics

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Draft Guidance for Stakeholders and Food and Drug Administration Staff

DRAFT GUIDANCE

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Preface

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This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA staff or Office responsible for this guidance as listed on the title page.

I. Introduction

This draft guidance document describes one part of FDA's effort to create a flexible and adaptive regulatory approach to the oversight of next generation sequencing (NGS)-based tests as part of the Precision Medicine Initiative (PMI). The goal of this effort is to help ensure patients receive accurate and meaningful results, while promoting innovation in test development. This draft guidance document describes how publicly accessible databases of human genetic variants can serve as sources of valid scientific evidence to support the clinical validity of genotype-phenotype relationships in FDA's regulatory review of NGS-based tests.

FDA's guidance documents, including this guidance document, do not establish legally enforceable responsibilities. Instead, guidance documents describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidance means that something is suggested or recommended, but not required.

II. Background

NGS can enable rapid, broad, and deep sequencing of a portion of a gene, an entire exome(s), or a whole genome and may be used clinically for a variety of diagnostic purposes, including risk

prediction, diagnosis, and treatment selection for a disease or condition. The rapid adoption of NGS-based tests in both research and clinical practice is leading to identification of an increasing number of genetic variants, including rare variants that may be unique to a single individual or family. Understanding the clinical significance of these genetic variants holds great promise for the future of personalized medicine.

Although the importance of genetic variant data aggregation is widely recognized, today much of the data that would be useful to support clinical validity of NGS-based tests is generally stored in a manner in which it is not publicly accessible. Aggregation of clinical genotype-phenotype associations and evaluation of the level of evidence underlying these associations under a well-defined process will continue to promote more rapid translation of genetic information into useful clinical evidence.

For the purposes of this draft guidance document, a "genetic variant database" is a publicly accessible database of human genetic variants that aggregates and curates reports of human phenotype-genotype relationships to a disease or condition with publicly available documentation of evidence supporting those linkages. Genetic variant databases may also include assertions[1] about specific genotype-phenotype correlations.

FDA believes that the aggregation,[2] curation,[3] and interpretation[4] of clinical genotype-phenotype associations in genetic variant databases could support the clinical validity of claims made about a variant detected by an NGS-based test and a disease or condition. In relying on assertions in genetic variant databases that follow the recommendations in this guidance, FDA hopes to encourage the deposition of variant information in such databases, reduce regulatory burden on test developers, and spur advancements in the interpretation and implementation of precision medicine.

Publicly Accessible Databases of Human Genetic Variants as Sources of Valid Scientific Evidence Supporting Clinical Validity

To determine whether an NGS-based test has a reasonable assurance of safety and effectiveness, the Agency relies upon the review of valid scientific evidence to support the analytical and clinical performance of the test. Valid scientific evidence is defined as evidence from well-controlled investigations, partially controlled studies, studies and objective trials without matched controls, well-documented case histories conducted by qualified experts, and reports of significant human experience with a marketed device, from which it can fairly and responsibly

[1] For the purposes of this guidance, an assertion is the informed assessment of a genotype-phenotype correlation (or lack thereof) given the current state of knowledge for a particular variant. An assertion is generally noted in the genetic variant database entry for a particular variant (e.g., benign, drug resistant, etc.).
[2] For the purposes of this guidance, the term aggregation refers to the process by which variant data are systematically input into a genetic variant database. This process may require that data conform to specified formats.
[3] For the purposes of this guidance, curation refers to the process by which data regarding a specific variant are collected from various sources, annotated, and maintained over time.
[4] For the purposes of this guidance, the term interpretation refers to the process by which genetic variant database personnel evaluate the evidence regarding a linkage between a genetic variant and a disease or condition and make an assertion about that linkage (or lack thereof).

be concluded by qualified experts that there is a reasonable assurance of safety and effectiveness.[5] In determining whether a particular NGS test has a reasonable assurance of safety and effectiveness, FDA must determine, based on valid scientific evidence that "in a significant portion of the target population, the use of the device for its intended uses and conditions of use, when accompanied by adequate directions for use and warnings against unsafe use, will provide clinically significant results."[6]

The evidence residing in many genetic variant databases has been collected from multiple sources that can meet the valid scientific evidence definition, such as evidence from well-controlled clinical investigations, clinical evidence generated in CLIA (Clinical Laboratory Improvement Amendments of 1988)-certified laboratories, published peer-reviewed literature, and certain case study reports. Some organizations that are currently developing genetic variant databases have adopted protocols and methodologies (e.g., quality measures) and/or external guidelines (e.g., from professional societies or standards development organizations) for evidence aggregation, curation, and interpretation practices. While interpretation processes may vary across databases and organizations, they typically involve the use of qualified experts who make informed conclusions about the presence or absence of a genetic variant and its meaning for a particular disease or clinical decision.

Further, there are several parallels between the standards set forth by well-recognized professional guidelines for variant interpretation and FDA review of clinical validity. Personnel interpreting variants use a range of evidence, including the types and positions of variants, inheritance, prevalence, well-established functional studies, and prior knowledge of gene-disease relationships. Generally, the standards for use of evidence appear to parallel the types of evidence appropriate to support an FDA premarket submission. Under 21 CFR 860.7(c)(2), isolated case reports, random experience, reports lacking sufficient details to permit scientific evaluation, and unsubstantiated opinions are not regarded as valid scientific evidence. Accordingly, FDA believes that summary literature is inferior in this respect to data available for independent evaluation. FDA assesses clinical validity based on the totality of available evidence provided in a given submission. Similarly, well-recognized professional guidelines dictate that database personnel interpreting variants integrate multiple lines of evidence to make an assertion of clinical validity.

The Agency believes such practices help assure the quality of data and assertions within genetic variant databases and has built upon these approaches in developing the recommendations in this guidance.

FDA has long believed that public access to data is important so that all interested persons (e.g., healthcare providers and patients) can make the best medical treatment decisions. To that end, for all IVDs that have received clearance or de novo classification from FDA since November 2003, FDA has published a Decision Summary containing a review of the analytical and clinical validity data and other information submitted by the applicant to support the submission and

[5] 21 CFR 860.7(c)(2).
[6] 21 CFR 860.7(e)(1).

FDA's justification for clearing or classifying the IVD; FDA is also required to publish Summaries of Safety and Effectiveness Data for approved PMAs under section 520(h) of the Federal Food, Drug and Cosmetic Act (FD&C Act) (21 U.S.C. 360j(h)).[7] FDA believes that similar public availability and access to data contained in genetic variant databases is important to patients and healthcare providers in order to make fully informed medical decisions.

FDA believes that if genetic variant databases follow the recommendations in this document, including transparency regarding evidence evaluation, and obtain FDA recognition as described below, the data and assertions within would generally constitute valid scientific evidence that can be used to support clinical validity.

III. Scope

This draft guidance document describes FDA's considerations in determining whether a genetic variant database is a source of valid scientific evidence that could support the clinical validity of an NGS-based test in a premarket submission. This draft guidance further outlines the process by which administrators[8] of publicly accessible genetic variant databases could voluntarily apply to FDA for recognition, and how FDA would review such applications and periodically reevaluate recognized databases.

The genetic variant databases discussed in this draft guidance only include those that contain human genetic variants, and do not include databases used for microbial genome identification and detection of antimicrobial resistance and virulence markers. This draft guidance does not apply to software used to classify and interpret genetic variants, but instead, only regards use of curated databases using expert human interpretation.

IV. Recommendations to Support Recognition of Publicly Accessible Genetic Variant Databases of Human Genetic Variants as Sources of Valid Scientific Evidence Supporting Clinical Validity of NGS Tests

FDA believes that evidence contained in a genetic variant database that conforms to the recommendations described below would generally constitute valid scientific evidence that can be used to support the clinical validity of an NGS-based test.

FDA believes that such a genetic variant database would: (1) operate in a manner that provides sufficient information and assurances regarding the quality of source data and its evidence

[7] No Decision Summaries or Summaries of Safety and Effectiveness Data are posted for those devices for which the applicant failed to demonstrate substantial equivalence or a reasonable assurance of safety and effectiveness.
[8] FDA acknowledges that many databases may not use the term "administrator" or may have a committee of individuals that oversee the database. Therefore, for the purposes of this guidance, a genetic variant database administrator is the entity or entities that oversee database operations.

review and variant assertions; (2) provide transparency regarding its data sources and its operations, particularly around how variant evidence is evaluated and interpreted; (3) collect, store, and report data and conclusions in compliance with all applicable requirements regarding protected health information, patient privacy, research subject protections, and data security; and (4) house sequence information generated by validated methods.

In the subsections below, FDA discusses recommendations for the operation of a genetic variant database, and the aggregation, curation, and interpretation of data therein, so that such data would generally constitute valid scientific evidence supportive of clinical validity. FDA acknowledges that individual genetic variant databases may have different, but equally scientifically valid, approaches to assuring data quality, clinical relevance, data security, patient privacy, and transparency. Additionally, FDA recognizes that several professional societies have or are developing guidelines for genetic variant curation and interpretation that may differ depending upon discipline, but may each be appropriate in the context of the intended use. Genetic variant database administrators should focus on ensuring that their procedures and quality requirements are sufficiently robust to provide a high degree of confidence in their conclusions regarding genotype-phenotype associations.

A. Database Procedures and Operations

Transparency and Public Accessibility: FDA recommends that genetic variant database administrators make publicly available sufficient information regarding data sources and standard operating procedures (SOPs) for evaluation and interpretation of evidence to allow FDA and the public to understand the criteria and processes used to collect and interpret evidence about variants and enable patients and healthcare providers to make fully informed medical decisions.

SOP Version Control: SOPs should define how variant information is aggregated, curated, and interpreted. These SOPs should be documented and versioned. Changes to SOPs should be clearly documented with sufficiently detailed information regarding the change accompanied by any necessary explanation to ensure all stakeholders understand any limitations created by or implications of the change in procedure. To maintain quality variant assertions and ensure that genetic variant database operations keep pace with advances in technology and scientific knowledge, operations and SOPs should be reviewed at least on an annual basis.

Data Preservation: FDA recommends that genetic variant database administrators have processes in place for assessing overall database stability and architecture and for ensuring that data linkages are properly maintained. When a genetic variant database contains linkages to secondary databases, the genetic variant database administrator should have predefined processes in place to recognize changes to the secondary databases and account for them in version control of the primary database. FDA recommends genetic variant database administrator back-up the database on a regular basis so that it can be reinstated as necessary.

Genetic variant database administrators should have a plan in place to ensure database content and processes are preserved in the event a genetic variant database ceases operations permanently or temporarily (e.g., a database loses funding, infrastructure upgrades). A location

to deposit data, including versioning information and supporting SOPs and documentation, in the event that the genetic variant database ceases operation should be identified.

Security and Privacy: Genetic variant database operations must be in compliance with all applicable federal laws and regulations (e.g., the Health Insurance Portability and Accountability Act, the Genetic Information Nondiscrimination Act, the Privacy Act, the Federal Policy for the Protection of Human Subjects ("Common Rule"), etc.) regarding protected health information, patient privacy, research involving human subjects, and data security, as applicable. It is the responsibility of the genetic variant database administrator to identify the applicable laws and regulations and to assure that any requirements are addressed. Genetic variant database administrators should also put in place adequate security measures to ensure the protection and privacy of patient and protected health information and provide training for database staff on security and privacy protection.

Data formats: To facilitate genetic variant database use for regulatory purposes and to help assure the accuracy and quality of variant assertions, genetic variant database administrators should employ commonly accepted data formats and identify which format is in use by the genetic database. This standardization will help minimize ambiguity regarding variants and better enable comparisons of variant assertions between different databases or other entities.

B. Data Quality

It is essential that the data and information regarding genotypes and phenotypes or clinical information placed into the genetic variant database are of sufficient quality, and based on current scientific knowledge, in order for there to be a reasonable assurance that the assertions made linking specific genetic variants to diseases or conditions are accurate.

Nomenclature: To aid in the accurate interpretation of genetic variants, genetic variant databases should use consistent nomenclature that is widely accepted by the genomics community for gene names and/or symbols, genomic coordinates, variants, described clinical and functional characteristics, and classifications. The genetic variant database administrator should also make available a detailed description of which nomenclature is used to allow FDA and external users to accurately interpret the information presented.

Metadata: Variant data in the genetic variant database should be accompanied by metadata, including the number of independent laboratories and/or studies reporting the variant classification, name of the laboratory(ies) that reported the variant, the name of the test used to detect the variant, and, to the extent possible, details of the technical characteristics of the test that was used (e.g., reference sequence version or build, instrument, software, bioinformatics tools, etc.) and variant characteristics (e.g., zygosity, phasing, and segregation). Genetic variant databases should clearly and transparently document evidence source(s) used to support variant interpretation (e.g., literature, well-documented case histories, etc.).

Data Uniqueness: Genetic variant database operations should also include methods to ensure that individual data points (e.g., a variant from one individual for a particular phenotype) are not represented more than once in the database.

C. Curation, Variant Interpretation and Assertions

The processes that genetic variant database personnel use for curation and variant interpretation should be based on well-defined SOPs and carried out by qualified professionals.

Curation and Variant Interpretation: Written SOPs for curation and variant interpretation, including evaluation of data from clinical practice guidelines, peer-reviewed literature, and pre-curated knowledge bases, should be available to the public for review. SOPs should generally include validated decision matrices, such as those based on well-recognized professional guidelines. All genetic variant database curation and interpretation rules, and future modifications of those rules, should be explained and made available to the public. Furthermore, if curated data or variant interpretations from other sources are to be integrated into the genetic variant database, then the curation and interpretation processes and data quality of those outside sources should be audited by the database administrator on a regular basis. Each interpretation should be performed independently by at least two qualified and trained professionals, as discussed below, and genetic variant databases should have SOPs for resolving differences in interpretation. Providing SOPs publicly for each of these activities will allow outside users to evaluate the evidence used in variant interpretation and thereby promote the consistency of interpretation.

FDA believes that use of publicly available decision matrices[9] for variant interpretation that are based on rigorous professional guidelines is central to assuring that assertions from genetic variant databases constitute valid scientific evidence supporting the clinical validity of a test. FDA reviewers must evaluate evidence in the context of a test's intended use and conditions of use, including specific facts about genes or diseases under consideration (e.g., population incidence of a disease, variant incidence) into their review. *See* 21 CFR 860.7(e)(1). Similarly, such factors should be incorporated into a finalized decision matrix.

Assertions: The types of evidence that personnel interpreting variants may use for an interpretation, and their corresponding strengths, should be defined, and combined into a scoring system. Assertions within an FDA-recognized genetic variant database should be appropriate to the level of certainty and the nature of the genotype-phenotype relationship and be adequately supported. Assertions should be versioned, such that changes in assertions over time are recorded and maintained. Assertions and the evidence underlying them should be truthful and not misleading and be made in language that is clear and understandable. In order to be FDA-recognized, a genetic variant database should not include any recommendations regarding clinical treatment or diagnosis.

For example, it is appropriate for an assertion to include descriptive language about a variant such as responder, non-responder, pathogenic, benign, likely pathogenic, likely benign, variant of unknown significance, etc. as long as such language is truthful, not misleading, and supported by adequate evidence detailed within the genetic variant database. FDA believes that it is

[9] For the purposes of this guidance, a decision matrix is an evidence-based tool used to guide the interpretation of the genotype-phenotype relationship between variants and diseases or conditions.

generally not scientifically appropriate to make a definitive assertion (e.g., pathogenic) about the clinical validity of a variant based on a single piece of evidence, or on only weak evidence. Assertions that a particular genotype-phenotype association is clinically valid should generally involve multiple lines of evidence and, at a minimum, should identify a primary source of scientific evidence and other supporting evidence. Further, wherever appropriate to avoid any potential misunderstanding regarding the strength of the evidence supporting an assertion, the assertion should include a clear description of the evidence associated with it.

D. Professional Training and Conflicts of Interest

Professional Training: FDA recognizes that many different types of genetics professionals may be involved in the curatorial and interpretive process as part of a team (e.g., genetic counselors, Ph.D.-level scientists, physicians). Adequate training and expertise of personnel interpreting variants plays an important role in the quality of variant review and interpretation. FDA believes that interpretation should be performed by qualified professionals with appropriate levels of oversight in place (e.g., multiple levels of review). Personnel interpreting variants should have received adequate training and there should be methodologies in place, such as proficiency testing, to ensure that such personnel meet and maintain high quality standards over time.

Finally, curation procedures should ensure that all data has been collected in compliance with all applicable requirements for protecting patient health information and research involving human subjects.

Conflicts of Interest: Conflicts of interest, especially financial ones, could introduce bias and undermine the quality of variant interpretations in genetic variant databases, as well as the confidence in such interpretations, if not adequately mitigated. To be considered for recognition by FDA, efforts should be made to minimize, and make transparent, any potential conflicts of interest pertaining to a genetic variant database or its personnel.

V. FDA's Genetic Variant Database Recognition Process

FDA believes that data and assertions from genetic variant databases that follow the recommendations discussed in this document would generally constitute valid scientific evidence supportive of clinical validity in a premarket submission. Therefore, FDA intends to implement a recognition process[10] for publicly accessible genetic variant databases and their assertions to streamline premarket review of NGS tests. Specific variant assertions and underlying data from a recognized genetic variant database could generally be submitted by NGS-test developers as part of their premarket review submission, if applicable, in some cases without submission of additional clinical data regarding that variant.

[10] The genetic variant database recognition process discussed in this document may be viewed as analogous to the standards recognition process under section 514 of the FD&C Act (21 U.S.C. 360d), but would not be conducted under this provision.

Participation in the FDA database recognition process is voluntary and participation would not subject the database to FDA oversight, beyond that needed to retain the recognition. For genetic variant database administrators who wish to undergo voluntary recognition, this section describes FDA's recommended process for genetic variant database recognition. When evidence from proprietary sources or genetic variant databases that have not been recognized by FDA are used to support the clinical performance of an NGS-based test, detailed information regarding such sources of evidence should be included in the premarket submission for that test.

FDA intends for its process for recognition of genetic variant databases to involve three steps: (1) voluntary submission of detailed information about the database; (2) FDA review of genetic variant database policies and procedures for obtaining and maintaining data and making variant assertions; and (3) maintenance of FDA recognition of a database. These steps are discussed in detail below.

A. Recognition Process for Genetic Variant Databases

1. Submission for Recognition

Administrators of genetic variant databases seeking to have their assertions be considered by FDA as valid scientific evidence that could provide support for the clinical validity of NGS-based tests should make a voluntary submission to FDA for genetic variant database recognition. Such a submission should demonstrate that the recommendations in this document have been followed. FDA encourages genetic variant database administrators seeking recognition of their genetic variant database to contact FDA through the Pre-Submission Program[11] prior to submission.

2. FDA Review of Genetic Variant Database Policies and Procedures

The intent of this section is to provide additional information to genetic variant database administrators regarding the type of documentation that should be provided to FDA staff for the purpose of voluntary genetic variant database recognition. Complete documentation should address all of the recommendations in this guidance.

The following types of documents, which show that the recommendations in this guidance have been followed, should be submitted in an application for recognition:

- Statement of the types of variants the genetic variant database assertions address (e.g., germline, somatic)
- SOPs, policies or other documents related to the following:
    - General operation of the genetic variant database

[11] Further information about the Pre-Submission Program can be found in the FDA guidance document entitled "Requests for Feedback on Medical Device Submissions: The Pre-Submission Program and Meetings with Food and Drug Administration Staff."

    - Patient health information confidentiality and privacy
    - Data security
    - Curation, variant interpretation, and reinterpretation
    - Training for curation, interpretation, privacy and security, and other relevant activities
- Documentation of personnel qualifications
- Data preservation plan
- Conflict of interest policies and disclosures of conflicts of interest
- Validation studies for interpretation SOPs

As part of its recognition process, FDA may verify variant assertions, as appropriate, to assure they are supported and that the genetic variant database is following its SOPs.

Prior to recognition, FDA generally intends to treat this information confidentially and not publicly disclose it except as required by law.[12] At the time of recognition, the database administrator should make this information publicly available and accessible on the genetic variant database's website. FDA also intends to make available on its own website a list of all FDA-recognized genetic variant databases and other relevant, public information about those databases.

3. Maintenance of FDA Recognition

FDA intends to review FDA-recognized databases regularly on a set schedule to verify they continue to follow their SOPs and the recommendations in this guidance. As part of the continuing database recognition process, FDA would consider the following when evaluating genetic variant databases for NGS-based tests:

a. Processes should incorporate multiple lines of scientific evidence, where available, with appropriate weights.
b. Processes should use a tiered system of assertions (e.g., pathogenic, likely pathogenic, etc.) and adequately describe the meanings of each tier.
c. Genetic variant databases should implement a decision matrix based on validated SOPs or rigorous professional guidelines that incorporate unique details of the gene/disease being evaluated, where available or applicable.
d. Genetic variant databases should include validation of the decision matrix.
e. All guidelines, decision matrices, and details supporting each variant's interpretation should be made available to the public.

Continued transparency about methods and assertions will play a critical role in maintaining confidence in a genetic variant database and thus, to maintaining recognition. FDA believes that it is important that users and the public have access to information about the capabilities and

[12] *See*, e.g., the FD&C Act sections 301(j) (21 U.S.C. 331(j)) and 520(c) (21 U.S.C. 360j(c)), the Trade Secrets Act, 18 U.S.C. 1905, the Freedom of Information Act, 5 U.S.C. 552, and FDA's regulations covering information disclosure at 21 CFR part 20.

limitations of a genetic variant database so that patients and healthcare providers can make fully informed medical decisions. Genetic variant database administrators should document and make publicly accessible any changes or updates to the database SOPs on its website. FDA plans to periodically review its recognition of a genetic variant database based upon this transparently documented and publicly available information. As part of this process, FDA will verify that updates to SOPs, as described in Section IV, have been posted. FDA may also "spot-check" assertions about genetic variants to assure they continue to be supported and that the genetic variant database continues to follow its SOPs for interpretation. If the genetic variant database is not maintained according to the specifications under which it was originally recognized, FDA may withdraw recognition. If recognition is withdrawn, it would be unlikely that FDA would consider assertions from such a genetic variant database to constitute valid scientific evidence supportive of the clinical validity of a test, and FDA would assess what regulatory actions may be appropriate with respect to IVDs supported by such assertions.

B. Use of Third Parties

FDA has an established third party 510(k) review program for eligible medical devices.[13] For genetic variant databases, FDA may consider utilizing third parties to assist with genetic variant database recognition in the future. FDA seeks to work with interested parties that have experience with genetic variant databases and NGS-based tests and can comply with FDA policies, including those regarding screening for conflicts of interest.

C. Use of Data and Assertions from Recognized Genetic Variant Databases

Data from FDA-recognized genetic variant databases would generally constitute valid scientific evidence that can be used to support the clinical validity of the genotype-phenotype relationships embodied in the assertions from such databases provided in a premarket submission. Under this policy, FDA expects that test developers will be able to use FDA-recognized genetic variant databases to establish, at least in part, the clinical validity of their test. For premarket submissions that rely upon genetic variant databases recognized by FDA, the Agency may determine that submission of any additional valid scientific evidence for certain variant assertions found in these genetic variant databases is not necessary, depending on the sufficiency of the evidence for these assertions.

[13] For additional information, including guidance documents on the topic, please see FDA's Third Party Review Program.