

# 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## Draft Guidance for Stakeholders and Food and Drug Administration Staff

### *DRAFT GUIDANCE*

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**Document issued on July 8, 2016.**

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U.S. Department of Health and Human Services  
Food and Drug Administration  
Center for Devices and Radiological Health  
Office of *In Vitro* Diagnostics and Radiological Health

Center for Biologics Evaluation and Research

## Preface

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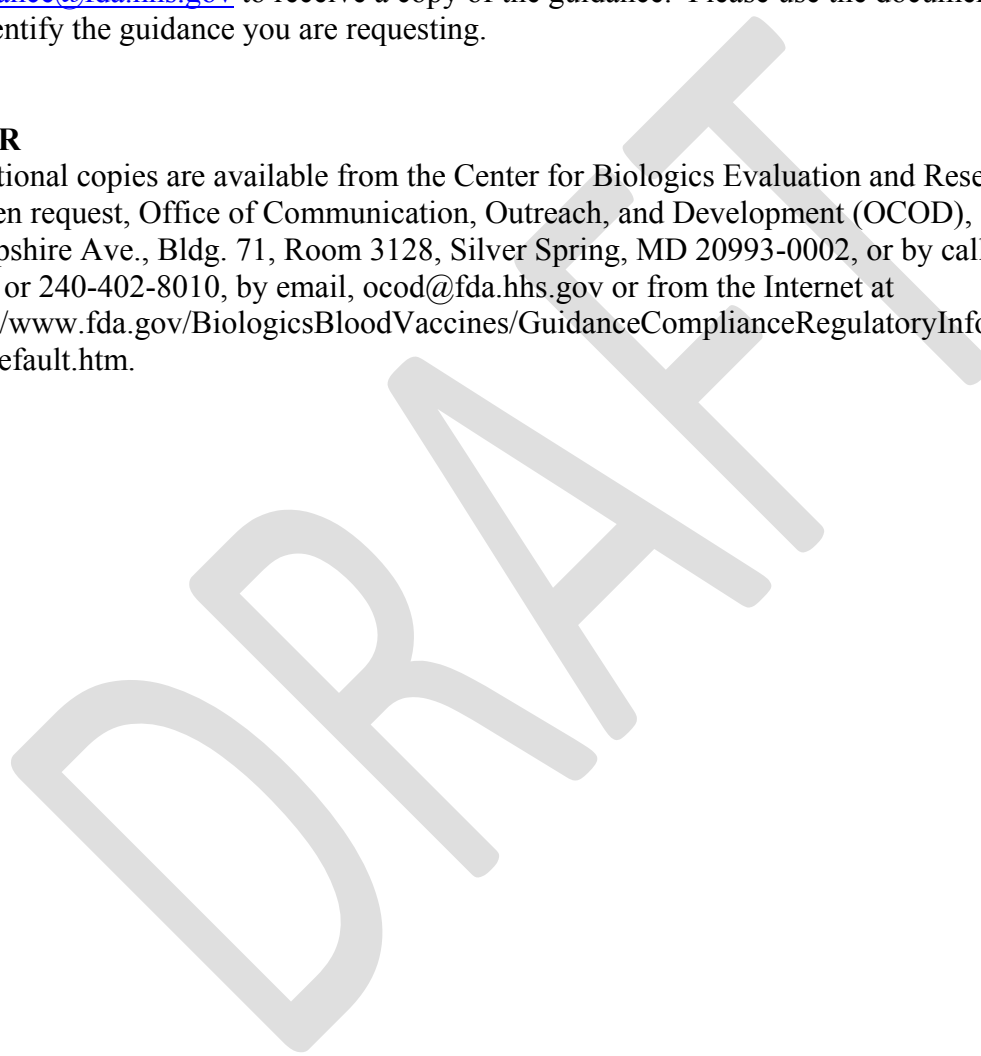
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## Draft Guidance for Stakeholders and Food and Drug Administration Staff

*This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic.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This draft guidance document describes one part of FDA’s effort to create a flexible and adaptive regulatory approach to the oversight of next generation sequencing (NGS)-based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 This draft guidance document describes how publicly accessible databases of human genetic variants can serve as sources of valid scientific evidence to support the clinical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

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

116  
117 Although the importance of genetic variant data aggregation is widely recognized, today much of  
118 the data that would be useful to support clinical validity of NGS-based tests is generally stored in  
119 a manner in which it is not publicly accessible. Aggregation of clinical genotype-phenotype  
120 associations and evaluation of the level of evidence underlying these associations under a well-  
121 defined process will continue to promote more rapid translation of genetic information into  
122 useful clinical evidence.

123  
124 For the purposes of this draft guidance document, a “genetic variant database” is a publicly  
125 accessible database of human genetic variants that aggregates and curates reports of human  
126 phenotype-genotype relationships to a disease or condition with publicly available  
127 documentation of evidence supporting those linkages. Genetic variant databases may also  
128 include assertions<sup>1</sup> about specific genotype-phenotype correlations.

129  
130 FDA believes that the aggregation,<sup>2</sup> curation,<sup>3</sup> and interpretation<sup>4</sup> of clinical genotype-phenotype  
131 associations in genetic variant databases could support the clinical validity of claims made about  
132 a variant detected by an NGS-based test and a disease or condition. In relying on assertions in  
133 genetic variant databases that follow the recommendations in this guidance, FDA hopes to  
134 encourage the deposition of variant information in such databases, reduce regulatory burden on  
135 test developers, and spur advancements in the interpretation and implementation of precision  
136 medicine.

137  
138 *Publicly Accessible Databases of Human Genetic Variants as Sources of Valid Scientific*  
139 *Evidence Supporting Clinical Validity*

140  
141 To determine whether an NGS-based test has a reasonable assurance of safety and effectiveness,  
142 the Agency relies upon the review of valid scientific evidence to support the analytical and  
143 clinical performance of the test. Valid scientific evidence is defined as evidence from well-  
144 controlled investigations, partially controlled studies, studies and objective trials without  
145 matched controls, well-documented case histories conducted by qualified experts, and reports of  
146 significant human experience with a marketed device, from which it can fairly and responsibly

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<sup>1</sup> 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.).

<sup>2</sup> 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.

<sup>3</sup> 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.

<sup>4</sup> 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).

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147 be concluded by qualified experts that there is a reasonable assurance of safety and  
148 effectiveness.<sup>5</sup> In determining whether a particular NGS test has a reasonable assurance of safety  
149 and effectiveness, FDA must determine, based on valid scientific evidence that “in a significant  
150 portion of the target population, the use of the device for its intended uses and conditions of use,  
151 when accompanied by adequate directions for use and warnings against unsafe use, will provide  
152 clinically significant results.”<sup>6</sup>

153  
154 The evidence residing in many genetic variant databases has been collected from multiple  
155 sources that can meet the valid scientific evidence definition, such as evidence from well-  
156 controlled clinical investigations, clinical evidence generated in CLIA (Clinical Laboratory  
157 Improvement Amendments of 1988)-certified laboratories, published peer-reviewed literature,  
158 and certain case study reports. Some organizations that are currently developing genetic variant  
159 databases have adopted protocols and methodologies (e.g., quality measures) and/or external  
160 guidelines (e.g., from professional societies or standards development organizations) for  
161 evidence aggregation, curation, and interpretation practices. While interpretation processes may  
162 vary across databases and organizations, they typically involve the use of qualified experts who  
163 make informed conclusions about the presence or absence of a genetic variant and its meaning  
164 for a particular disease or clinical decision.

165  
166 Further, there are several parallels between the standards set forth by well-recognized  
167 professional guidelines for variant interpretation and FDA review of clinical validity. Personnel  
168 interpreting variants use a range of evidence, including the types and positions of variants,  
169 inheritance, prevalence, well-established functional studies, and prior knowledge of gene-disease  
170 relationships. Generally, the standards for use of evidence appear to parallel the types of  
171 evidence appropriate to support an FDA premarket submission. Under 21 CFR 860.7(c)(2),  
172 isolated case reports, random experience, reports lacking sufficient details to permit scientific  
173 evaluation, and unsubstantiated opinions are not regarded as valid scientific evidence.  
174 Accordingly, FDA believes that summary literature is inferior in this respect to data available for  
175 independent evaluation. FDA assesses clinical validity based on the totality of available  
176 evidence provided in a given submission. Similarly, well-recognized professional guidelines  
177 dictate that database personnel interpreting variants integrate multiple lines of evidence to make  
178 an assertion of clinical validity.

179  
180 The Agency believes such practices help assure the quality of data and assertions within genetic  
181 variant databases and has built upon these approaches in developing the recommendations in this  
182 guidance.

183  
184 FDA has long believed that public access to data is important so that all interested persons (e.g.,  
185 healthcare providers and patients) can make the best medical treatment decisions. To that end,  
186 for all IVDs that have received clearance or de novo classification from FDA since November  
187 2003, FDA has published a Decision Summary containing a review of the analytical and clinical  
188 validity data and other information submitted by the applicant to support the submission and

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<sup>5</sup> 21 CFR 860.7(c)(2).

<sup>6</sup> 21 CFR 860.7(e)(1).

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189 FDA’s justification for clearing or classifying the IVD; FDA is also required to publish  
190 Summaries of Safety and Effectiveness Data for approved PMAs under section 520(h) of the  
191 Federal Food, Drug and Cosmetic Act (FD&C Act) (21 U.S.C. 360j(h)).<sup>7</sup> FDA believes that  
192 similar public availability and access to data contained in genetic variant databases is important  
193 to patients and healthcare providers in order to make fully informed medical decisions.  
194

195 FDA believes that if genetic variant databases follow the recommendations in this document,  
196 including transparency regarding evidence evaluation, and obtain FDA recognition as described  
197 below, the data and assertions within would generally constitute valid scientific evidence that can  
198 be used to support clinical validity.  
199

### 200 **III. Scope**

201  
202 This draft guidance document describes FDA’s considerations in determining whether a genetic  
203 variant database is a source of valid scientific evidence that could support the clinical validity of  
204 an NGS-based test in a premarket submission. This draft guidance further outlines the process by  
205 which administrators<sup>8</sup> of publicly accessible genetic variant databases could voluntarily apply to  
206 FDA for recognition, and how FDA would review such applications and periodically reevaluate  
207 recognized databases.  
208

209 The genetic variant databases discussed in this draft guidance only include those that contain  
210 human genetic variants, and do not include databases used for microbial genome identification  
211 and detection of antimicrobial resistance and virulence markers. This draft guidance does not  
212 apply to software used to classify and interpret genetic variants, but instead, only regards use of  
213 curated databases using expert human interpretation.  
214

### 215 **IV. Recommendations to Support Recognition of Publicly** 216 **Accessible Genetic Variant Databases of Human** 217 **Genetic Variants as Sources of Valid Scientific Evidence** 218 **Supporting Clinical Validity of NGS Tests**

219  
220 FDA believes that evidence contained in a genetic variant database that conforms to the  
221 recommendations described below would generally constitute valid scientific evidence that can  
222 be used to support the clinical validity of an NGS-based test.  
223

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

---

<sup>7</sup> 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.

<sup>8</sup> 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.

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

231  
232 In the subsections below, FDA discusses recommendations for the operation of a genetic variant  
233 database, and the aggregation, curation, and interpretation of data therein, so that such data  
234 would generally constitute valid scientific evidence supportive of clinical validity. FDA  
235 acknowledges that individual genetic variant databases may have different, but equally  
236 scientifically valid, approaches to assuring data quality, clinical relevance, data security, patient  
237 privacy, and transparency. Additionally, FDA recognizes that several professional societies have  
238 or are developing guidelines for genetic variant curation and interpretation that may differ  
239 depending upon discipline, but may each be appropriate in the context of the intended use.  
240 Genetic variant database administrators should focus on ensuring that their procedures and  
241 quality requirements are sufficiently robust to provide a high degree of confidence in their  
242 conclusions regarding genotype-phenotype associations.

243

## 244 **A. Database Procedures and Operations**

245

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

252

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

260

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

268

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



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

274  
275 *Security and Privacy:* Genetic variant database operations must be in compliance with all  
276 applicable federal laws and regulations (e.g., the Health Insurance Portability and Accountability  
277 Act, the Genetic Information Nondiscrimination Act, the Privacy Act, the Federal Policy for the  
278 Protection of Human Subjects (“Common Rule”), etc.) regarding protected health information,  
279 patient privacy, research involving human subjects, and data security, as applicable. It is the  
280 responsibility of the genetic variant database administrator to identify the applicable laws and  
281 regulations and to assure that any requirements are addressed. Genetic variant database  
282 administrators should also put in place adequate security measures to ensure the protection and  
283 privacy of patient and protected health information and provide training for database staff on  
284 security and privacy protection.

285  
286 *Data formats:* To facilitate genetic variant database use for regulatory purposes and to help  
287 assure the accuracy and quality of variant assertions, genetic variant database administrators  
288 should employ commonly accepted data formats and identify which format is in use by the  
289 genetic database. This standardization will help minimize ambiguity regarding variants and  
290 better enable comparisons of variant assertions between different databases or other entities.

291

## **B. Data Quality**

292

293  
294 It is essential that the data and information regarding genotypes and phenotypes or clinical  
295 information placed into the genetic variant database are of sufficient quality, and based on  
296 current scientific knowledge, in order for there to be a reasonable assurance that the assertions  
297 made linking specific genetic variants to diseases or conditions are accurate.

298

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

305

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

314

315 *Data Uniqueness:* Genetic variant database operations should also include methods to ensure that  
316 individual data points (e.g., a variant from one individual for a particular phenotype) are not  
317 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<sup>9</sup> 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

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<sup>9</sup> 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.

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360 generally not scientifically appropriate to make a definitive assertion (e.g., pathogenic) about the  
361 clinical validity of a variant based on a single piece of evidence, or on only weak evidence.  
362 Assertions that a particular genotype-phenotype association is clinically valid should generally  
363 involve multiple lines of evidence and, at a minimum, should identify a primary source of  
364 scientific evidence and other supporting evidence. Further, wherever appropriate to avoid any  
365 potential misunderstanding regarding the strength of the evidence supporting an assertion, the  
366 assertion should include a clear description of the evidence associated with it.  
367

## **D. Professional Training and Conflicts of Interest**

368  
369 *Professional Training:* FDA recognizes that many different types of genetics professionals may  
370 be involved in the curatorial and interpretive process as part of a team (e.g., genetic counselors,  
371 Ph.D.-level scientists, physicians). Adequate training and expertise of personnel interpreting  
372 variants plays an important role in the quality of variant review and interpretation. FDA believes  
373 that interpretation should be performed by qualified professionals with appropriate levels of  
374 oversight in place (e.g., multiple levels of review). Personnel interpreting variants should have  
375 received adequate training and there should be methodologies in place, such as proficiency  
376 testing, to ensure that such personnel meet and maintain high quality standards over time.  
377

378  
379 Finally, curation procedures should ensure that all data has been collected in compliance with all  
380 applicable requirements for protecting patient health information and research involving human  
381 subjects.  
382

383 *Conflicts of Interest:* Conflicts of interest, especially financial ones, could introduce bias and  
384 undermine the quality of variant interpretations in genetic variant databases, as well as the  
385 confidence in such interpretations, if not adequately mitigated. To be considered for recognition  
386 by FDA, efforts should be made to minimize, and make transparent, any potential conflicts of  
387 interest pertaining to a genetic variant database or its personnel.  
388

## **V. FDA’s Genetic Variant Database Recognition Process**

389  
390  
391 FDA believes that data and assertions from genetic variant databases that follow the  
392 recommendations discussed in this document would generally constitute valid scientific evidence  
393 supportive of clinical validity in a premarket submission. Therefore, FDA intends to implement a  
394 recognition process<sup>10</sup> for publicly accessible genetic variant databases and their assertions to  
395 streamline premarket review of NGS tests. Specific variant assertions and underlying data from a  
396 recognized genetic variant database could generally be submitted by NGS-test developers as part  
397 of their premarket review submission, if applicable, in some cases without submission of  
398 additional clinical data regarding that variant.  
399

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<sup>10</sup> 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.

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

407  
408 FDA intends for its process for recognition of genetic variant databases to involve three steps:  
409 (1) voluntary submission of detailed information about the database; (2) FDA review of genetic  
410 variant database policies and procedures for obtaining and maintaining data and making variant  
411 assertions; and (3) maintenance of FDA recognition of a database. These steps are discussed in  
412 detail below.

## 413 **A. Recognition Process for Genetic Variant Databases**

### 414 **1. Submission for Recognition**

415  
416 Administrators of genetic variant databases seeking to have their assertions be considered by  
417 FDA as valid scientific evidence that could provide support for the clinical validity of NGS-  
418 based tests should make a voluntary submission to FDA for genetic variant database recognition.  
419 Such a submission should demonstrate that the recommendations in this document have been  
420 followed. FDA encourages genetic variant database administrators seeking recognition of their  
421 genetic variant database to contact FDA through the Pre-Submission Program<sup>11</sup> prior to  
422 submission.

### 423 **2. FDA Review of Genetic Variant Database Policies and** 424 **Procedures**

425  
426 The intent of this section is to provide additional information to genetic variant database  
427 administrators regarding the type of documentation that should be provided to FDA staff for the  
428 purpose of voluntary genetic variant database recognition. Complete documentation should  
429 address all of the recommendations in this guidance.

430  
431 The following types of documents, which show that the recommendations in this guidance have  
432 been followed, should be submitted in an application for recognition:

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

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<sup>11</sup> 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.](#)”

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- 441 ○ Patient health information confidentiality and privacy
- 442 ○ Data security
- 443 ○ Curation, variant interpretation, and reinterpretation
- 444 ○ Training for curation, interpretation, privacy and security, and other relevant
- 445 activities
- 446 ● Documentation of personnel qualifications
- 447 ● Data preservation plan
- 448 ● Conflict of interest policies and disclosures of conflicts of interest
- 449 ● Validation studies for interpretation SOPs

450  
451 As part of its recognition process, FDA may verify variant assertions, as appropriate, to assure  
452 they are supported and that the genetic variant database is following its SOPs.

453  
454 Prior to recognition, FDA generally intends to treat this information confidentially and not  
455 publicly disclose it except as required by law.<sup>12</sup> At the time of recognition, the database  
456 administrator should make this information publicly available and accessible on the genetic  
457 variant database’s website. FDA also intends to make available on its own website a list of all  
458 FDA-recognized genetic variant databases and other relevant, public information about those  
459 databases.

### 460 **3. Maintenance of FDA Recognition**

461  
462  
463 FDA intends to review FDA-recognized databases regularly on a set schedule to verify they  
464 continue to follow their SOPs and the recommendations in this guidance. As part of the  
465 continuing database recognition process, FDA would consider the following when evaluating  
466 genetic variant databases for NGS-based tests:

- 467  
468 a. Processes should incorporate multiple lines of scientific evidence, where  
469 available, with appropriate weights.
- 470 b. Processes should use a tiered system of assertions (e.g., pathogenic, likely  
471 pathogenic, etc.) and adequately describe the meanings of each tier.
- 472 c. Genetic variant databases should implement a decision matrix based on validated  
473 SOPs or rigorous professional guidelines that incorporate unique details of the  
474 gene/disease being evaluated, where available or applicable.
- 475 d. Genetic variant databases should include validation of the decision matrix.
- 476 e. All guidelines, decision matrices, and details supporting each variant’s  
477 interpretation should be made available to the public.

478  
479 Continued transparency about methods and assertions will play a critical role in maintaining  
480 confidence in a genetic variant database and thus, to maintaining recognition. FDA believes that  
481 it is important that users and the public have access to information about the capabilities and

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<sup>12</sup> 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.

*Contains Nonbinding Recommendations*  
*Draft – Not For Implementation*

482 limitations of a genetic variant database so that patients and healthcare providers can make fully  
483 informed medical decisions. Genetic variant database administrators should document and make  
484 publicly accessible any changes or updates to the database SOPs on its website. FDA plans to  
485 periodically review its recognition of a genetic variant database based upon this transparently  
486 documented and publicly available information. As part of this process, FDA will verify that  
487 updates to SOPs, as described in Section IV, have been posted. FDA may also “spot-check”  
488 assertions about genetic variants to assure they continue to be supported and that the genetic  
489 variant database continues to follow its SOPs for interpretation. If the genetic variant database is  
490 not maintained according to the specifications under which it was originally recognized, FDA  
491 may withdraw recognition. If recognition is withdrawn, it would be unlikely that FDA would  
492 consider assertions from such a genetic variant database to constitute valid scientific evidence  
493 supportive of the clinical validity of a test, and FDA would assess what regulatory actions may  
494 be appropriate with respect to IVDs supported by such assertions.  
495

496 **B. Use of Third Parties**

497  
498 FDA has an established third party 510(k) review program for eligible medical devices.<sup>13</sup> For  
499 genetic variant databases, FDA may consider utilizing third parties to assist with genetic variant  
500 database recognition in the future. FDA seeks to work with interested parties that have  
501 experience with genetic variant databases and NGS-based tests and can comply with FDA  
502 policies, including those regarding screening for conflicts of interest.  
503

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

506  
507 Data from FDA-recognized genetic variant databases would generally constitute valid scientific  
508 evidence that can be used to support the clinical validity of the genotype-phenotype relationships  
509 embodied in the assertions from such databases provided in a premarket submission. Under this  
510 policy, FDA expects that test developers will be able to use FDA-recognized genetic variant  
511 databases to establish, at least in part, the clinical validity of their test. For premarket  
512 submissions that rely upon genetic variant databases recognized by FDA, the Agency may  
513 determine that submission of any additional valid scientific evidence for certain variant  
514 assertions found in these genetic variant databases is not necessary, depending on the sufficiency  
515 of the evidence for these assertions.

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<sup>13</sup> For additional information, including guidance documents on the topic, please see [FDA’s Third Party Review Program](#).