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Scientific Standards for 23andMe's Health and Trait Reports

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Introduction

23andMe's mission is to help people *access*, *understand*, and *benefit* from the human genome. One of the main ways we do this is by providing personalized genetic reports related to Carrier Status, Genetic Health Risks, Pharmacogenetics, Wellness (collectively "Health"), and Traits. These reports must meet strict standards of clinical and scientific validity, as well as analytical validity. This article provides a detailed overview of the scientific standards we use in our report development.

Our Health and Trait reports provide results based on associations between specific genetic variants and various health conditions, medication processing, and traits. All Carrier Status, Genetic Health Risk, and Pharmacogenetics reports are based on hand-curated genetic associations supported by peer-reviewed scientific papers (curated reports). While many of our Wellness and Trait reports are also hand-curated, some are based on statistical models utilizing up to hundreds of genetic associations (modeled reports). This approach is described in detail in a separate white paper

entitled "Estimating Complex Phenotype Prevalence Using Predictive Models"[1]. The following information focuses on the science behind our curated reports only.

The scientific, clinical, and analytical validity of 23andMe curated reports

For a genetic association to be included in a curated Health or Trait report, there must be multiple sources of scientific evidence supporting the link between the genetic variant and the underlying phenotype. We also look for functional and biological evidence supporting a causative role for the variant's effect on the condition, trait, or medication processing. There must also be no compelling contradictory evidence refuting the genetic association. Taken together, the evidence should establish a consensus that the variant has a meaningful and real effect on the condition of interest or medication processing.

The evidence supporting the genetic associations underlying our curated reports is drawn primarily from two sources: clinical guidelines and peer-reviewed scientific publications. For Carrier Status and Genetic Health Risk reports, clinical guidelines summarize entire bodies of evidence and thus are considered sufficient on their own in the absence of more recent contradictory evidence. For all Health reports, the two types of studies we look for in peer-reviewed literature are *clinical* and *functional* studies. Clinical studies demonstrate an association between a variant and a specific phenotype observed in certain populations. Functional studies demonstrate the functional effects of the variant in pathologically relevant cell lines, animal models, or human subjects. Literature evidence can also include consensus statements or review articles supporting the effect of the variant or the class of variants to which the variant belongs.

Our scientists and medical professionals evaluate these published studies to make sure the findings are supported by strong study designs and appropriate methods. Some of the factors we consider include:

- **The study population** -- Is the population studied large enough to give a meaningful interpretation of the study results, and can the results be generalized to 23andMe customers?
- **Methodology** -- Did the study use an appropriate study design to address the hypothesis? Did the authors adjust for covariates and account for possible confounding factors?
- **Clinical and statistical significance** -- What is the strength of the statistical evidence supporting the researchers' conclusions? Did they correct for multiple hypotheses? What is the magnitude of the effect?

[1] https://permalinks.23andme.com/pdf/23-12_predictivemodel_methodology_02oct2015.pdf

In addition to the clinical and scientific validity criteria described in this article, we also perform extensive studies in CLIA-certified laboratories to ensure high genotyping accuracy and reproducibility for genetic variants used in our reports.

The following sections detail the criteria specific to each report type.

Carrier Status Reports[2]

23andMe Carrier Status reports identify whether a person carries specific genetic variants known to cause autosomal recessive conditions. Carriers do not typically have the condition themselves, but they can pass the genetic variant down to their children. Our Carrier Status reports are regulated by the U.S. Food and Drug Administration (FDA) and meet FDA requirements for being clinically and analytically valid. For our Carrier Status reports, see our package insert[3] for detailed clinical and analytical performance information.

Genetic variants must meet one of the following criteria to be included in a Carrier Status report:

- Clinical guidelines recommend carrier screening for the variant for the given recessive condition.
- At least two independent clinical studies demonstrate a genotype-phenotype correlation and at least one study provides functional evidence supporting a causative role for the variant.

Curated Wellness and Trait Reports

23andMe Wellness reports describe how genetics influences traits and conditions related to lifestyle and environment, such as one's likelihood of being lactose intolerant. 23andMe Trait reports describe how genetics influences traits like eye color, hair texture, and taste preference.

Similar to Carrier Status reports, a genetic association must be supported by multiple lines of evidence to be included in a curated Wellness or Trait report. However, research on many of these phenotypes is challenging or sparse. Thus, our criteria reflect the availability of research and also consider evidence from 23andMe's large database of over millions of genotyped and phenotyped individuals. Our database is

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[2] The 23andMe PGS test uses qualitative genotyping to detect select clinically relevant variants in the genomic DNA of adults for the purpose of reporting carrier status and reporting and interpreting genetic health risks. The relevance of each report may vary based on ethnicity. Our carrier status reports can be used to determine carrier status, but cannot determine if you have two copies of any genetic variant. These carrier reports are not intended to tell you anything about your risk for developing a disease in the future or anything about the health of your fetus, or your newborn child's risk of developing a particular disease later in life. For certain conditions, we provide a single report that includes information on both carrier status and genetic health risk.

[3] https://www.23andme.com/test-info/carrier-status

a unique resource that allows us to evaluate genetic associations with high statistical power and enables us to study these relatively under-studied phenotypes.

Genetic variants must demonstrate a consistent and statistically significant genotype-phenotype association across multiple cohorts to be included in a Wellness or Trait report. These associations can be demonstrated through any of the following:

- Two independent published studies.
- One published study with two independent cohorts, or one published study with replication of the association in a 23andMe cohort, in addition to at least one published functional study providing biological evidence.
- Two separate 23andMe cohorts, in addition to at least one published functional study providing biological evidence. For associations in the Wellness category, a non-23andMe external expert must also review and agree on the validity of the 23andMe analyses.

Genetic Health Risk Reports[4]

23andMe Genetic Health Risk reports identify whether a person has specific genetic variants associated with various health conditions, and provide information about risk for these conditions. In some cases, a single copy of a variant is associated with increased risk; in other cases two copies or a combination of variants may be necessary. Many of these conditions are also influenced by non-genetic factors and genetic variants not covered by our reports. Thus, having a variant or combination of variants associated with increased risk does not mean a person will definitely develop the disease or condition, and vice versa.

Although these reports include some conditions that are inherited in an autosomal recessive manner, they are distinct from Carrier Status reports in that the conditions described by Genetic Health Risk reports are lower penetrance, tend to be adult-onset or have milder symptoms, or are not typically considered relevant for reproductive decision-making.

Our Genetic Health Risk reports are regulated by the U.S. Food and Drug Administration (FDA) and meet FDA requirements for being clinically and

[4] The 23andMe PGS test uses qualitative genotyping to detect select clinically relevant variants in the genomic DNA of adults from saliva for the purpose of reporting and interpreting genetic health risks. It is not intended to diagnose any disease. Your ethnicity may affect the relevance of each report and how your genetic health risk results are interpreted. Each genetic health risk report describes if a person has variants associated with a higher risk of developing a disease, but does not describe a person's overall risk of developing the disease. The test is not intended to tell you anything about your current state of health, or to be used to make medical decisions, including whether or not you should take a medication, how much of a medication you should take, or determine any treatment.

analytically valid. For these reports, see our package insert[5] for detailed clinical and analytical performance information.

Genetic variants must meet one of the following criteria to be included in a Genetic Health Risk report:

- Clinical guidelines recommend screening for the variant for the given condition.
- At least two independent clinical studies demonstrate a genotype-phenotype correlation and at least one study provides functional evidence supporting a causative role for the variant. In addition, the risk associated with at least one combination of genotypes that includes the variant is substantial or clinically significant.

When reporting quantitative measures of risk in these reports, preference is given to absolute risk over relative risk and to larger and more recent studies when available. Likelihood ratios may also be provided when data is available to derive these estimates. The populations to which risk estimates apply are always reported, as these risk estimates may not be accurate across populations.

Pharmacogenetics Reports[6]

23andMe Pharmacogenetics reports identify whether a person has specific genetic variants associated with medication processing, and provide information about predicted phenotypes (e.g., drug metabolism or drug transport) based on genotype. Predicted phenotypes are based on the functional activity of variant combinations and follow standardized translation tables published by clinical guidelines. The ability to process medications is also influenced by many non-genetic and genetic factors not covered by our reports. Thus, having a variant or combination of variants may have no noticeable effects on how medications are processed.

Our Pharmacogenetics reports are regulated by the U.S. Food and Drug Administration (FDA) and meet FDA requirements for being clinically and

[5] https://www.23andme.com/test-info/genetic-health

[6] 23andMe PGS Pharmacogenetics reports: The 23andMe test uses qualitative genotyping to detect 6 variants in 3 genes in the genomic DNA of adults from saliva for the purpose of reporting and interpreting information about the processing of certain therapeutics to inform discussions with a healthcare professional. It does not describe if a person will or will not respond to a particular therapeutic and does not describe the association between detected variants and any specific therapeutic. Results should be confirmed by an independent genetic test prescribed by your own healthcare provider before taking any medical action. Warning: Test information should not be used to start, stop, or change any course of treatment and does not test for all possible variants that may affect metabolism or protein function. The PGS test is not a substitute for visits to a healthcare professional. Making changes to your current regimen can lead to harmful side effects or reduced intended benefits of your medication, therefore consult with your healthcare professional before taking any medical action. For a complete list of the 6 variants tested, visit https://www.23andme.com/test-info/pharmacogenetics

analytically valid. For these reports, see our package insert[7] for detailed clinical and analytical performance information.

Genetic variants must meet the following criteria to be included in a gene-based Pharmacogenetics report:

- At least two independent clinical studies, including *in vivo* or *ex vivo* studies, must demonstrate that the genetic variant alters a drug's pharmacokinetics. Pharmacokinetic studies are designated as those that assess drug absorption, distribution, metabolism, and excretion over time.
- In addition, at least one of the following studies: one study that provides preclinical functional evidence supporting the variant's effect on enzyme/protein function, or one study that shows the genetic variant affects clinical outcomes in response to a drug.

Some Pharmacogenetics reports include examples of medications whose processing may be affected by the genetic variants included in the report. The list of medications (if included) is not a comprehensive list and may change over time as new evidence emerges.

Medications must meet one of the following criteria to be included in a gene-based Pharmacogenetics report:

- FDA drug labeling includes pharmacogenetic information related to the gene in the report.
- Clinical guidelines and/or reputable pharmacogenetic databases assign a high level of evidence to the gene-drug pair.

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For more information about 23andMe reports, please visit:
https://customercare.23andme.com/hc/en-us/categories/201645477-Reports

Revision history

April 17, 2017: Included criteria for Genetic Health Risk reports.
March 2, 2020: Included criteria for Pharmacogenetics reports.
March 30, 2021: Updated the Pharmacogenetics category disclaimer. Updated hyperlinks.

[7] https://www.23andme.com/test-info/pharmacogenetics

Glossary

Autosomal recessive: One of several patterns of inheritance through which a trait or phenotype can be passed down through families. In an autosomal recessive disorder, two copies of a specific genetic variant must be present in order to play a causative role in disease development.

Clinical guideline: A document created by a specific medical or clinical society summarizing the most current scientific evidence, criteria, and recommendations in that field. An example would be a carrier screening guideline published by the American College of Medical Genetics, such as Watson MS et al. (2004). "Cystic fibrosis population carrier screening: 2004 revision of American College of Medical Genetics mutation panel." Genet Med. 6(5):387-91.

Drug metabolism: The process of breaking down a drug into an active or inactive metabolite.

Drug transport: The process of moving a drug into or out of cells in the body, by way of a transporter protein.

Genetic variant: A version of a DNA sequence at a specific genomic location.

Genotype: An individual's genetic (DNA) sequence at a specific genomic location, taking into account both chromosome copies.

Peer-reviewed scientific publications: Articles that have been vetted by other experts in the field before being published.

Pharmacokinetics: The activity of drugs in the body over time, including drug absorption, distribution, metabolism, and excretion.

Phenotype: An observable characteristic.