Introduction

As the first personal genomics platform, we're excited to provide each and every person the ability to learn about themselves through our marketplace of novel DNA-powered products. Helix collaborates with our partners to help make sure their products are safe, accurate and transparent.

One way we do this is by reviewing each of the products before they become available to our customers. The Helix science team performs three evaluations of new products. The first is a risk assessment of the product. The second, *Scientific Evidence Evaluation*, evaluates the underlying scientific content and claims of each partner product. The third is a technical review of integration between Helix and the partner product, to ensure our customers receive accurate insights about themselves.

Product Risk Assessment

We believe it should be easy for everyone to access their DNA information, but our first consideration is safety. There is always a slim possibility someone could get a positive result about themselves that *isn't true* (false positive), or could receive a negative result when it *is true* (false negative). Because of this, we assess the risk of each product by asking ourselves, "what is the potential for harm if an individual uses this product?"

For products with a higher risk of harm, we work more closely with our partners to mitigate possible risks. For example, with many health products we require these products be available only from partners with CLIA (Clinical Laboratory Improvements Act) certifications and that a customer's health history must be reviewed by a licensed physician to ensure a test is right for them before testing. We also review the science behind the products more intensively- spending greater effort validating the underlying scientific content and recommendations. Lastly, we strongly encourage more explicit consent, clear language, great product design, educational resources, and access to genetic counseling to help individuals understand how the information they learn should be considered. If a health product cannot provide the appropriate support for our users, we do not allow that product on Helix.

Scientific Evidence Evaluation

Helix's partner products utilize the scientific literature and data science to produce novel DNA-powered products. We are excited (and humbled) by the amount of scientific knowledge being generated every day; millions of articles have been added to PubMed in the past decade (Vardakas et al. 2015). Further, the pace of new peer-reviewed articles is accelerating (Bornmann and Mutz 2015). As a result, Helix has adopted a risk-based approach to reviewing the scientific content of its partner products that maintains safety (see above) but still allows access to cutting-edge products, flexibly manages the ever-changing state of science, and increases user transparency (see below).

Evaluation of scientific interpretations in partner products

Helix's partners develop and deliver the scientific content of their products. Our partners typically develop this through curation of the scientific literature that supports a genetic interpretation or through the development of custom algorithms that combine genetic data and other data about a user. Helix asks partners to submit their supporting data for evaluation. However, while Helix evaluates the scientific basis of partner products, each of our partners is ultimately responsible for their interpretation of genetic insights in their products.

Genetic interpretations typically fall into one of two categories. The first is a direct association between a single variant and a trait (phenotype). For example, a product may state "a change from cytosine to thymine (C to T) in the gene *MCM6* is associated with lactose tolerance." We review the underlying science of these interpretations by using a standard rubric scientists use to evaluate the quality of a scientific finding. The evidence is typically peer-reviewed scientific literature, although some partners will have proprietary algorithms. These standards include the number of people studied (sample size), the accuracy and description of the phenotypes, replication of the finding in independent cohorts, corrected statistical significance, and bias (e.g., are the results more accurate for people of certain ethnicities).

The second category is the combination of many variants via an algorithm into a single interpretation. For example, an ancestry calculation uses data from hundreds of thousands of individual variants to estimate your ancestral background (Shringarpure et al. 2016). Products may also combine variants to predict your risk for a specific condition, such as coronary artery disease (Khera et al. 2016). Lastly, products may combine your genetic data with other data about you to predict another outcome. For example, partners may combine self-reported information with genetic markers to make predictions. In these cases, Helix evaluates multi-variant products using a standard rubric scientists would use to evaluate the quality of a prediction. These standards include the number of people studied (sample size), replication of the finding using a training and validation set, and bias (such as the ethnic composition of the study participants). In summary, we are looking for evidence that is appropriate to the claim. Helix does not allow interpretations or claims of specific outcomes that do not reflect the underlying evidence, and will ask partners to remove them if discovered.

Evaluation of recommendations in partner products

Many of our partners will follow-up an interpretation with a recommendation. These recommendations take three main forms. 1) Logical extrapolation based on the trait: "If you have stomachaches and an increased risk for lactose intolerance, try removing dairy from your diet." 2) Expert advice: "Our physical trainers suggest doing more quad strengthening exercises based on your genetic profile." 3) Direct outcomes-based recommendations: "Use of this product will result in weight loss."

Helix reviews the recommendations within partner products using a framework that assesses product risk (see above) and the type of recommendation. Low-risk recommendations in nutrition and fitness are typically based on "logical extrapolation" or on "expert advice" have not been validated with rigorous clinical trials. However, these recommendations encourage our users to adopt better behaviors that contribute to general wellness and typically draw on widely accepted recommendations commonly given by nutritionists, trainers, and other professionals.

In contrast, if a partner makes a direct recommendation that purports to lead to a specific outcome, we review the evidence to see if the recommendation is validated in the literature. For example, if you have a variant in *MC1R* that results in predisposition to red hair and fair skin, a "logical" recommendation would be "we suggest you wear sunscreen as individuals with fair skin are predisposed to sunburns." A direct recommendation would be "individuals with your specific *MC1R* variant have been proven to benefit from SPF50." Helix does not permit claims of specific outcomes that do not reflect the underlying evidence and will remove them if discovered.

Helix and Partner Product Integration Testing

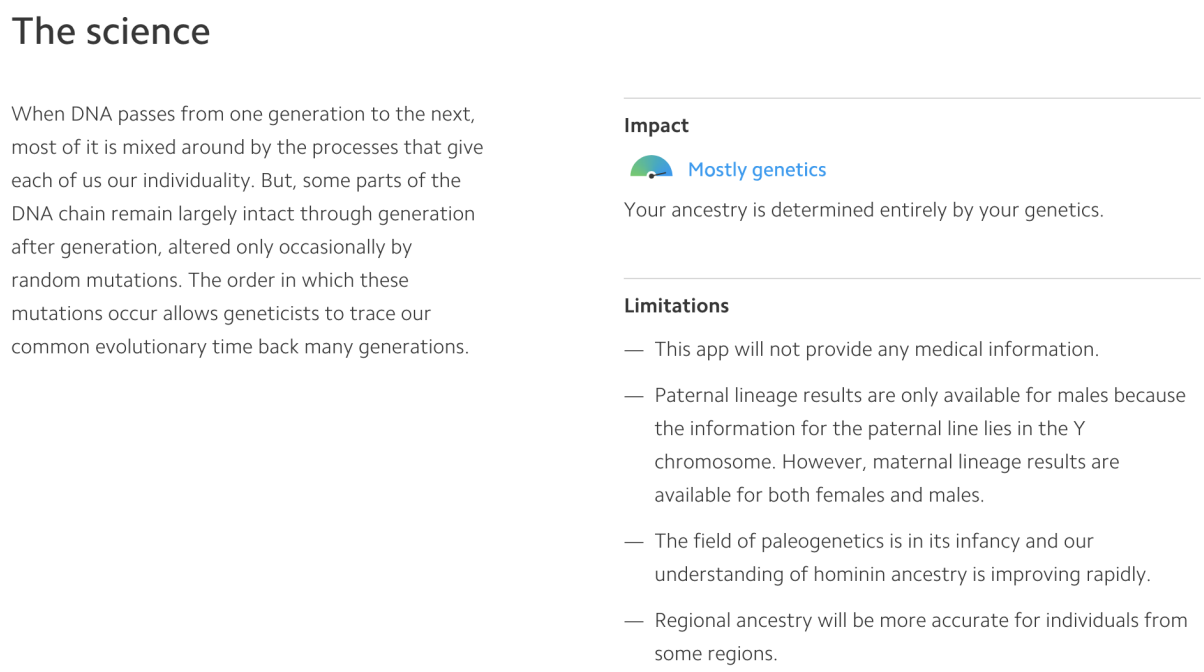
In order for users to engage with the DNA-powered products they buy on Helix, we share the required portions of their DNA data with their consent. This data are accessed by partners through the Helix platform. Testing this process helps ensure our partners are able to accurately integrate data into their products and reduces the likelihood the product will have errors such as false negatives or false positives.

To test, Helix delivers DNA data packages made up of positive and negative controls including different sets of variants, individual replicates, and familial replicates. This process helps ensure partners return the expected results for an individual and do so in a repeatable manner. For our health partners, Helix expands this process to include blinded testing of Helix's sequencing (Helix runs positive control samples that contain important variants that Helix is blinded to) and blinded testing of partners (Helix delivers data to partners with important variants that they should report on). Ultimately, this process provides confidence to Helix and its partners that the product is returning the expected DNA insights.

Encouraging educated users through transparency

We believe our users should make educated purchasing decisions. As part of this philosophy, we first encourage our partners to cite literature in their products and publish white papers if their methods are proprietary. Further on Helix's product detail pages, our science team provides editorial that describe the relative state of the science behind the product, the impact of genetics in the product relative to the environment, and limitations of the products. You can see sections like the one below for each partner

product on helix.com. We believe this information will help our users make more educated purchasing decisions.



Science Section from Geno 2.0 Next Generation: *Each product will have a long form description on left side, a gauge describing the impact of genetics on the product (from "mostly other factors" to "mostly genetics"), and limitations of the product.*

Conclusion

Our goal is to provide users safe, accurate, and transparent products as they explore the new world of personal genomics. We seek to enable partners to build innovative products that engage and inform users while staying true to our current scientific understanding of DNA. We have established a process that we hope is consistent and fair, with a clear rationale for acceptance or rejection. However this is a living process, we regularly see new products and experiences powered by DNA that teach us something new. We invite feedback so that we can refine our policies as we learn.