Ambry Genetics®
A TEMPUS COMPANY

WHITE PAPER

# Patient for Life™: An Innovative Laboratory-Initiated Cohort Reanalysis Program

## Introduction

In 2011, Ambry Genetics became the first commercial laboratory to offer clinical whole exome sequencing (ES). Since that time, ES has become the first-line diagnostic test for patients with suspected genetic disorders.[1-4] Findings from ES are often presumed to be invariant over time, like most clinical tests. However, advances in novel gene-disease discoveries, changes or updates in patient clinical features, and improvements in bioinformatics tools may yield additional diagnoses missed on the initial analysis, thus warranting regular reanalysis of ES data.[5]

### Two Distinct But Complimentary Approaches

The clinical validity and utility of ES reanalysis has been well established, and the American College of Medical Genetics and Genomics (ACMG) has published a series of points to consider regarding the reevaluation and reanalysis of genomic test results.[6] However, a consensus recommendation on the specific approach to use has not been made. Two approaches have been proposed: clinician-initiated patient-level reanalysis, and laboratory-initiated cohort-level reanalysis[7] (Table 1).

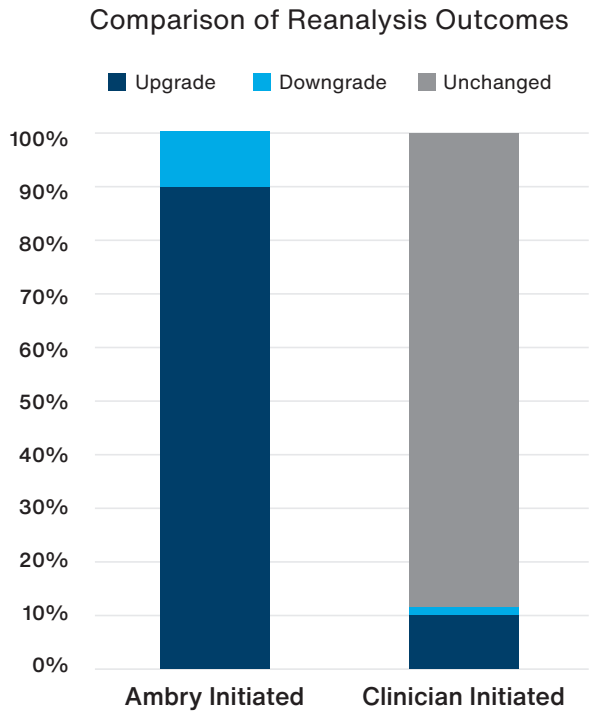


Figure 1. Ambry-initiated reanalysis leads to increased clinically-relevant reclassifications.[8]

| Clinician-Initiated Patient-Level Reanalysis | Laboratory-Initiated Cohort-Level Reanalysis |
|---|---|
| Traditional approach | Proactive approach |
| Ad hoc; lacks systematic reevaluation of all patients[7] | Triggered by updates to gene-disease classifications and/or variant classifications |
| Most useful when there are updates to clinical phenotype and/or family history | Systematically reviews all previously undiagnosed cases |

Table 1. Description of reanalysis approaches.

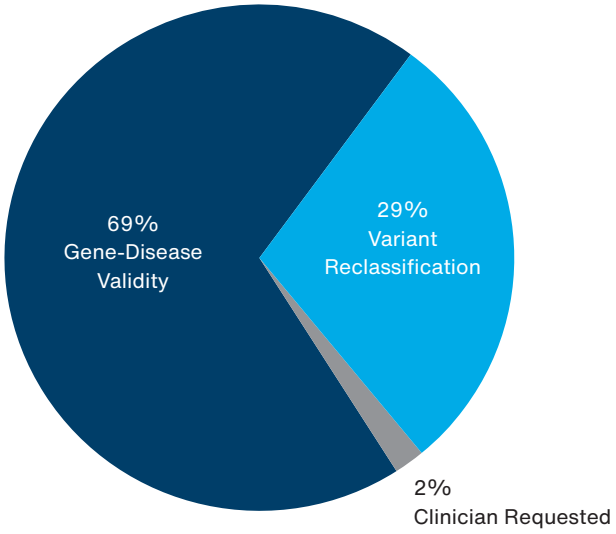


Figure 2. Over two-thirds of reclassifications are the result of advances in gene-disease validity.[8]

## Ambry's Patient for Life™ Program

Launched in 2011, the Patient for Life Program is the first of its kind laboratory-initiated cohort-level reanalysis program. This unique service proactively reviews patient exome data for new diagnostic findings based on advances in gene-disease validity and variant classification. Reclassification reports are then issued to ordering clinicians. This service is provided indefinitely without any additional cost to the patient. The program has proven to be an effective tool for identifying patients with rare diseases, leading to a diagnostic finding in 5% of patients with previously negative exome results.[8]

Over the tenure of the program, Ambry's proactive approach to reanalysis has provided more clinically-relevant reclassifications than the traditional clinician-initiated approach[8] (Fig. 1). The majority (69%) of reclassifications are the result of advances in gene-disease validity[8] (Fig 2). With over 100 new gene-disease relationships characterized annually, it is improbable that clinicians could anticipate when a new characterization would impact each patient they follow.

## Gene-Disease Validity Impacts Diagnostic Yield

Gene-Disease Validity (GDV) represents a measurement of the evidence strength that pathogenic variants in a specific gene result in a defined disease phenotype.[9] The process involves a meticulous assessment in which existing evidence is collated, scrutinized, and translated into numerical totals.[10] Subsequently, these totals are assigned to categories of descending strength (Fig 3). Given the nature of GDV, each gene could be evaluated against multiple diseases, leading to multiple distinct gene-disease validity classifications. GDV assessment forms the crux of reliable evidence-based test result reporting and serves as a major catalyst in the resolution of previously undiagnosed cases.

Ambry Genetics, in 2017, emerged as the sole laboratory to publish criteria for their GDV assessment processes.[10] Ambry's expert team of scientists, The Gene Team, conducts an exhaustive, daily review of gene discovery publications. This methodical approach allows for validation and continual maintenance of the GDV database. Their ongoing efforts in characterizing genes influence clinical exome analysis, aid in the detection of genetic causes for previously undiagnosed patients, and allow for initiation of appropriate patient management.

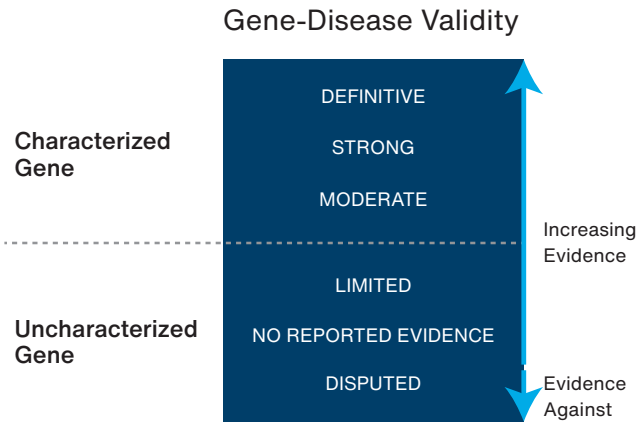


Figure 3. Gene-Disease validity assessment classifies the strength of gene-disease relationships.[10]

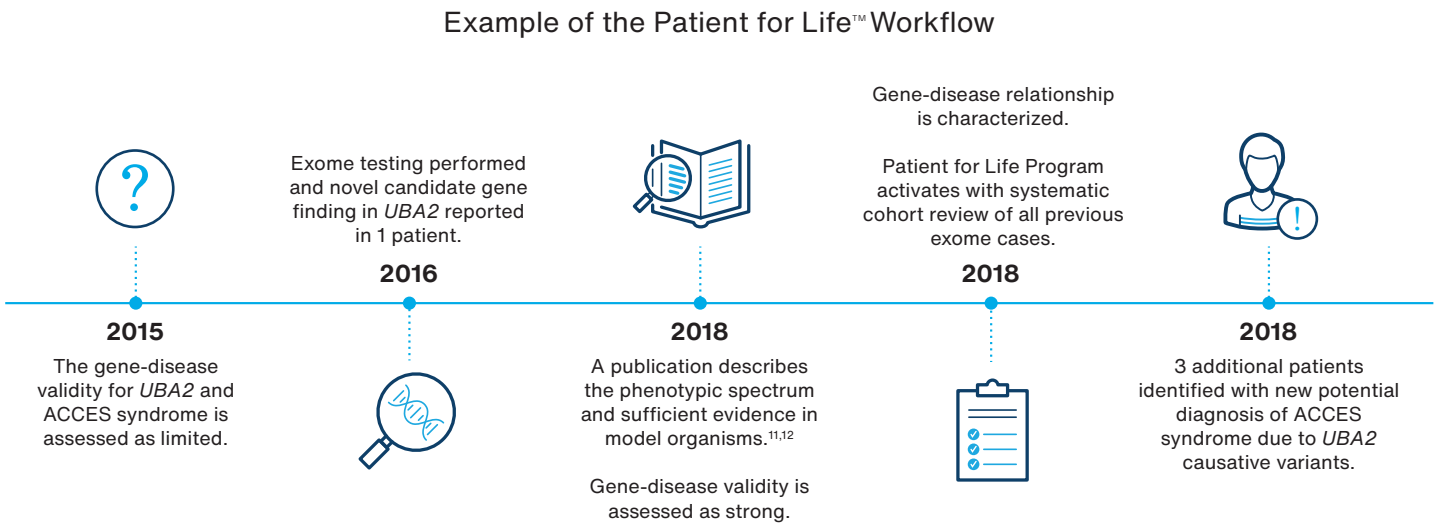


Figure 4. The *UBA2* gene was characterized for ACCES syndrome (an autosomal dominant disorder characterized by aplasia cutis congenita and other ectodermal variations) in 2018. Approximately one-third of the cases that were re-assessed after the gene was characterized had sufficient phenotypic overlap to meet reporting criteria. One of these cases had a variant in this gene reported as a novel finding in 2016.

## Changes in Gene-Disease Validity Initiate the Patient for Life Program

When the GDV of a gene changes, Ambry's cohort of previously tested exome patients is systematically reviewed for impacted patients. Reclassification reports are generated for patients with alterations previously reported as novel candidates for causing the disease. Cases without previously reported alterations in the newly characterized gene are also reviewed. Cases undergo reanalysis if an alteration is suspected to be pathogenic or likely pathogenic. All cases assigned for reanalysis then undergo variant classification and phenotypic assessment to determine whether a clinical reclassification report is issued.

As an example, the *UBA2* gene was characterized for ACCES syndrome (an autosomal dominant disorder presenting with aplasia cutis congenita and other ectodermal variations) in 2018. Subsequently, about one-third of the cases reassessed based on this characterization had sufficient phenotypic overlap to meet reporting criteria. One of these cases had a variant in this gene reported as a novel finding in 2016 (Fig 4).

## Laboratory-Initiated Reanalysis Reduces Disparities Between REA Groups

Patient race, ethnicity, and ancestry (REA) significantly impact the likelihood of a clinician requesting a reanalysis, reanalysis rates, and reclassification rates.[13] For example, it has been shown that patients identifying as African American and Black are among the least likely to receive clinician-initiated reanalysis despite over half receiving reclassifications when reanalysis is initiated[13] (Fig 5). By systematically screening all previous cases, the Patient for Life program can help bridge these disparities by ensuring equitable access to updated and accurate genetic testing results for all patients, regardless of their racial or ethnic background.

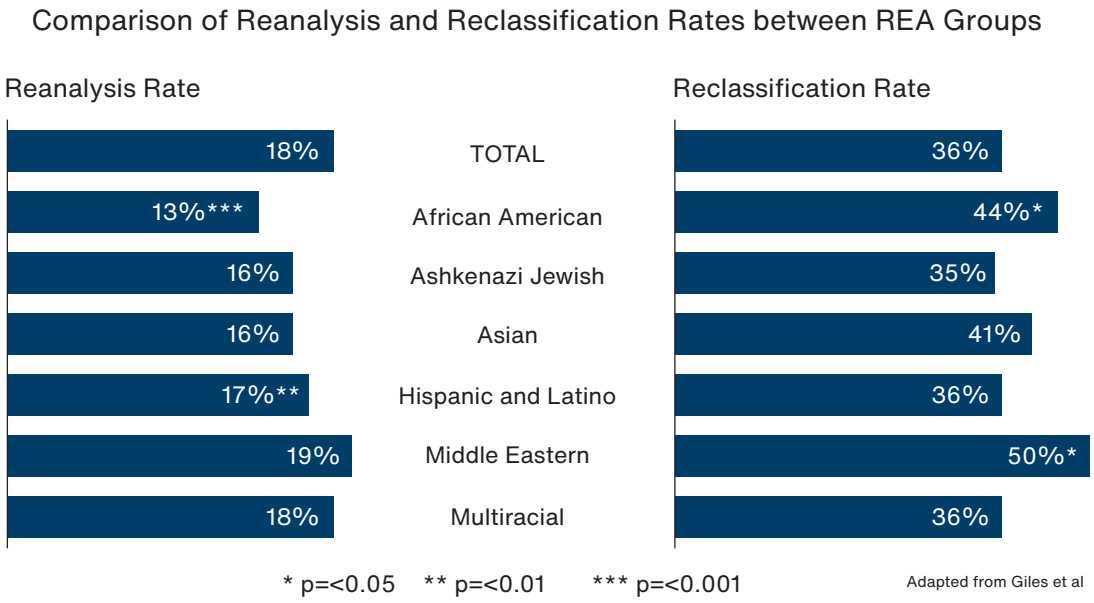


Figure 5. African American and Black patients are less likely to undergo reanalysis despite having higher rates of reclassification.[12]

## Conclusions

Ambry Genetics pioneered clinical exome sequencing in 2011 that included a first of its kind laboratory-initiated reanalysis program: Patient for Life.™ Since its inception, Ambry's Patient for Life program has provided clinically relevant reclassifications to 5% of patients with previously negative ES results. Ambry's approach to ES reanalysis provides an unmatched model for the use of genomic reanalysis in elevating the standard of care for all patients.

**References**

1. Manickam K et al. Exome and genome sequencing for pediatric patients with congenital anomalies or intellectual disability: an evidence-based clinical guideline of the American College of Medical Genetics and Genomics (ACMG). *Genet Med*. 2021;23(11):2029-37. doi: 10.1038/s41436-021-01242
2. Smith L et al. Genetic testing and counseling for the unexplained epilepsies: An evidence-based practice guideline of the National Society of Genetic Counselors. *J Genet Couns*. 2022 Oct 24. doi. org/10.1002/jgc4.1646
3. Srivastava S et al. Meta-analysis and multidisciplinary consensus statement: exome sequencing is a first-tier clinical diagnostic test for individuals with neurodevelopmental disorders. *Genet Med*. 2019 Nov;21(11):2413-21; https://doi.org/10.1038/s41436- 019-0554-6
4. Srivastava S et al. Molecular diagnostic yield of exome sequencing and chromosomal microarray in cerebral palsy: A systematic review and meta-analysis. *JAMA Neurol*. 2022 Dec 1;79(12):1287-1295.doi: 10.1001/jamaneurol.2022.3549
5. Ji et al. A. Clinical Exome Reanalysis: Current Practice and Beyond. *Mol Diagn Ther*. 2021;25(5):529-536. doi:10.1007/s40291-021-00541-7
6. Deignan et al. Points to consider in the reevaluation and reanalysis of genomic test results: a statement of the American College of Medical Genetics and Genomics (ACMG). *Genet Med*. 2019;21(6):1267-1270. doi:10.1038/s41436-019-0478-1
7. Leung ML, Ji J, Baker S, et al. A Framework of Critical Considerations in Clinical Exome Reanalyses by Clinical and Laboratory Standards Institute. *J Mol Diagn*. 2022;24(2):177-188. doi:10.1016/j. jmoldx.2021.11.004
8. Internal data on file at Ambry Genetics
9. Strande NT, et al. Evaluating the Clinical Validity of Gene-Disease Associations: An Evidence-Based Framework Developed by the Clinical Genome Resource. *Am J Hum Genet*. 2017;100(6):895-906. doi:10.1016/j.ajhg.2017.04.015
10. Smith ED et al. *Hum Mutat*. 2017 May;38(5):600-608. doi: 10.1002/humu.23183. Epub 2017 Feb 13.
11. Schnur RE, et al. UBA2 variants underlie a recognizable syndrome with variable aplasia cutis congenita and ectrodactyly. *Genet Med*. 2021;23(9):1624-1635. doi:10.1038/s41436-021-01182-1
12. Marble M, et al. Missense variant in UBA2 associated with aplasia cutis congenita, duane anomaly, hip dysplasia and other anomalies: A possible new disorder involving the SUMOylation pathway. Am J Med Genet A. 2017;173(3):758-761. doi:10.1002/ajmg.a.38078
13. Giles A et al. Addressing equity in exome sequencing: Proactive reanalysis helps to reduce racial, ethnic and ancestral disparities. Platform presented at: National Society of Genetic Counselors conference; October 2023; Chicago, IL, USA.

Ambry Genetics®
A TEMPUS COMPANY

1 Enterprise, Aliso Viejo, CA 92656 USA Toll Free +1.866.262.7943 Fax +1.949.900.5501 **ambrygen.com**

MKT-SPEC-WPPR-50064-EN v3 02.04.26