

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 disorders¹⁻⁴. 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 data⁵.

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 results⁶. 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 reanalysis⁷ (Table 1).

Comparison of Reanalysis Outcomes

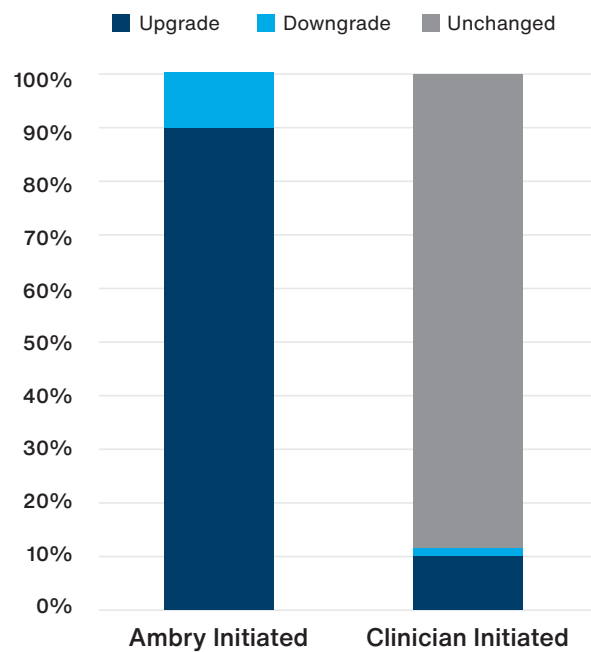


Figure 1. Ambry-initiated reanalysis leads to increased clinically-relevant reclassifications⁸

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.

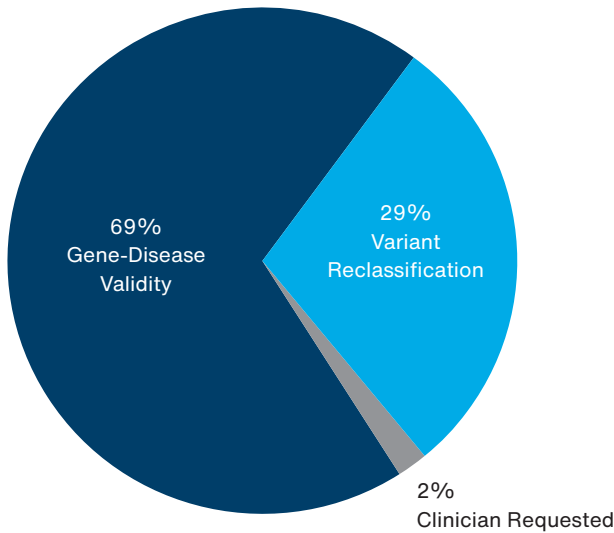


Figure 2. Over two-thirds of reclassifications are the result of advances in gene-disease validity⁸

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 results⁸.

Over the tenure of the program, Ambry’s proactive approach to reanalysis has provided more clinically- relevant reclassifications than the traditional clinician-initiated approach⁸ (Fig. 1). The majority (69%) of reclassifications are the result of advances in gene-disease validity⁸ (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 phenotype⁹. The process involves a meticulous assessment in which existing evidence is collated, scrutinized, and translated into numerical totals¹⁰. Subsequently, these totals are assigned to categories of descending strength (Fig 4). 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, aids in the detection of genetic causes for previously undiagnosed patients, and allows for initiation of appropriate patient management.

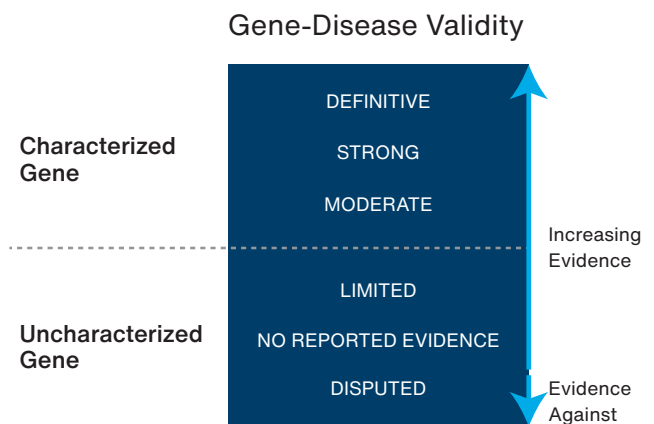


Figure 4. Gene-Disease validity assessment classifies the strength of gene-disease relationships¹⁰

Example of the Patient for Life Workflow

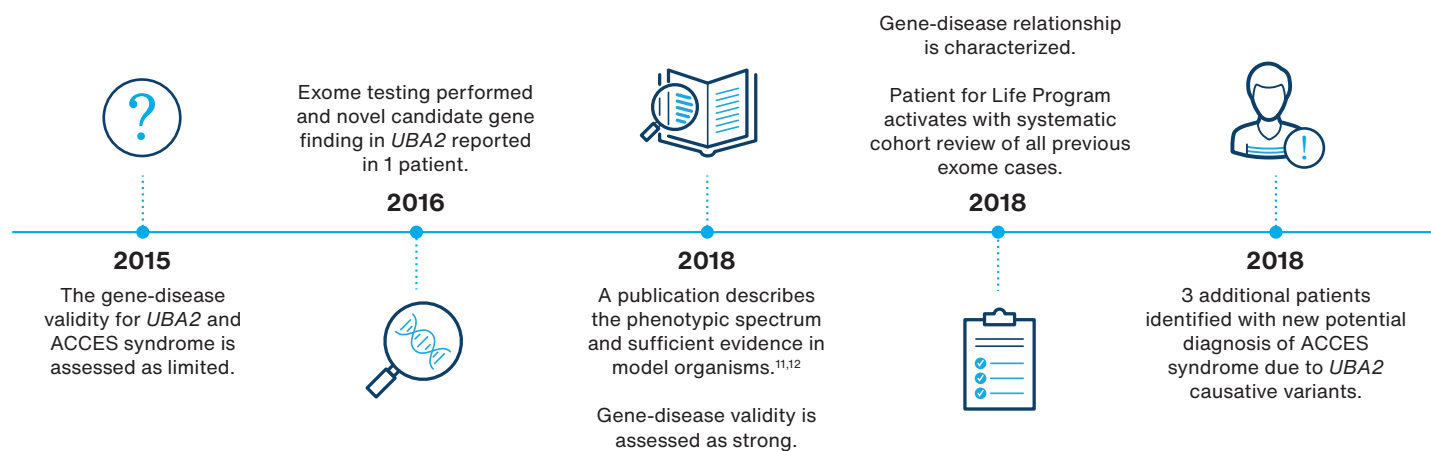


Figure 5. The *UBA2* gene was characterized for ACCES syndrome (an autosomal dominant disorder characterized by aplasia cutis congenita and other ectodermal variations) in 2021. Approximately a third of the cases that were re-assessed after the gene was characterized had sufficient phenotypic overlap 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 2021. Subsequently, about a 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 5).

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 rates¹³. 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 initiated¹³ (Fig 6). 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.

Comparison of Reanalysis and Reclassification Rates between REA Groups

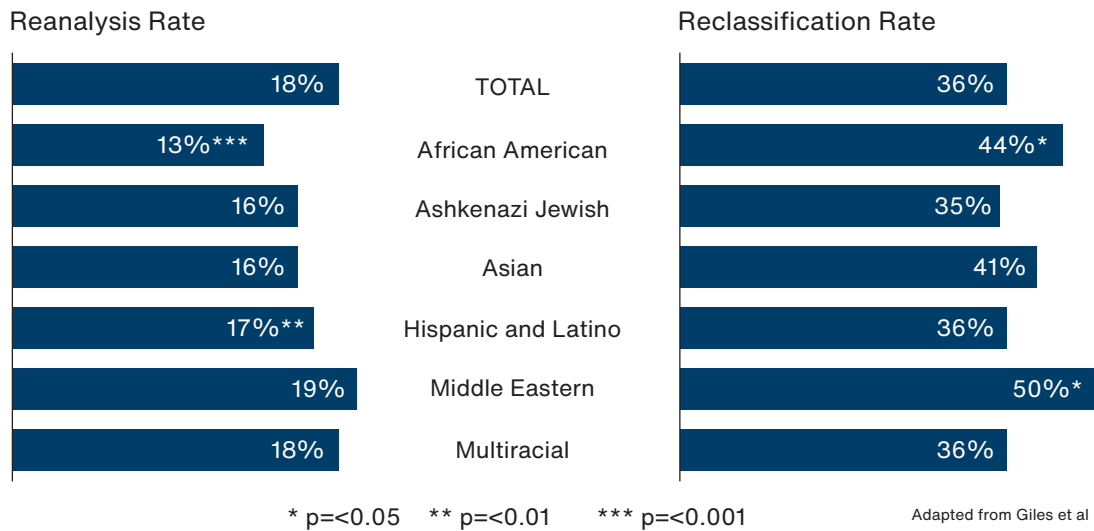


Figure 6. African American and Black patients are less likely to undergo reanalysis despite having higher rates of reclassification¹²

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.

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