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Redefining Precision: Functional and Clinical Correlation in *TP53* Variants

INTRODUCTION

We have often treated hereditary cancer test results as binary, in which a positive result yields high risk for cancer and a negative result corresponds to average risk. However, advances in functional genomics, large scale variant assays, and longitudinal clinical data show that in many genes, **pathogenic variants confer risk across a continuum** rather than as a simple pathogenic or benign distinction (Figure 1).

This evolution is underscored by a recent ACMG multidisciplinary statement recognizing that heritable cancer risk presents on a complex spectrum influenced by specific genomic variants and modifiers.[1] Receiving a test result that doesn't fit neatly into a standard pathogenic category can be challenging for providers and patients. For example: do special designations such as "reduced penetrance" or "moderate risk" represent uncertainty—or a distinct biological middle ground that warrant a tailored clinical approach?

In a recent study, investigators from Ambry Genetics and Queensland Institute of Medical Research (QIMR) demonstrated that *TP53* is an important example of how statistical and functional data can be incorporated with clinical history to provide **more accurate and clinically meaningful variant classification**[2].

Figure 1. Inherited cancer risk exists as a continuum

HOW QUANTITATIVE METRICS BUILD A CASE FOR MODERATE RISK

Study investigators set out to evaluate how a variant's functional activity, *in silico* bioinformatic scores, and population frequency collectively correlate with a carrier's clinical history (Figure 2). Their analysis highlights how **reduced penetrance variants consistently occupy a biological "middle ground"** across these independent metrics, effectively bridging the gap between benign and standard pathogenic profiles. For instance, bioinformatic *in silico* tools frequently flag these variants as deleterious, yet they yield scores that are significantly less severe than those associated with standard pathogenic alleles. Similarly, while their population frequency is higher than that of standard pathogenic variants, they typically remain rare enough in the general population to meet the formal criteria for pathogenicity.

Figure 2. Functional and computational metrics evaluated


Functional assays


Predictive Tools

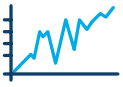
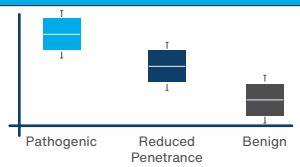
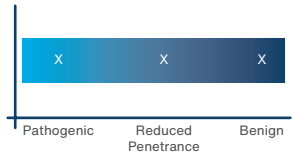
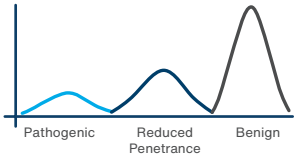

Allele Frequency

Figure 3. Correlation between quantitative metrics and clinical presentation

Metric	Result	Reduced Penetrance Profile
Functional Data		Likely to exhibit intermediate functional activity.
in silico Models		Generally predicted as deleterious, but with lower average scores.
Population Frequency		More common in the population than standard pathogenic variants.

A BIOLOGICAL AND CLINICAL GRADIENT

By mapping these data points against real-world patient histories, the researchers demonstrated that this intermediate biological profile serves as a reliable predictor of an attenuated clinical presentation (Figure 3). Patients carrying these variants tend to have a **later age of cancer diagnosis**, at an average age of 47.7 years compared to 36.6 years for those with standard pathogenic variants.

Furthermore, these individuals were still impacted by core Li-Fraumeni Syndrome (LFS) cancers like early-onset breast cancer and sarcomas, but the **cancer risk is markedly lower**, with an odds ratio for breast cancer before age 31 of 3.05 compared to 16.07 in the standard high-risk group. This biological gradient mirrors the clinical gradient, confirming that reduced penetrance variants are a distinct medical reality rather than a reflection of ambiguity.

UNMASKING VUS

Another impactful finding of this research was the identification of 106 variants, currently listed in ClinVar as VUS or conflicting, that exhibit the same functional and frequency characteristics as known reduced penetrance variants. By applying a random forest prediction model, the researchers were able to spotlight these “hidden” risk alleles that might otherwise be overlooked. Understanding these can help **prevent missed diagnoses** of individuals who may not meet the classic clinical criteria of a typical pathogenic variant but may still benefit from increased management. The ability to characterize pathogenic variants as reduced penetrance allows patients to receive protective surveillance without the psychological or physical burden of the most intensive LFS interventions.

CONCLUSIONS

Ultimately, categorizing a variant as moderate risk or reduced penetrance is a data-driven decision and should not be viewed as a limitation of uncertainty, but rather as a step forward in diagnostic precision.

This study provides an evidence-based framework with broader implications across other cancer predisposition genes and aligns with ACMG’s call to refine our understanding of a cancer risk continuum to guide clinical management[1]. Laboratories that incorporate a phenotypic gradient into variant assessment prevent a ‘one-size-fits-all’ model that often leaves patients either under-screened or over-burdened by generalized interventions.

1. Pal T, et al; ACMG Professional Practice and Guidelines Committee. Consideration of inherited cancer risk on a continuum: An international and multidisciplinary perspective: A points to consider statement of the American College of Medical Genetics and Genomics (ACMG). Genet Med. 2026 Mar;28(3):101659.
2. Fortuno C, et al. Characteristics predicting reduced penetrance variants in the high-risk cancer predisposition gene TP53. HGG Adv. 2025 Oct 9;6(4):100484. This document summarizes results and adapts images from Fortuno et al, 2025. Used under CC-BY.

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