Germline Cancer Testing Challenges:
Assessing Cancer Risk and PARP Inhibitor Response

Karla Bowles, PhD, FACMG

Key Objectives

- Participants should be able to describe examples of genetic testing technical challenges which may affect the accuracy of test results.
- Participants should gain a basic understanding of robust and novel approaches to genetic variant classification.
- Participants should be able to describe how HRD analysis and genetic testing can be used to appropriately identify patients who may respond to PARP inhibitors.

Tests offered by Myriad Genetics

MYRIAD myRisk® Hereditary Cancer

Myriad myRisk® Hereditary Cancer is a multigene panel that analyzes clinically-significant genes across a number of hereditary cancer syndromes, with a focus on eight primary cancer sites.

MYRIAD myPath® Melanoma

Myriad myPath® Melanoma is a unique molecular diagnostic test that analyzes 23 genes to differentiate benign nevi from malignant melanoma.

MYRIAD myPlan® Lung Cancer

Myriad myPlan® Lung Cancer is a molecular diagnostic test that measures the expression levels of cell cycle progression genes to provide an accurate assessment of cancer aggressiveness in early-stage non-small cell lung cancer.

Prolaris®

Prolaris® is a molecular diagnostic test that measures the expression level of genes involved with tumor proliferation to predict disease outcome. Prolaris can be used in conjunction with other clinical parameters to determine prostate cancer aggressiveness.

EndoPredict®

EndoPredict® is a diagnostic test that accurately determines the likelihood of cancer recurrence 10 years after diagnosis, allowing physicians to determine which patients can safely forgo chemotherapy.

BRACAnalysis CDx®

BRAC*Analysis* CDx® is an FDA-approved companion diagnostic test to identify germline *BRCA1* and *BRCA2* mutations and is intended to be used as an aid in treatment decision making for LynparzaTM (olaparib), a PARP inhibitor.

MYRIAD myChoice® HRD

Myriad myChoice® HRD is a molecular diagnostic test that measures a tumor's ability to repair DNA damage by assessing tumor *BRCA1/2* status and three biomarkers of homologous recombination deficiency. myChoice HRD can help identify patients who are most likely to benefit from cancer therapies that damage DNA.

MYRIAD myRisk® Hereditary Cancer

Myriad is Committed to Patients and Providers Throughout the Entire Testing Process

Pre-Testing Support
- Provider education
- Customized risk assessment tools
- Lean management experts
- Electronic test requisition forms
- Financial assistance

State of the Art Variant Identification
- Sequencing variants
- Large rearrangements
- Unusual Cases

State of the Art Variant Interpretation
- Classification of novel variants
- Reclassification of Uncertain Variants (VUS)
- Lifetime commitment to patients

Post-Testing Support
- Genetic counselors available to answer patient and provider questions
- myRisk Medical Management Tool

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WHEN DECISIONS MATTER

Analytical and Interpretive Accuracy Affect Patient Medical Management and Outcomes

Analytical Accuracy
Did the Lab Find All of the Variants (DNA Changes)?

- False negative: A pathogenic mutation was missed
- False positive: The lab reported a pathogenic mutation that was not actually present

+

Interpretive Accuracy
Did the Lab Correctly Classify the Variants as Pathogenic or Benign

- False negative: A pathogenic variant is classified and reported as benign
- False positive: A benign variant is classified and reported as pathogenic

=

Overall Accuracy
Will the Test Result Correctly Inform Medical Management?

- False negative: A pathogenic variant is not reported *or* mistakenly reported as benign
- False positive: A pathogenic variant, which is not actually present, is reported *or* a benign variant is classified and reported as pathogenic

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We Use State-of-the-Art Analytical Technologies For Typical Patients

Variant Type	High Sensitivity: Primary Technologies Detect Variants	High Specificity: Orthogonal Technologies Confirm Variants
Sequencing	Next Generation Sequencing (NGS) – 50X Minimum Depth of Coverage	Sanger Sequencing
Large Rearrangement	Dosage NGS	Targeted Microarray MLPA Long Range PCR

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WHEN DECISIONS MATTER

Our Unusual Cases Team Custom Designs Assays for Your Rare and Challenging Patients

Lab Directors
Oversee test result quality and accuracy

Genetic Counselors
Communicate with patients and providers

PhD-Level Scientists
Investigate biological mechanisms

Data Analysts
Provide expert data review

Technical Development
Develop and validate all assays

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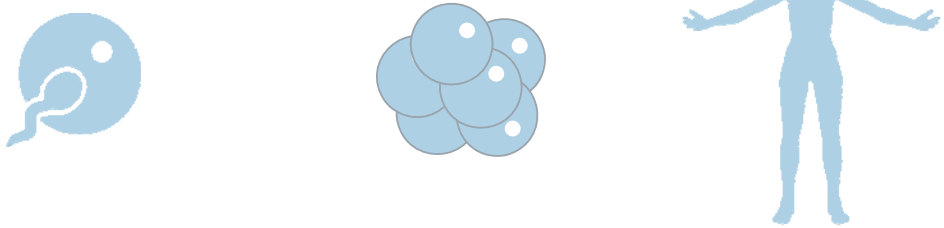
Mosaicism Results When a Mutation Arises After Conception. The Mutation is Only Present in Some Tissues.

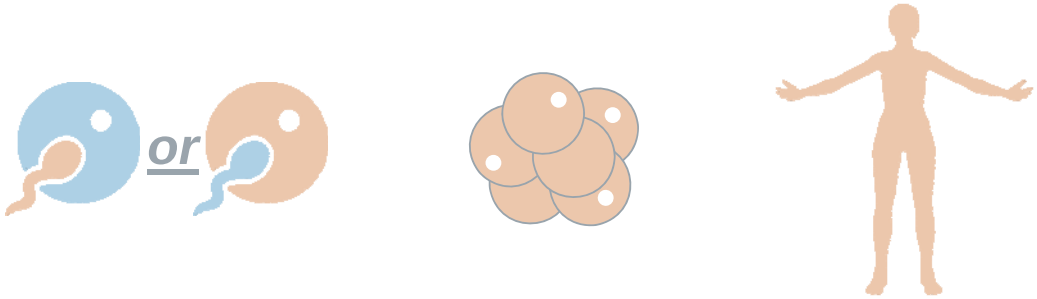
No Mutation



Cells normal

Population Cancer Risk

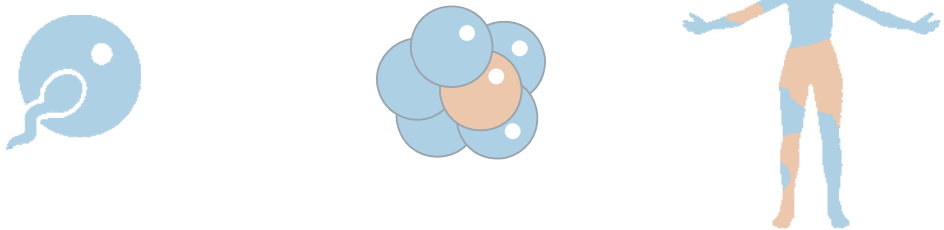
Mutation in Sperm *or* Egg



Mutation in all cells

High Cancer Risk

Mosaic Mutation During Development



Mosaicism

Mutation in some cells

Cancer risks depend on cancer type and affected tissue(s)

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WHEN DECISIONS MATTER

Mosaicism Can Lead to Unexpected Test Results (Especially for *TP53)*

Patients who inherit *TP53* mutations have Li-Fraumeni syndrome

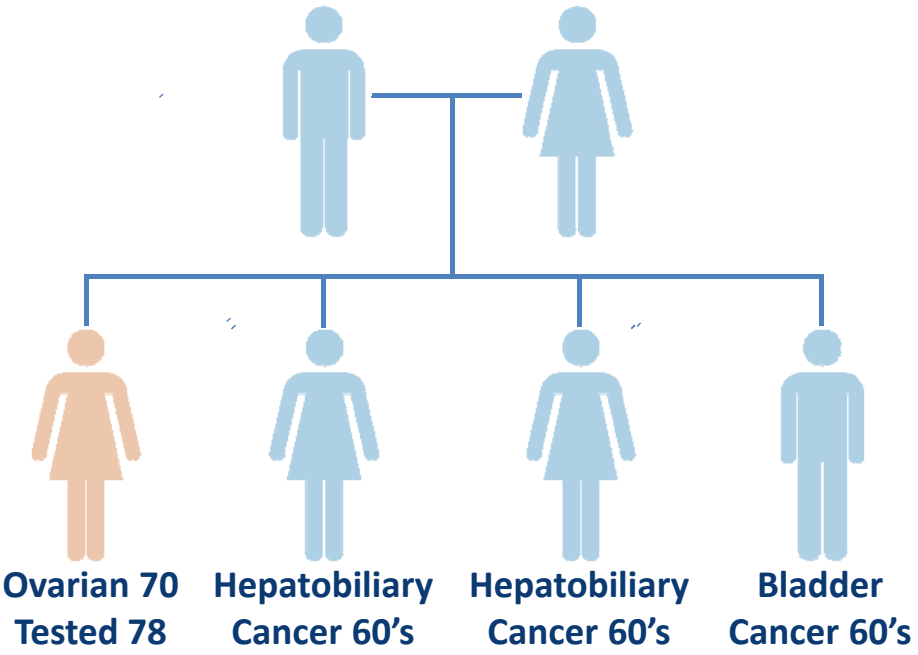
Mosaic (acquired) *TP53* mutations do not cause Li-Fraumeni syndrome. The patient is not at risk for most Li-Fraumeni associated cancers, if the mutation is confined to blood.

Analytical Data

- Blood – 70% of sequences are normal and 30% have the mutation
- Cultured fibroblasts – Confirms <50% mutant sequence

Most Likely Interpretation

- Patient is mosaic – Medical management should be customized to the patient



Proband (in pink) has a *TP53* mutation but family history does not look like Li-Fraumeni syndrome

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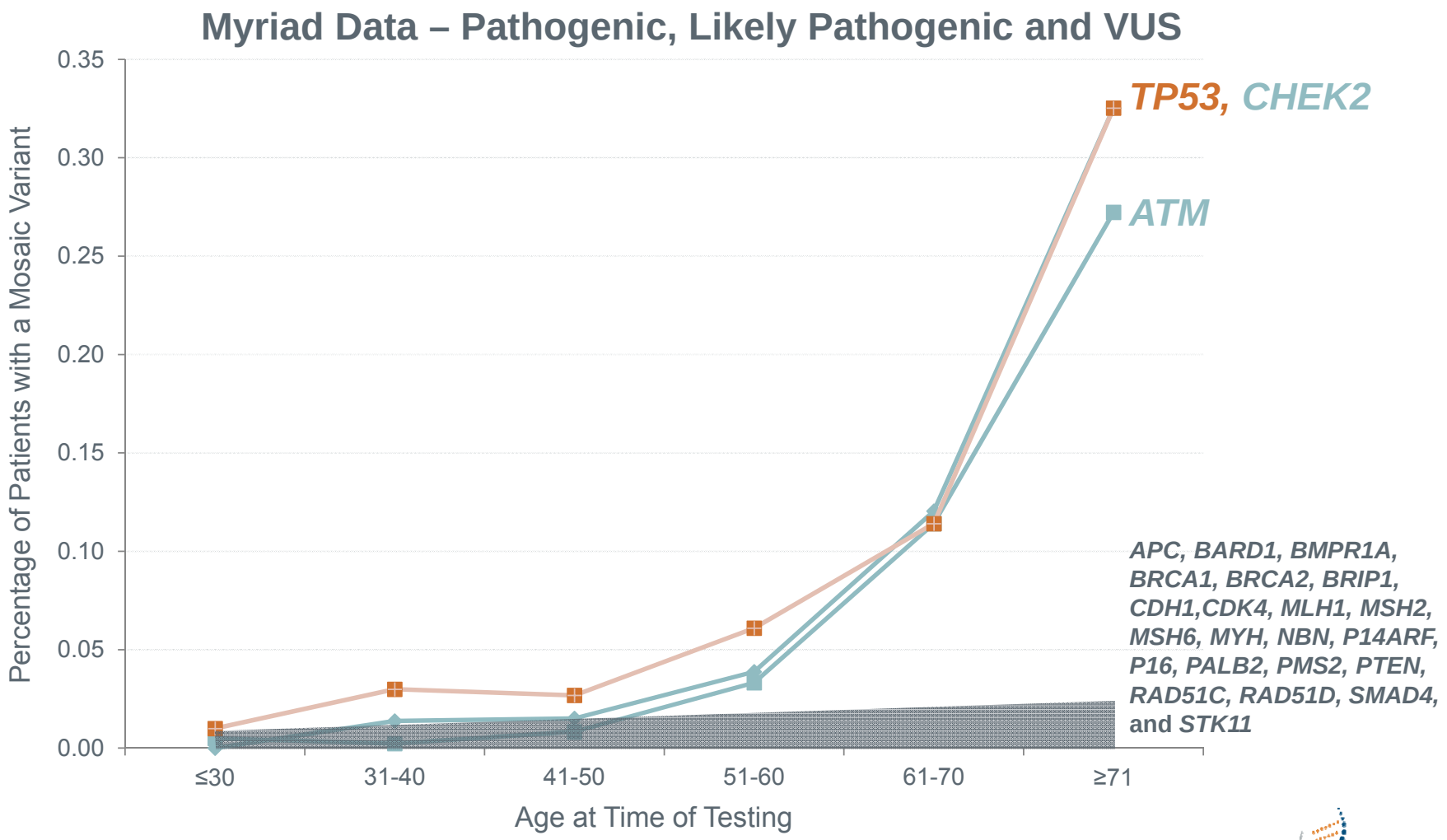
There is an Increased Probability of Identifying Likely Somatic Variants in Older Individuals



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Myriad Takes a Customized Approach to *TP53* Testing and Reporting

- Frontline NGS testing cannot distinguish between inherited and acquired mosaic mutations, which is critical for patient care
- Myriad customizes its reporting and follow-up testing processes

Initial Patient Report: *TP53* "Special Interpretation" Variant

- All *TP53* pathogenic mutations are reported
- Mutations are classified as "Special Interpretation"
- A Genetic Counselor Calls the provider to discuss the interpretation

Myriad Offers Free Family Member and Fibroblast Testing

- Found in family member: Most likely inherited
- Found in fibroblasts: Present in multiple tissues (patient is most likely high risk)

Myriad Issues Amended Report

- Summarizes testing performed
- Provides additional clinical interpretation, if appropriate

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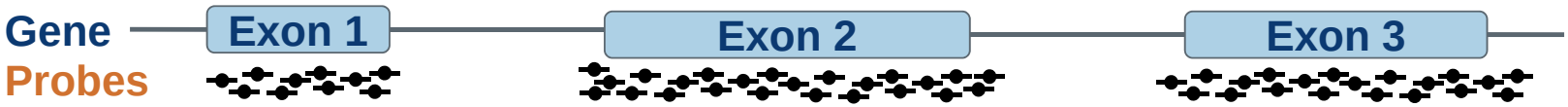
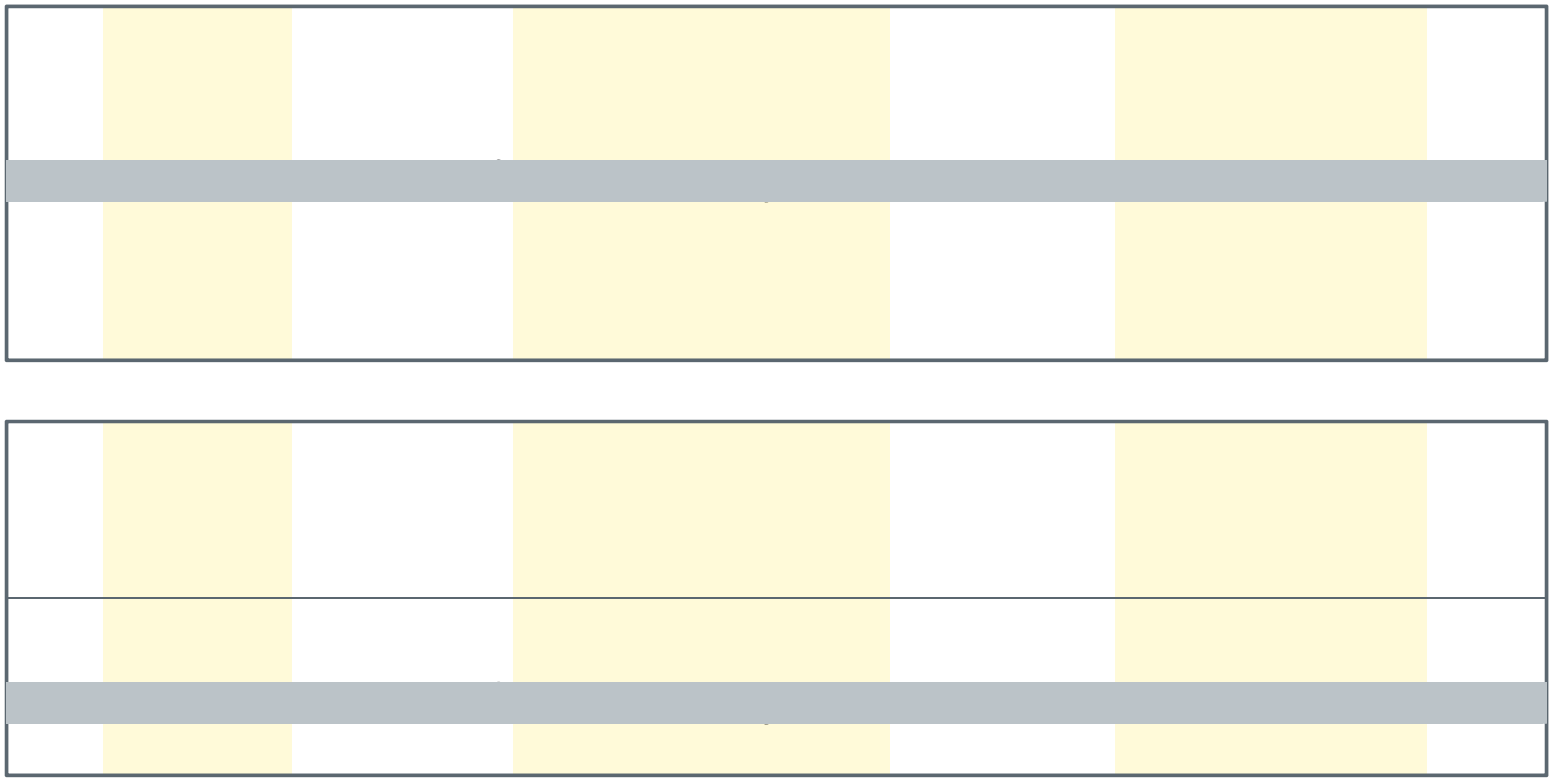
Targeted Microarray May Identify Mosaic Large Rearrangements





Normal
2 Copies

Deletion
1 Copy

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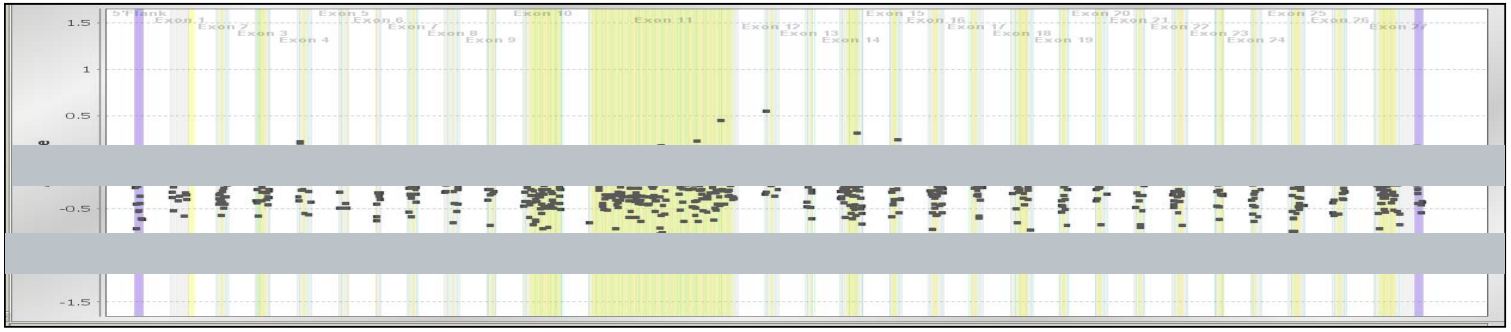
Some Mosaic Mutations May Not Be Harmless

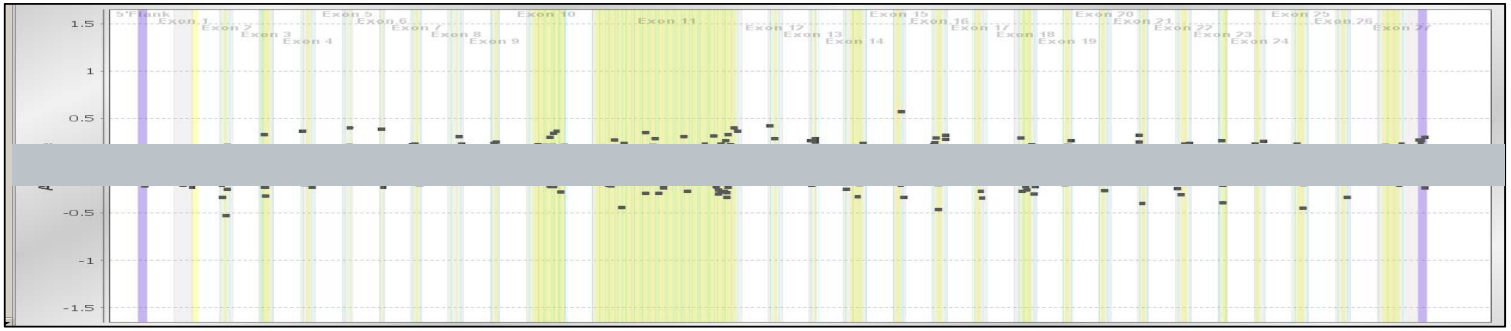
BRCA2 Deleted but Potentially Mosaic – Blood Sample



Normal Range

Deletion Range

BRCA2 Not Deleted – Fibroblast Sample



Normal Range

This Patient Had an Undiagnosed CLL

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Myriad provides accurate test results for common and uncommon patients.

Rare patients are common

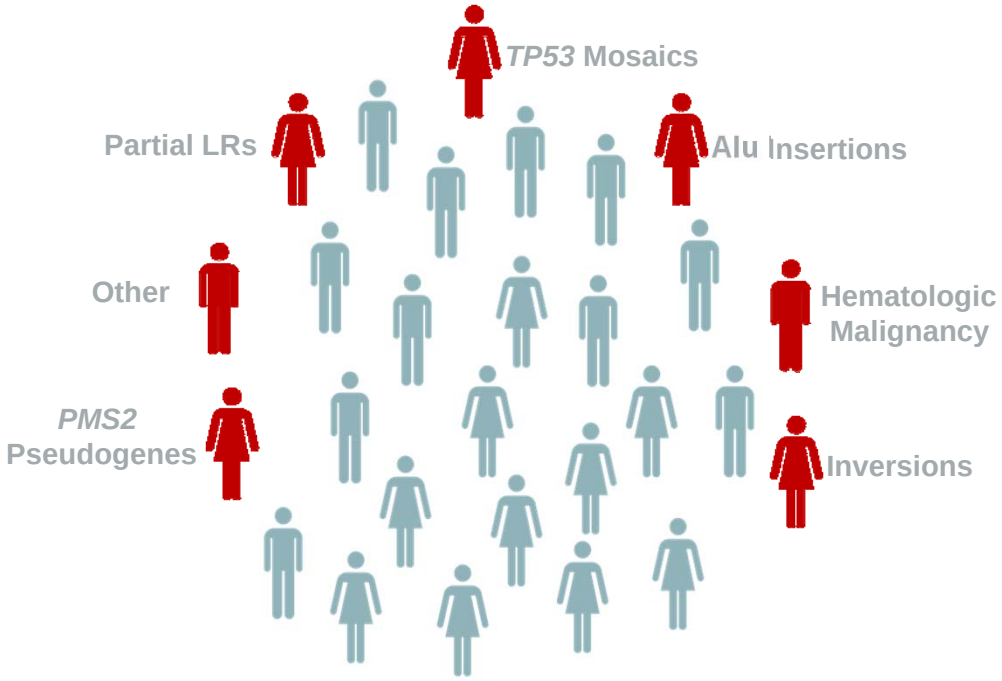
Individually rare patients are common as a group

Other labs

Your uncommon patients may receive wrong or inconclusive test results if labs do not customize testing.

Myriad

We customize testing so that your uncommon patients receive accurate test results and appropriate medical management.



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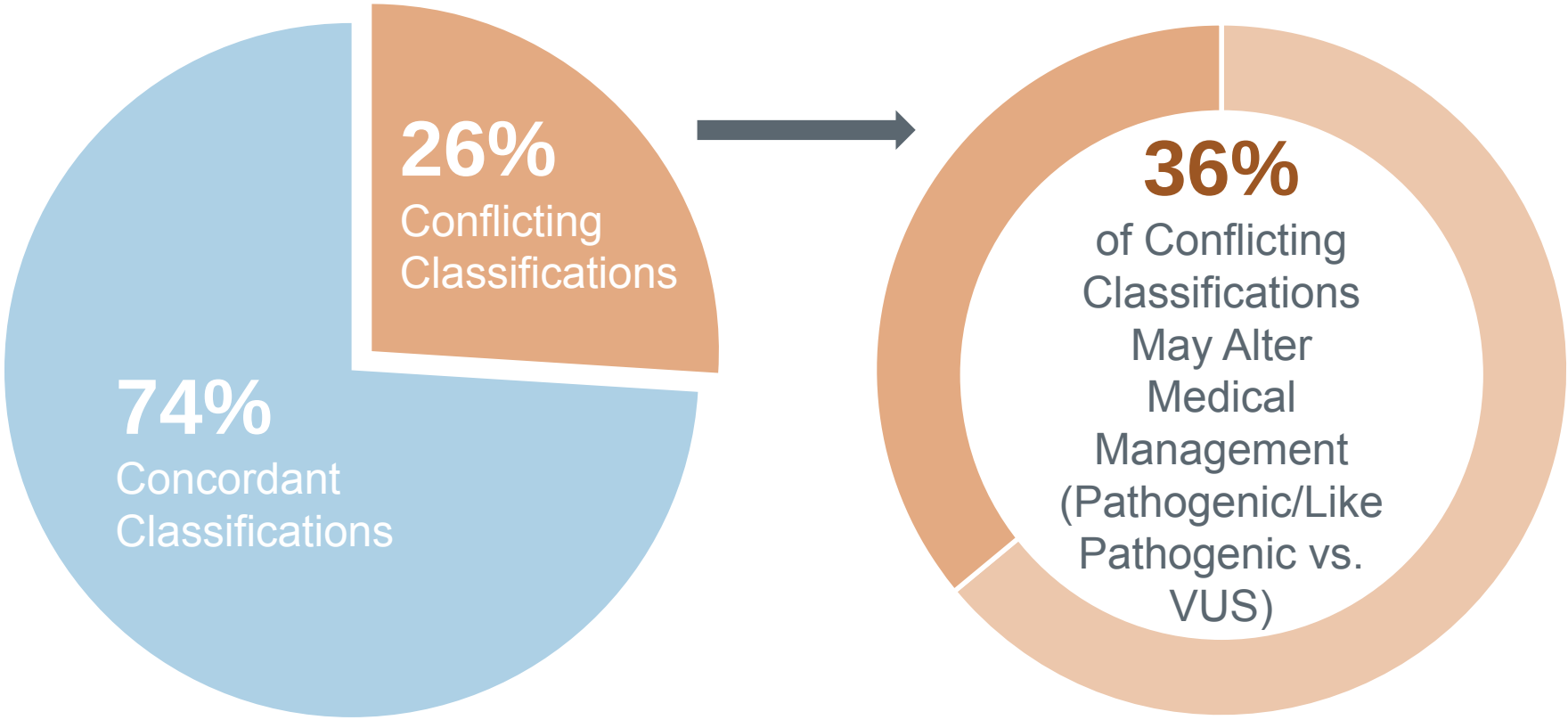
Discordant Variant Classifications are Common Between Laboratories



Total Classifications n=603 Variants

Conflicting Classifications n=155 Variants

Balmana *et al.*, Conflicting Interpretation of Genetic Variants and Cancer Risk by Commercial Laboratories as Assessed by the Prospective Registry of Multiplex Testing. *Journal of Clinical Oncology* 2016; 34(34):4071-78.

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INDICATION DE TESTER ET RECOMMANDATIONS DE SUIVI Our ASSOCIÉES AVEC CHAQUE CLASSE DE VARIANTS - *IARC*

RÉSULTAT	Classe	Indication de tester apparentés en clinique	Recommandations de suivi	Tester apparentés pour la recherche*	Probabilité d'être pathogène
POSITIVE FOR A DELETERIOUS MUTATION or Variant with clinical significance	5	Tester apparentés	Suivre les lignes directrices de surveillance pour personnes à risque	Non indiqué	IARC: > 99%
GENETIC VARIANT, SUSPECTED DELETERIOUS	4	Tester apparentés	Suivre les lignes directrices de surveillance pour personnes à risque	Peut être utile pour reclassification du variant	IARC: 95 à 99%
GENETIC VARIANT OF UNCERTAIN SIGNIFICANCE or VUS	3	Ne pas tester les apparentés	Suivi adapté à l'histoire familiale et autres facteurs de risques	Peut être utile pour reclassification du variant	IARC: 5.0 à 94.9%
GENETIC VARIANT, FAVOR POLYMORPHISM	2	Ne pas tester les apparentés	Traiter comme un résultat "No mutation detected"	Peut être utile pour reclassification du variant	IARC: 0.1 à 4.9%
NO MUTATION DETECTED or normal	1	Ne pas tester les apparentés	Traiter comme un résultat "No mutation detected"	Non indiqué	IARC: < 0.1%

International Agency for Research on Cancer (IARC)- Centre international de recherche sur le cancer. Plon et al. Human mutation,29 :1282-1291 (2008)

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Discordant Classifications Between Laboratories are Common

Analysis of 4,250 unique *BRCA1/BRCA2* variants with entries in ClinVar by one or more commercial labs

Table 1. Concordance between variant classifications from the reference laboratory and all database entries, as well as database entries from contributing commercial laboratories

Concordance	ClinVar	GeneDx	Invitae	Ambry
Concordant—identical classification	73.2%	81.5%	85.4%	80.7%
Partially concordant—multiple classifications with ≥1 concordant	12.3%	—	—	—
Discordant—opposite classification	0.1%	0.1%	0%	0.1%
Discordant—RL uncertain classification	0.3%	0.7%	0.7%	1.2%
Discordant—DB uncertain classification	14.0%	17.7%	13.8%	18.1%
Proportion of VUSs with a definitive RL classification	—	42.5% (322/757)	63.2% (151/239)	56.9% (58/102)

Abbreviations: —, not applicable; DB, database; RL, reference laboratory; VUS, variant of uncertain significance.

Myriad provides definitive classifications for ~50% of *BRCA1* or *BRCA2* VUS reported by other labs

Gradishar *et al.*, Clinical Variant Classification: A Comparison of Public Databases and a Commercial Testing Laboratory. *The Oncologist.* 2017; epub ahead of print.

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Once Variants are Identified, They Must be Correctly Interpreted (Classified)

Myriad's state-of-the-art variant classification program focuses on correctly classifying variants so that patients receive correct test results

Our Expertise

- Over 25 years of data
- Approximately 3 million patients tested
- Classification team of over 30 scientists

Our Methods

- Enhancement of publicly available classification methods
- We develop and validate our own powerful methods
- The FDA has reviewed our *BRCA1/2* classification program

Our Commitment

- We will never give up trying to reclassify variants of uncertain clinical significance (VUS)
- We will issue amended reports to patients for as long as we can find them

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WHEN DECISIONS MATTER

Our myVision™ Variant Classification Team Classifies All Variants

Lab Directors
Oversee test result quality and accuracy

Genetic Counselors
Communicate with patients and providers

PhD-Level Scientists
Clinical and population genetics, structural biology, biochemistry, bioinformatics, biostatistics

Knowledge Management
PhD scientists who curate the literature

Variant Specialists
Provide technical support to the team

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WHEN DECISIONS MATTER

Literature is Reviewed in Real-Time Throughout the Lifetime of a Variant

Before test launch, a complete literature search identifies previously reported variants, which are stored in our database with their associated papers.

A **daily literature search** is performed by PhD-level scientists to keep our database current.

Upon **first observation** of a variant at Myriad, targeted analysis verifies that critical papers were previously captured.

Daily monitoring of the literature is performed in case new literature, which may allow us to reclassify a VUS, becomes available.

During the **reclassification** process, a final search verifies that relevant data is considered.

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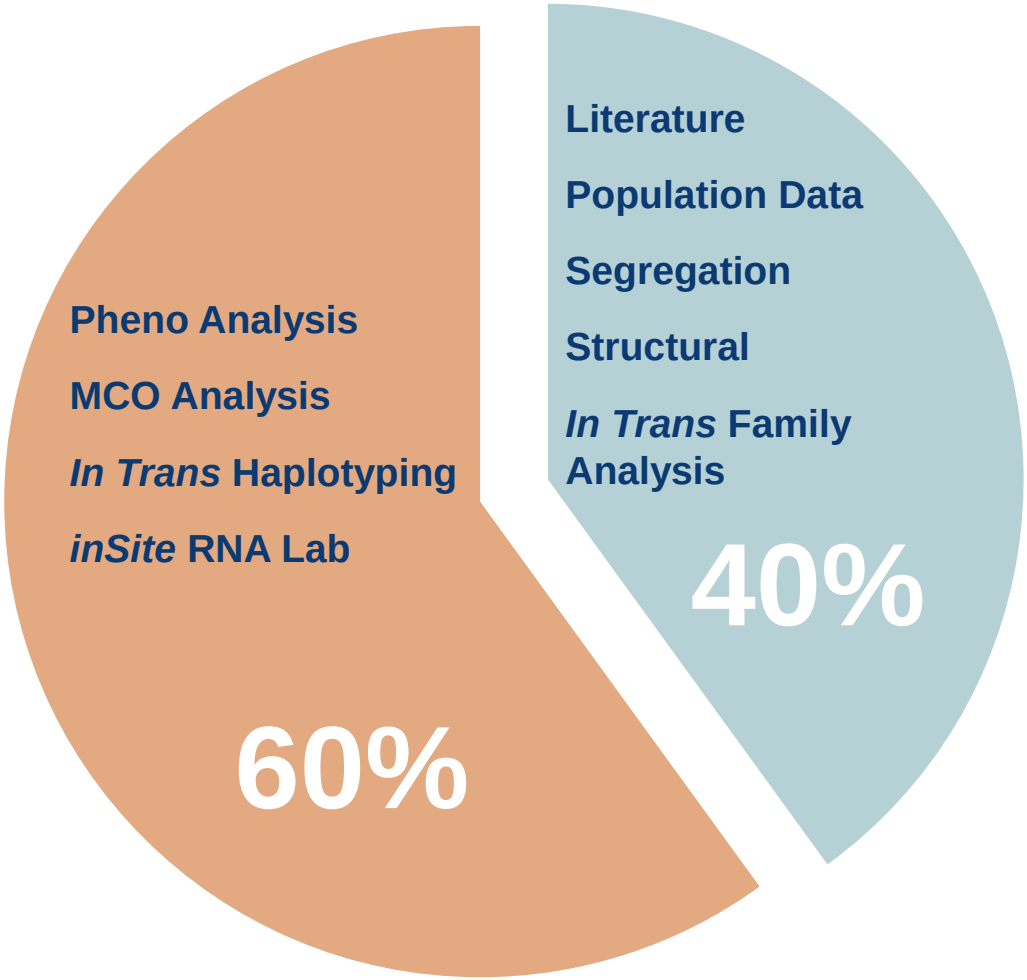
Myriad Develops and Validates it Own Highly Accurate Reclassification Tools

Developed by Myriad

State-of-the-art reclassification tools are developed and validated by Myriad to be >99% accurate.

These tools are unique to Myriad and are critical for patients receiving correct and definitive test results.

Myriad invests in the science of variant reclassification.



Enhanced by Myriad

Publicly available tools are more error-prone.

Myriad enhances these tools and verifies their accuracy before use.

Use of these tools without modification may result in incorrect variant interpretation.

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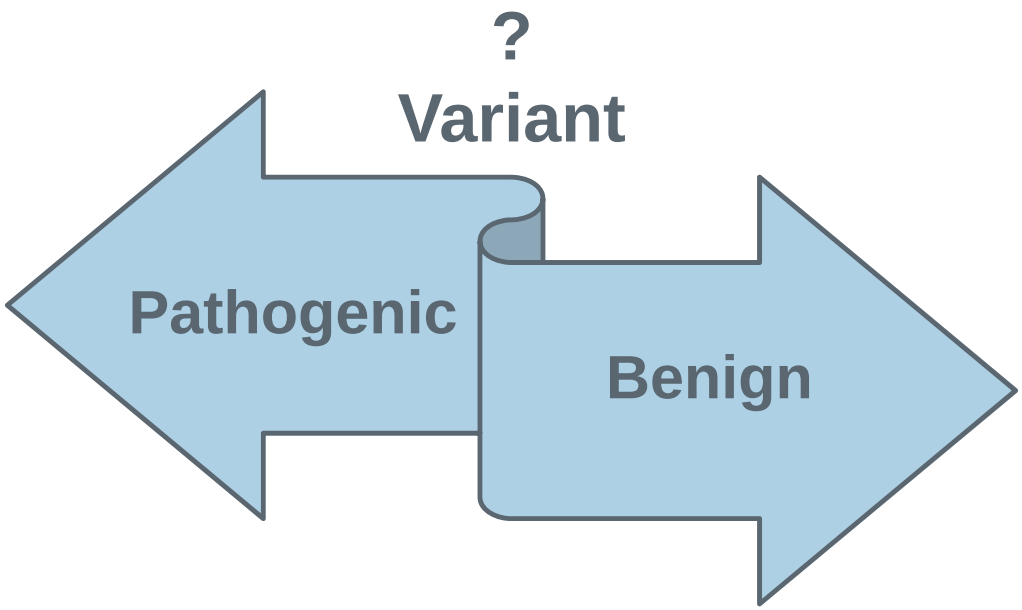
Pheno is One of Myriad's Most Powerful and Accurate Reclassification Tools

Pheno measures the severity of personal and family cancer history associated with a particular variant.

If a variant is truly pathogenic, people who carry it typically have strong personal and family histories of cancer.



If a variant is truly benign, cancer histories may be strong or weak.

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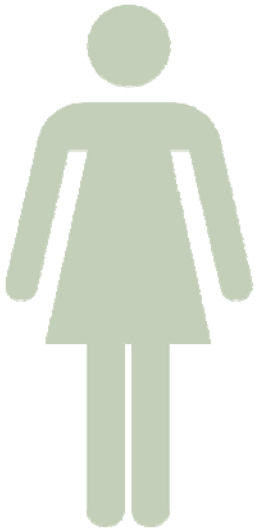
Pheno Starts By Scoring Family History for a Single Proband Carrying the Variant of Interest

Proband A
Self – Breast 38
Mother – Ovarian 55
Brother – Male Breast 55

Proband B
Self – Breast 55
Mother – Breast 60
Maternal Aunt – Breast 80



Proband C
Self – Breast 78
Father – Prostate 82

Severity of Cancer History

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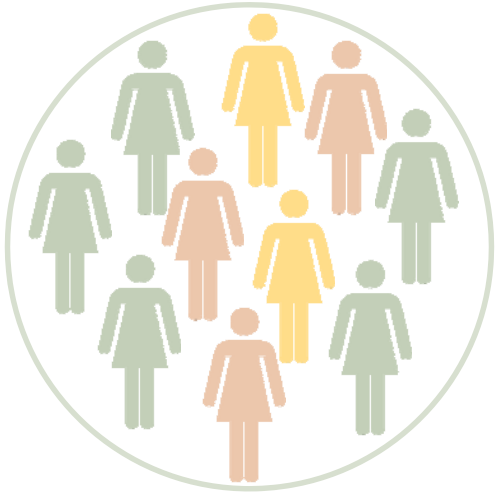
Pheno Combines the Severities of All Probands Carrying the Same Variant into a Pheno Score

Pathogenic Variant
Proband scores are mostly severe, moderate scores are possible, benign scores are more rare



Benign Variant
Proband scores are a more even mixture of severe, moderate and benign

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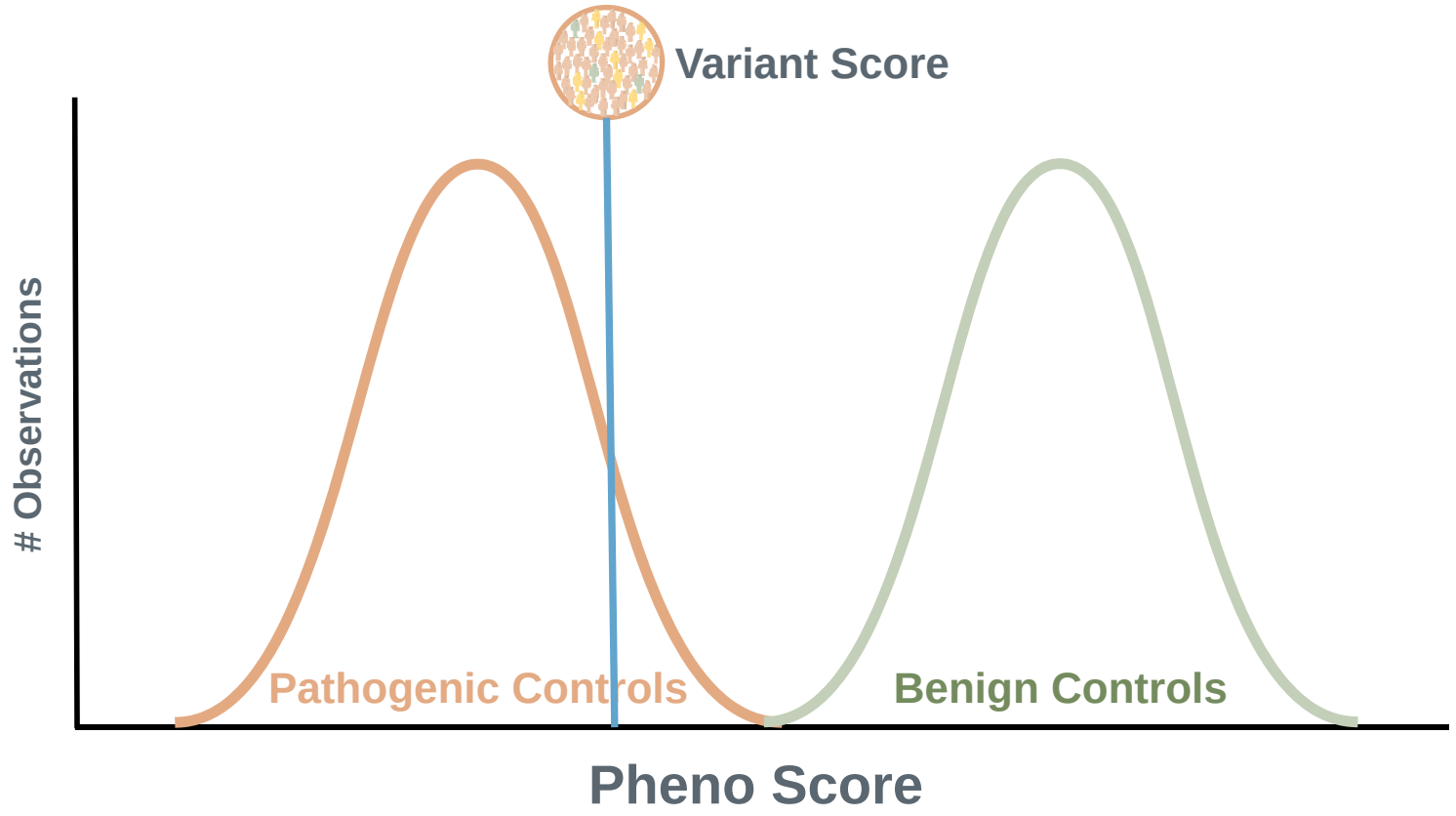
WHEN DECISIONS MATTER

Pheno Compares the Variant-Specific Score to Scores from 10,000 Known Pathogenic or Benign Variants



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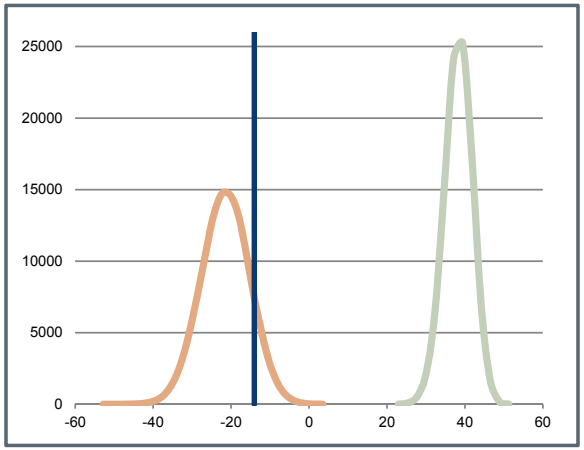
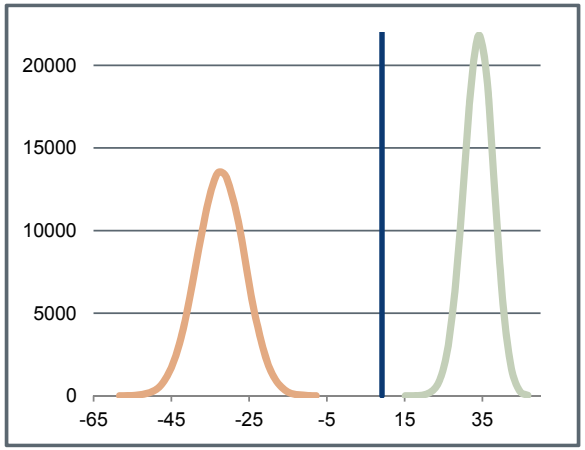
Pheno Typically Calls a Variant as Pathogenic or Benign, but Some Variants May Have Intermediate Cancer Risks

***BRCA1* p.C61G**



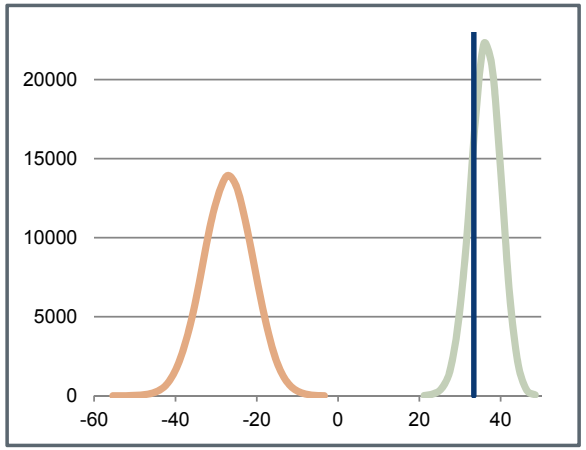
Pathogenic

***BRCA1* p.R1699Q**



Intermediate Risk

***BRCA1* p.K355K**



Benign

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We Have Multiple Publications and Presentations Detailing Our Validations

Method	Shared	
Database Entries	Balmana J, et al.; 2016; JCO	Published
Standardized classification system	Eggington J, et al.; 2013; Clinical Genetics	Published
Pheno – History Weighting Algorithm	Morris B, et al.; 2016; BMC Genetics Pruss D, et al.; 2014; Breast Cancer Research and Treatment Bowles K, et al.; 2016; International Symposium on HBOC	Published
M-Co	Coffee B, et al.; 2015; ACMG	Presented
RNA splice site analysis	Warf B, et al.; 2015; ASHG	Presented
Structural biology analysis	Kerr I, et al.; 2016; International Symposium on HBOC	Presented
In trans co-occurrence and homozygosity	Fernandes P, et al.; 2015; ACMG Mundt E, et al.; 2016; International Symposium on HBOC	Presented
Segregation analysis	Eggington J, et al.; 2013; ACMG	Presented
Literature reviews	Esterling L, et al.; 2015; ASHG	Presented

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In Contrast to Validated Classification Tools, the Accuracy of the ACMG Guidelines is Variable

ACMG STANDARDS AND GUIDELINES

Standards and guidelines for the interpretation of seque
variants: a joint consensus recommendation of the Amer
College of Medical Genetics and Genomics and the
Association for Molecular Pathology

ACMG Classification Guidelines

- NOT definitive: Open to human interpretation
- NOT specific: Designed to cover all genes and diseases
- NOT validated: Accuracy for any particular gene is unknown
- Following the guidelines does not guarantee accuracy

Richards, S. et al. *Genetics in Medicine.* 2015 Mar; 17: 405–423

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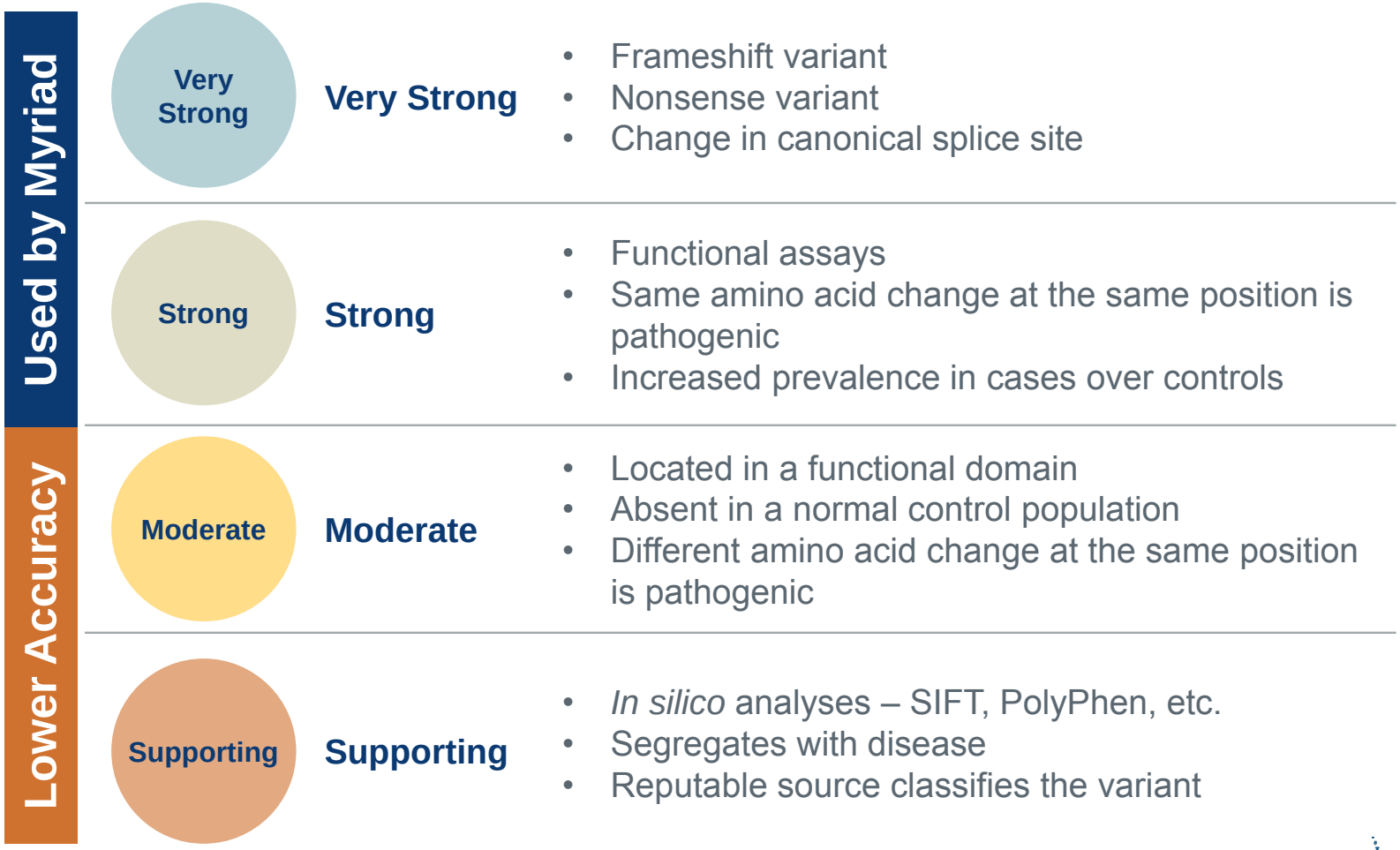
The ACMG Guidelines Start with Categorizing Evidence by Strength



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ACMG Then Combines Data to Make a Final Classification

Myriad uses high quality data for variant classification because the correct test result matters

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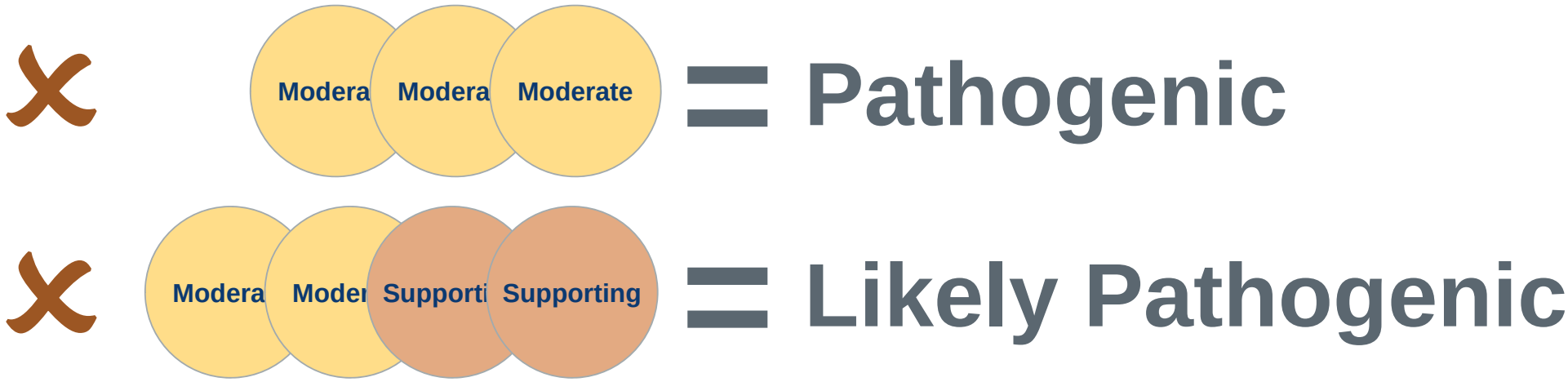
ACMG Then Combines Data to Make a Final Classification

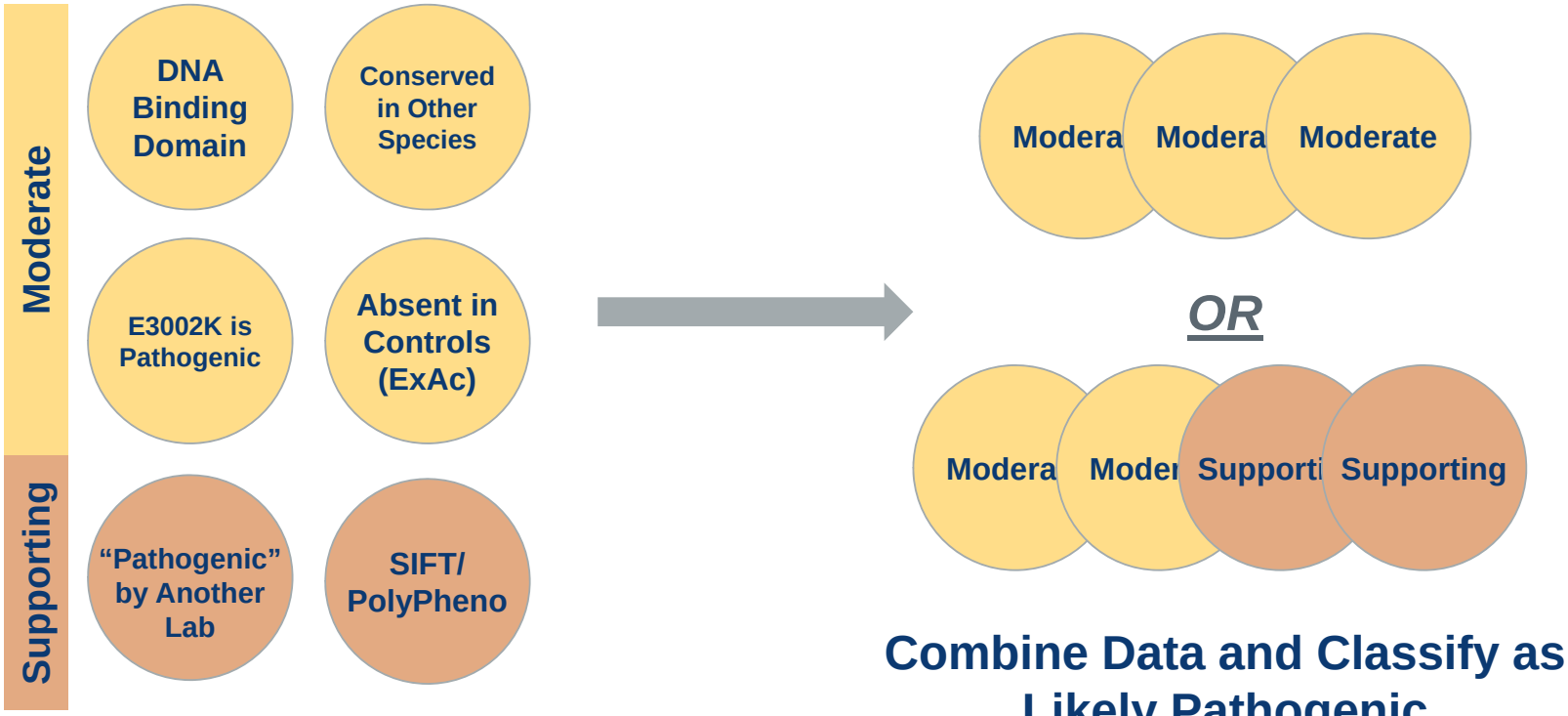
Myriad does not use lower quality data because it may result in incorrect classifications and inappropriate medical management



Following the ACMG Guidelines Does Not Guarantee Accuracy

BRCA2 E3002D can be Classified as Likely Pathogenic Based on Lower Quality Evidence

BRCA2 E3002D



Combine Data and Classify as Likely Pathogenic

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BRCA2 E3002D can also be classified as Likely Benign Based on Lower Quality Evidence

BRCA2 E3002D

Combine Data and Classify as Likely Benign

Two different classifications for the same variant using the same guidelines!

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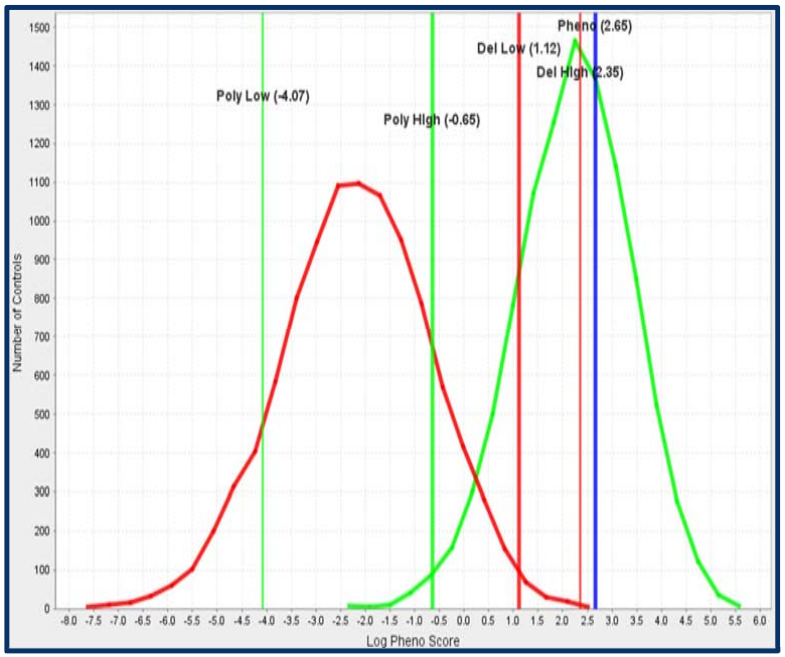
High Quality Validated Data Gives the Correct Classification

BRCA2 E3002D



Validated Pheno

Likely Benign – NPV > 99.5%

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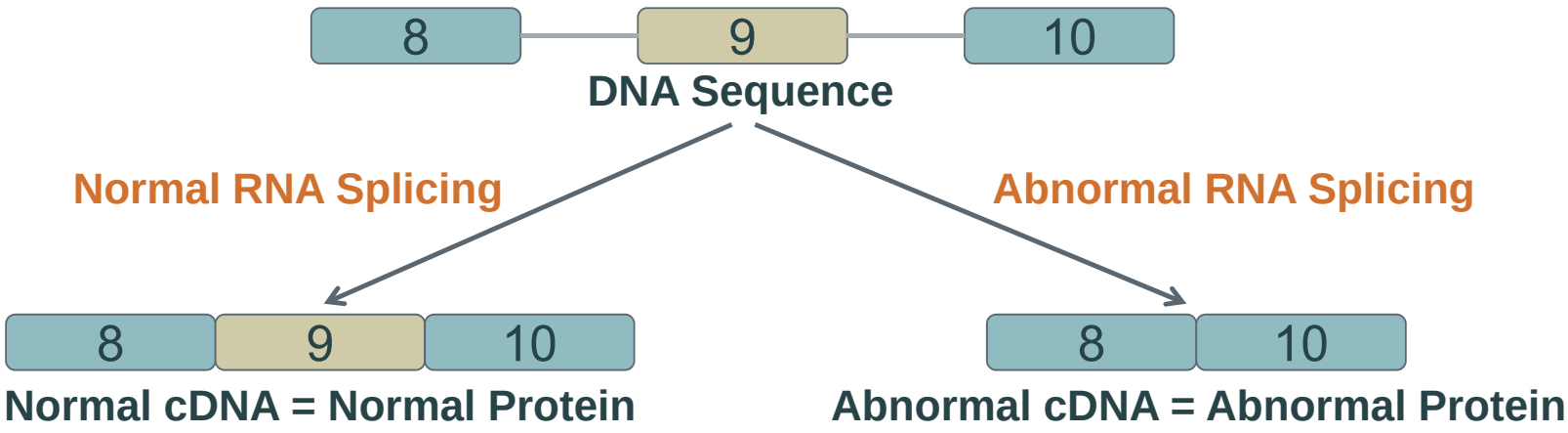
WHEN DECISIONS MATTER

We Offer Free RNA Analysis if it May Allow Us to Reclassify a VUS to Pathogenic or Benign

***MSH6* R1334Q (c.4001G>A) is located at the last base of exon 9 and may result in abnormal RNA splicing**



Myriad requested an RNA sample from a patient with this variant

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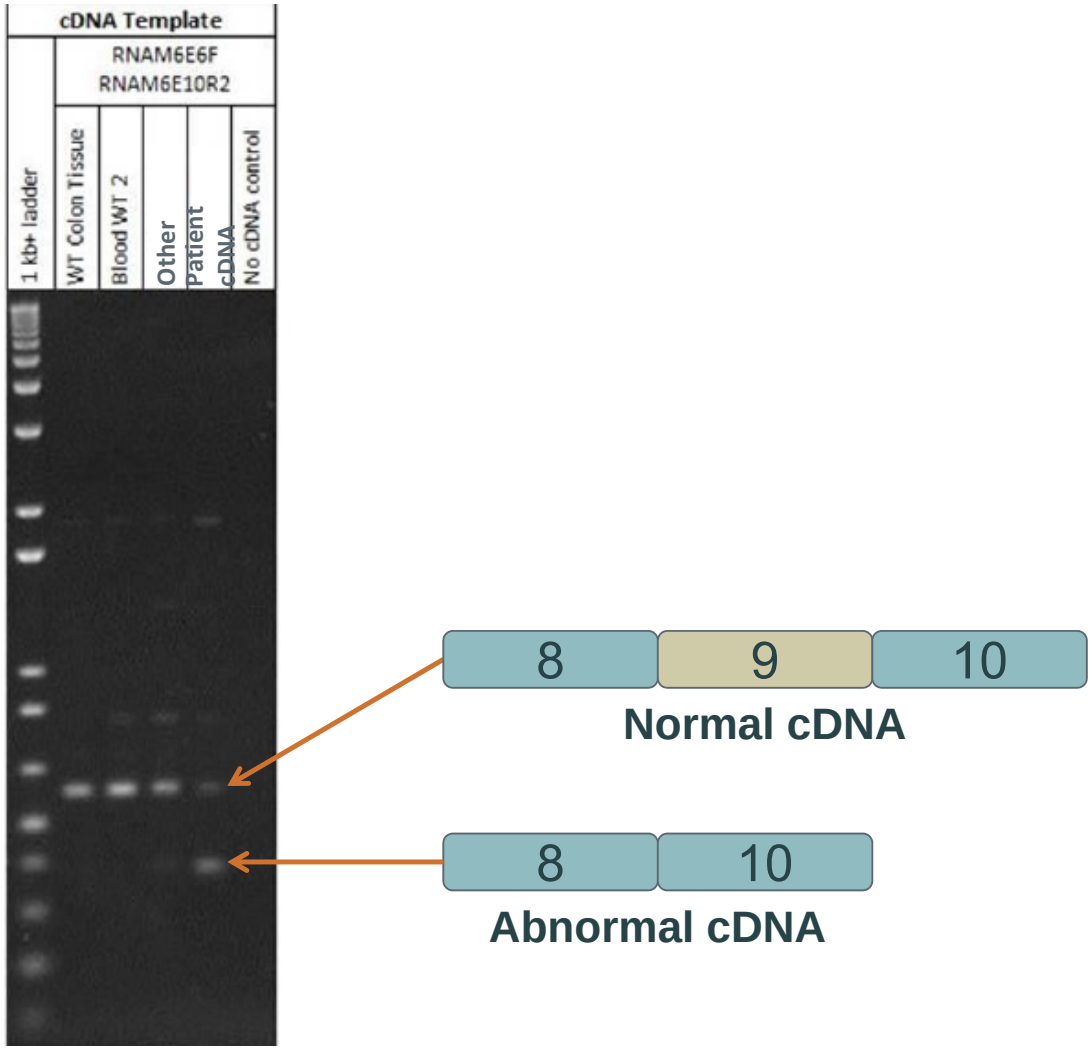
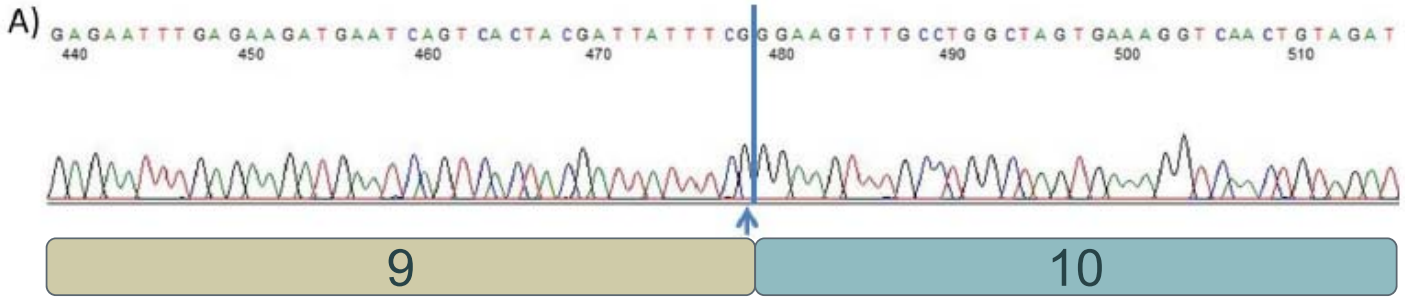
WHEN DECISIONS MATTER

MSH6 R1334Q: RNA Analysis Shows that the Patient Produces an Abnormal cDNA Product

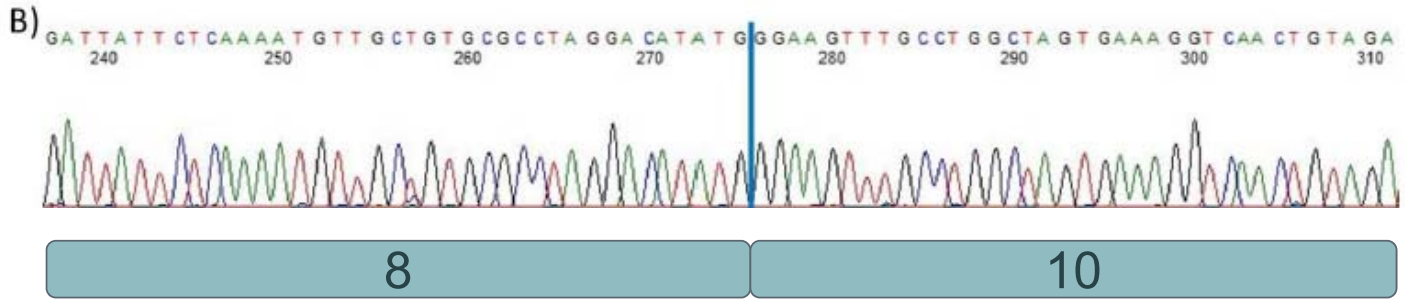


MSH6 R1334Q: Sequencing Analysis Confirms that the R1334Q Causes Abnormal mRNA Splicing

Normal cDNA



Abnormal cDNA



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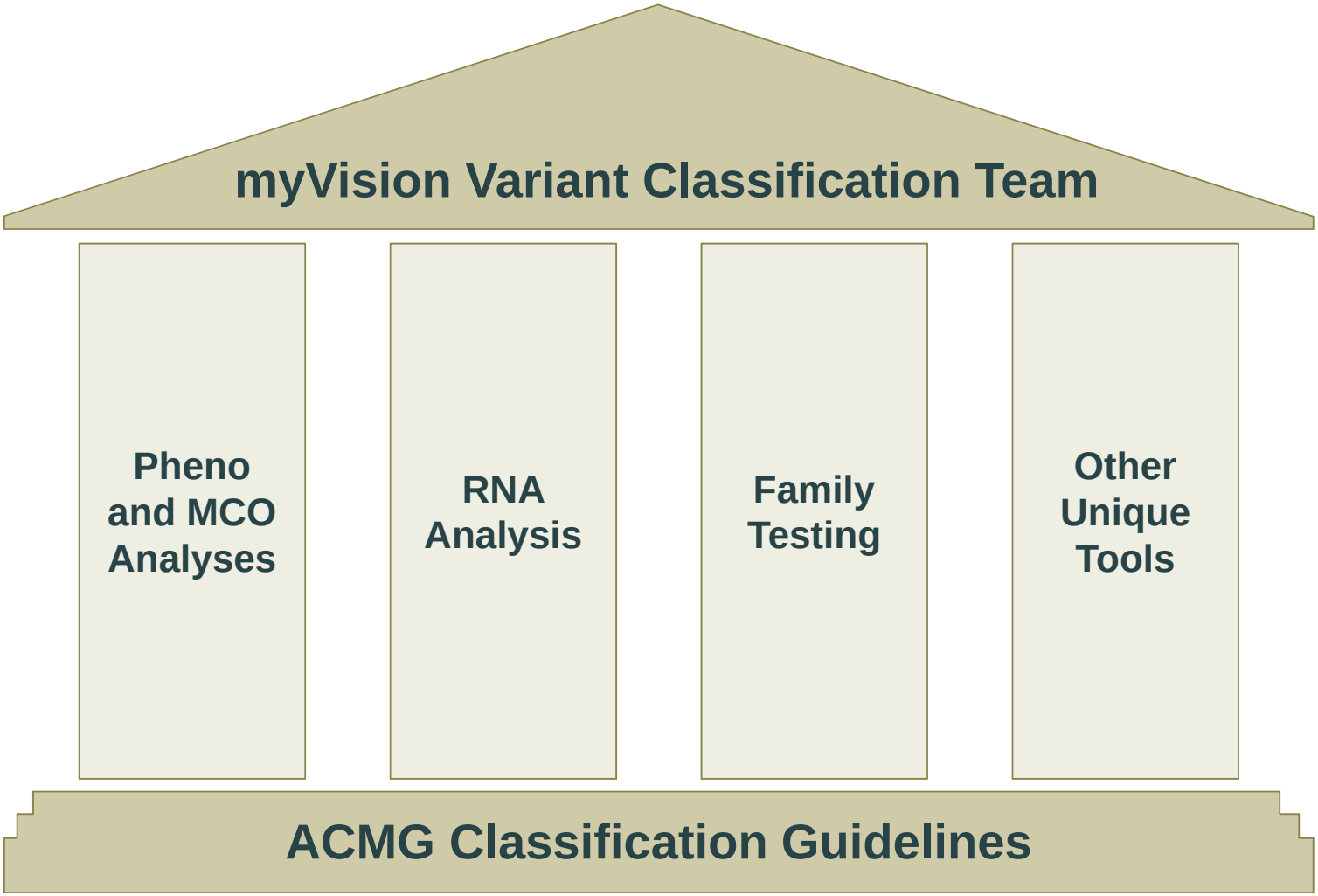
WHEN DECISIONS MATTER

ACMG is Our Foundation, But We Go Above and Beyond for Our Patients



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WHEN DECISIONS MATTER

Our Reclassification Efforts Benefit Many Patients and Their Families

In 2016, We Sent 23,337 Amended Reports with More Definitive Variant Classifications

23,337 Patients and Countless Family Members Will Benefit from More Clinically Actionable Test Results

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WHEN DECISIONS MATTER

Myriad is Committed to Patients and Providers Throughout the Entire Testing Process

Pre-Testing Support

- We will work with you to provide education and support before testing

State of the Art Variant Identification

- High quality technologies
- Optimization and validation
- Unusual Cases – Customization allows patients receive definitive answers

State of the Art Variant Interpretation

- World-class variant team
- Powerful and unique classification tools
- Lifetime commitment to patients

Post-Testing Support

- Clinical management support: Medical Management Tool
- Patient and provider support after testing is completed

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WHEN DECISIONS MATTER

DNA Repair Pathways

Single Strand Break

Poly ADP Ribose Polymerase

Double Strand Break

Homologous Recombinational Repair

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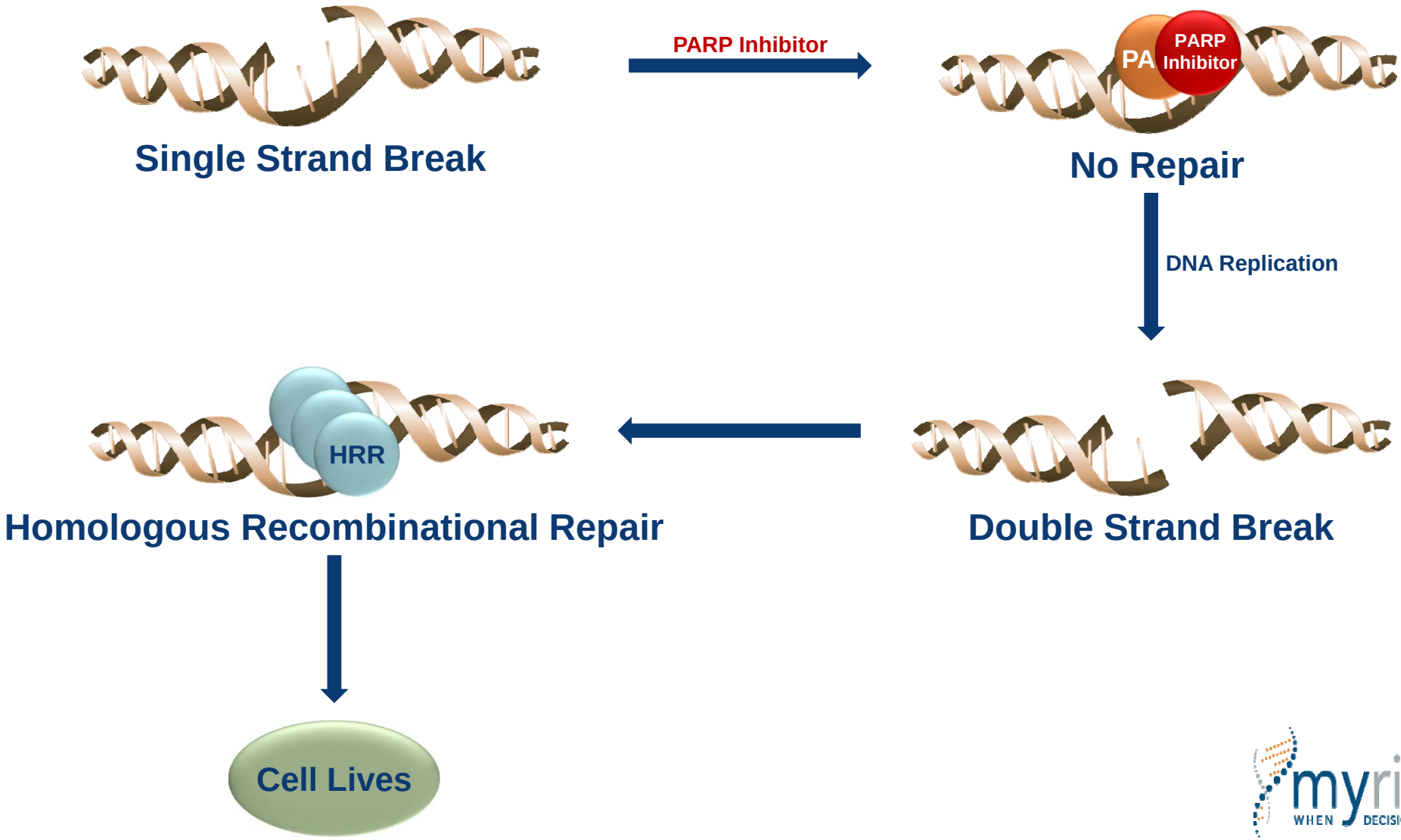
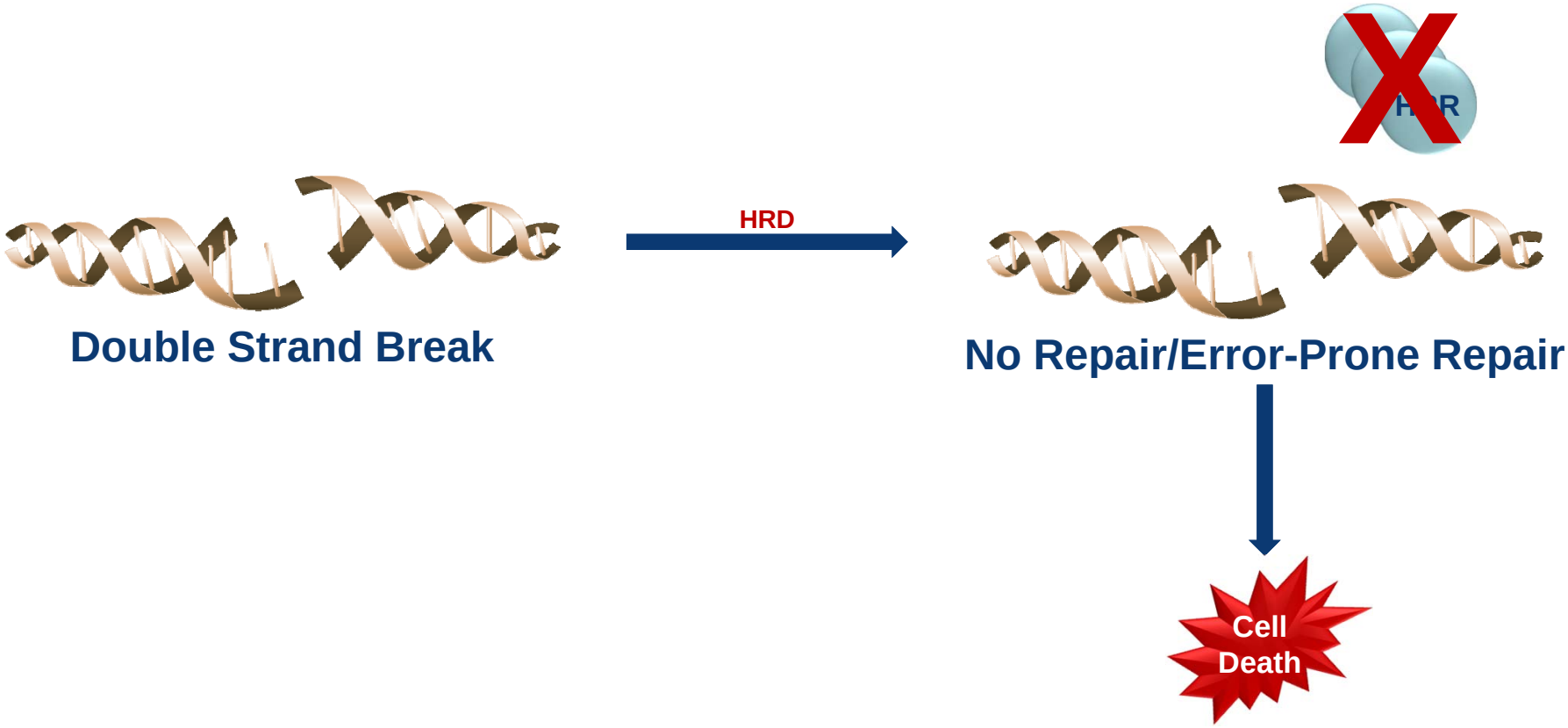
WHEN DECISIONS MATTER

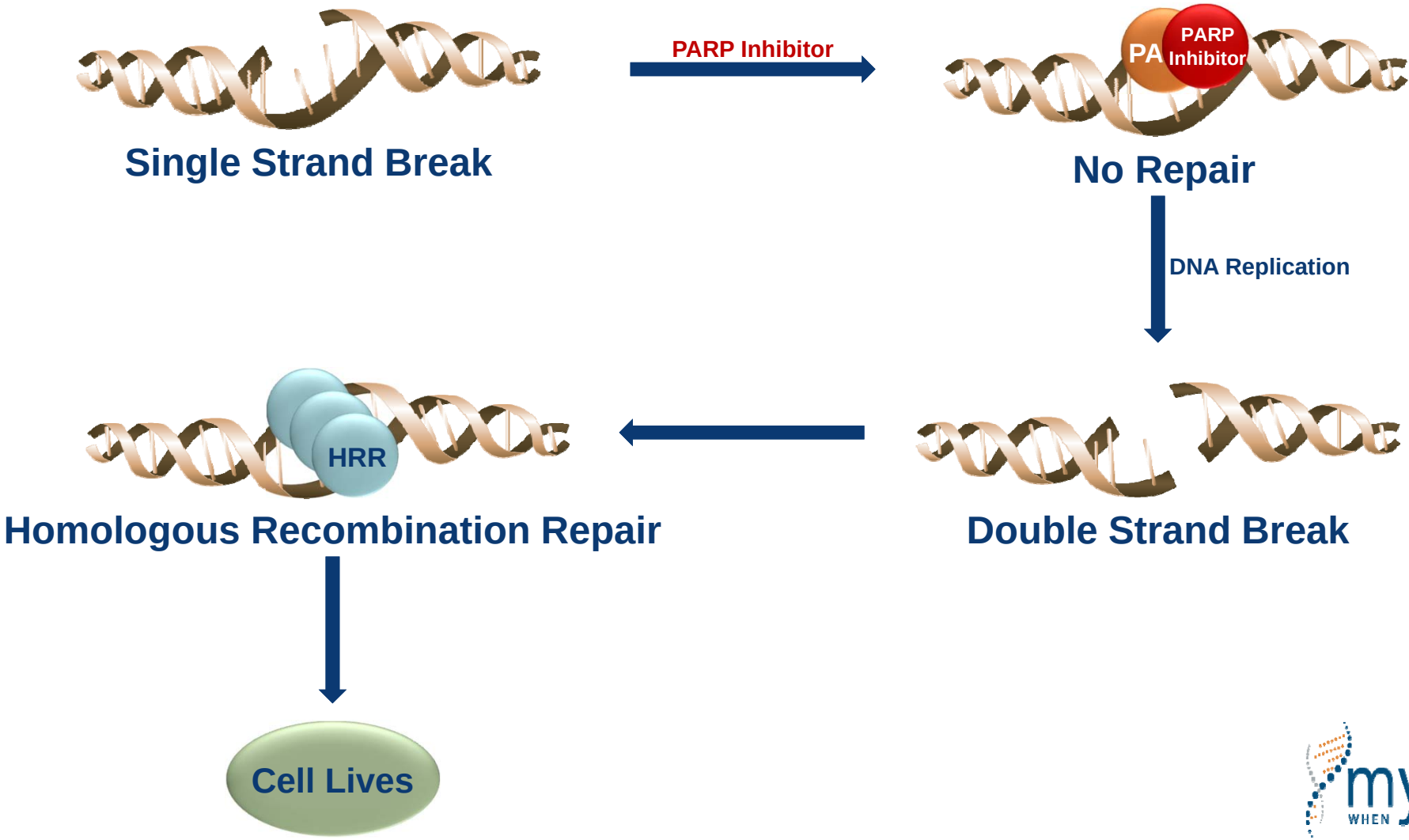
PARP Inhibitors



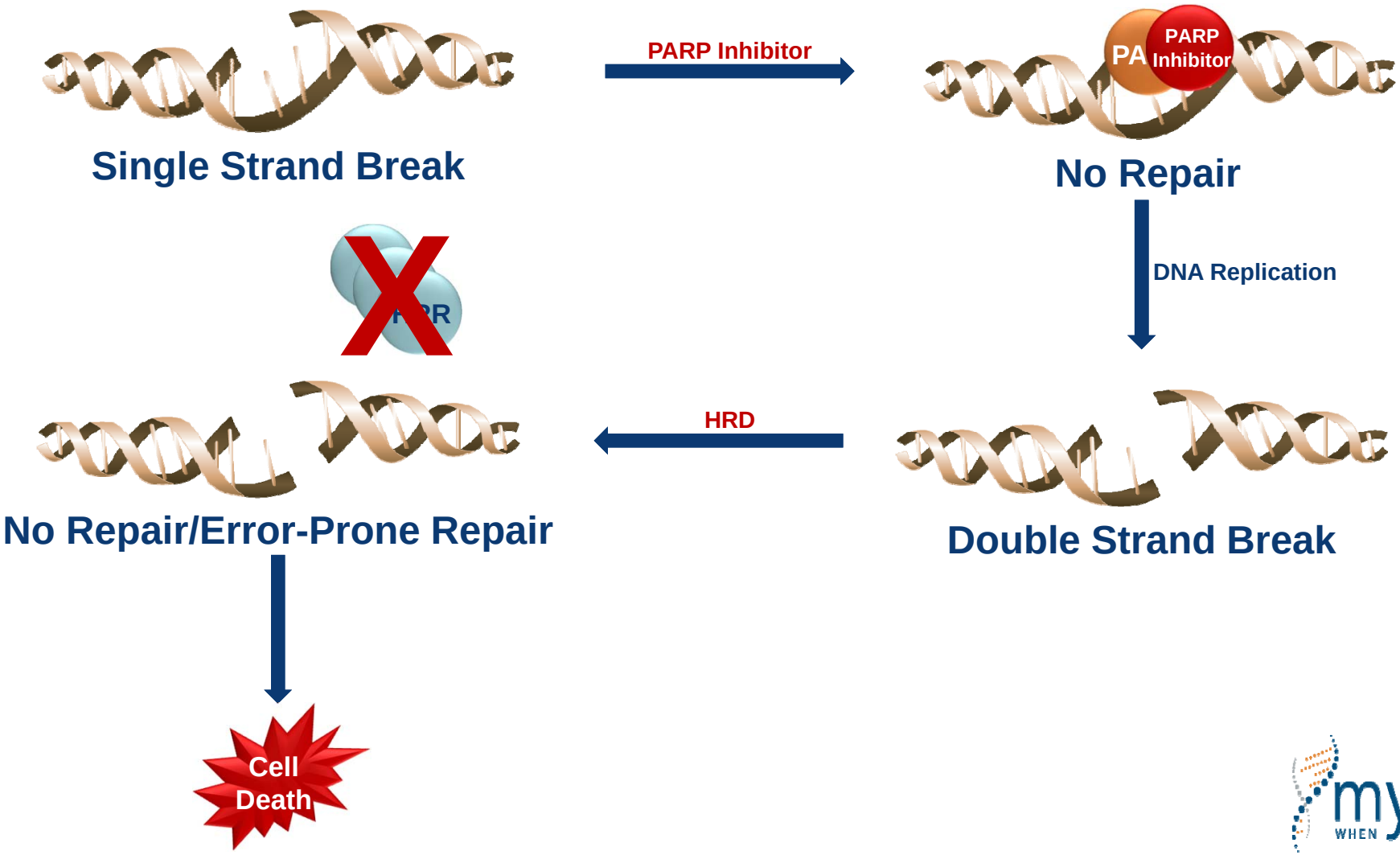
Homologous Recombination Deficiency



Patient 1: PARP Inhibitor / HRR Proficient



Patient 2: PARP Inhibitor / HRR Deficient



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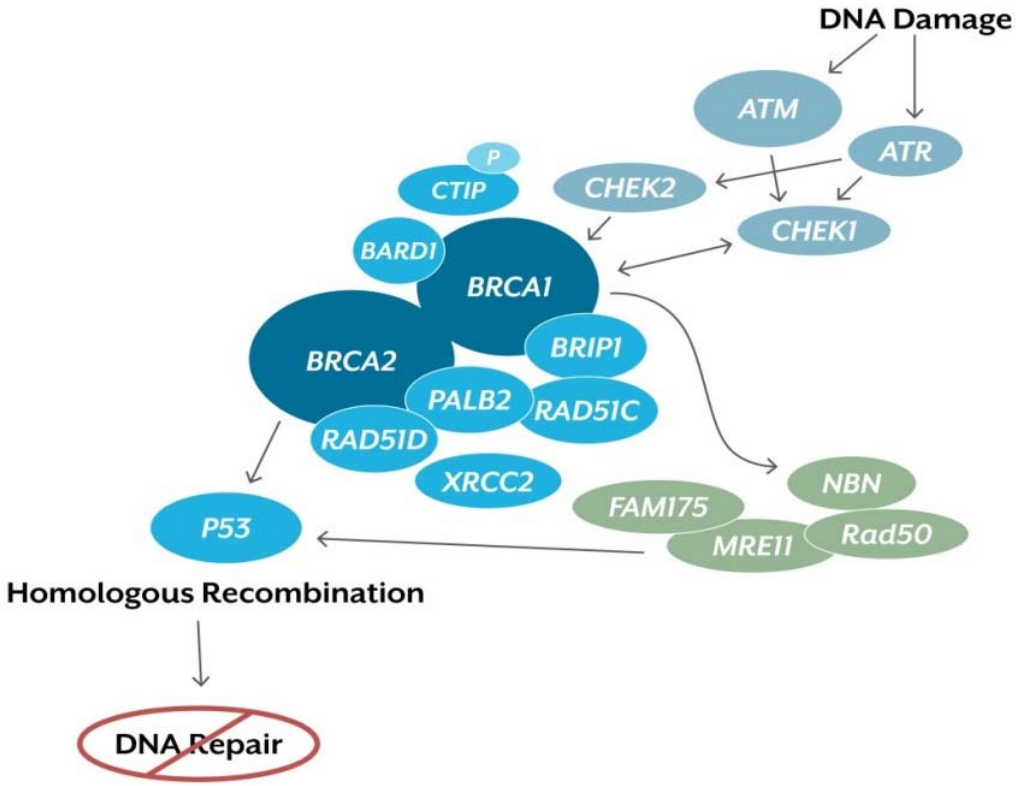
HRR Pathway



Pennington et al. Clin Cancer Res (2013) 20(3):764-75.

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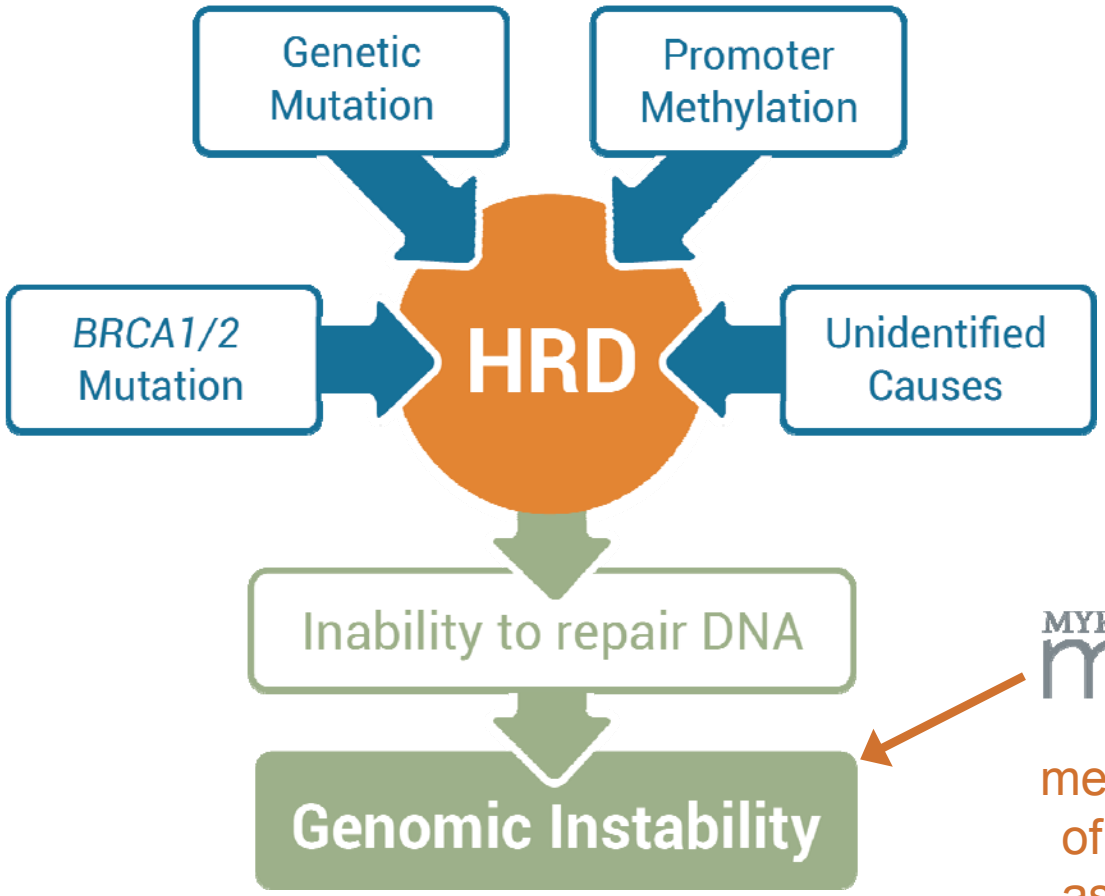
A Better Approach: Look at the Genomic Phenotype That Results From HRD



MYRIAD myChoice® HRD measures a phenotype of genomic instability associated with HRD

Watkins et al. Breast Ca Res (2014) 16:211.

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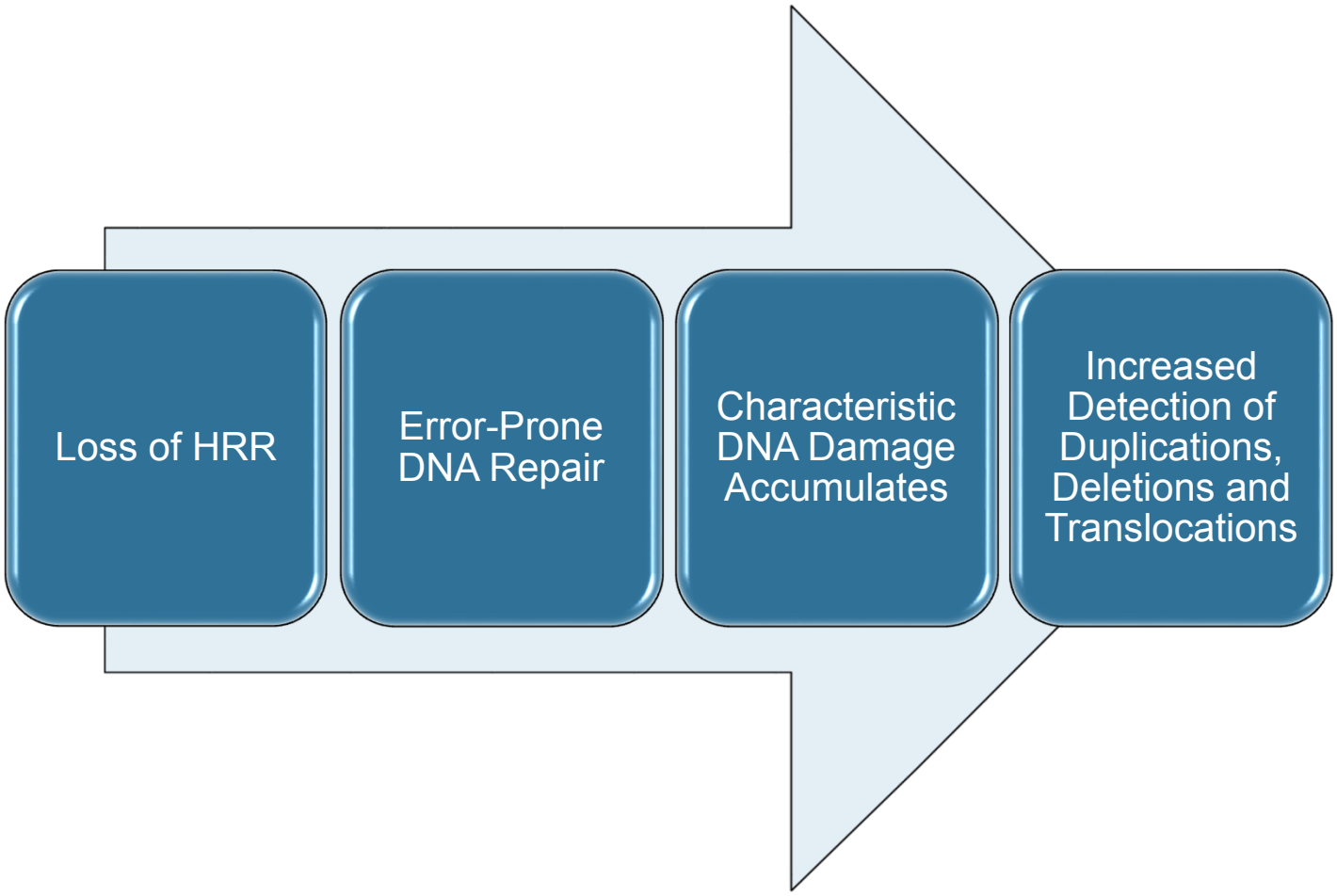
A Better Approach: Look at the Genomic Phenotype That Results From HRD



Abkevich et al. Br J Cancer (2012) 107:1776–1782.
Popova et al. Cancer Res (2012) 72(21):5454-62.
Birkback et al. Cancer Discov (2012) 2(4):366-75.

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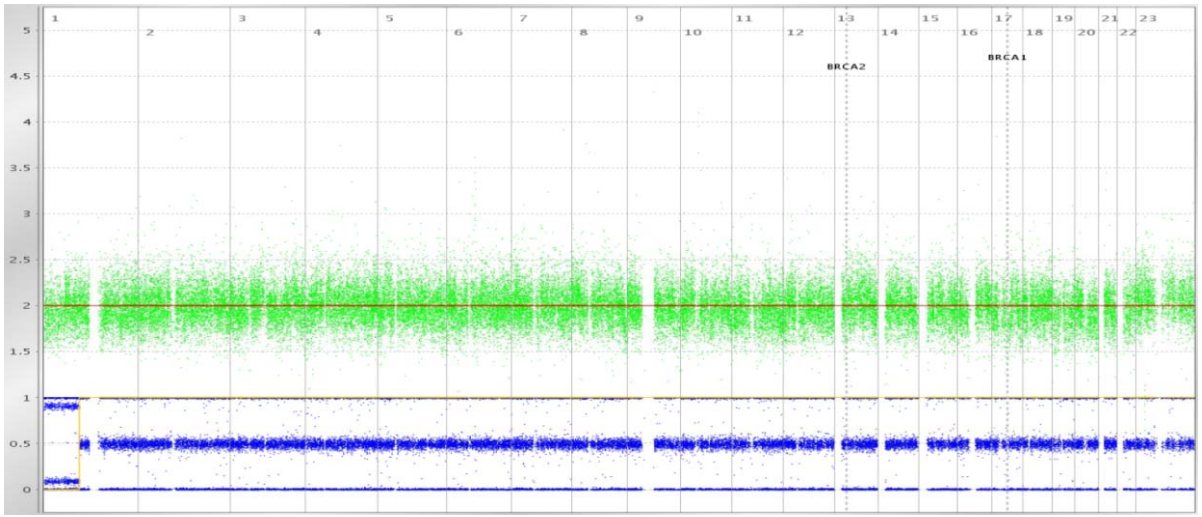
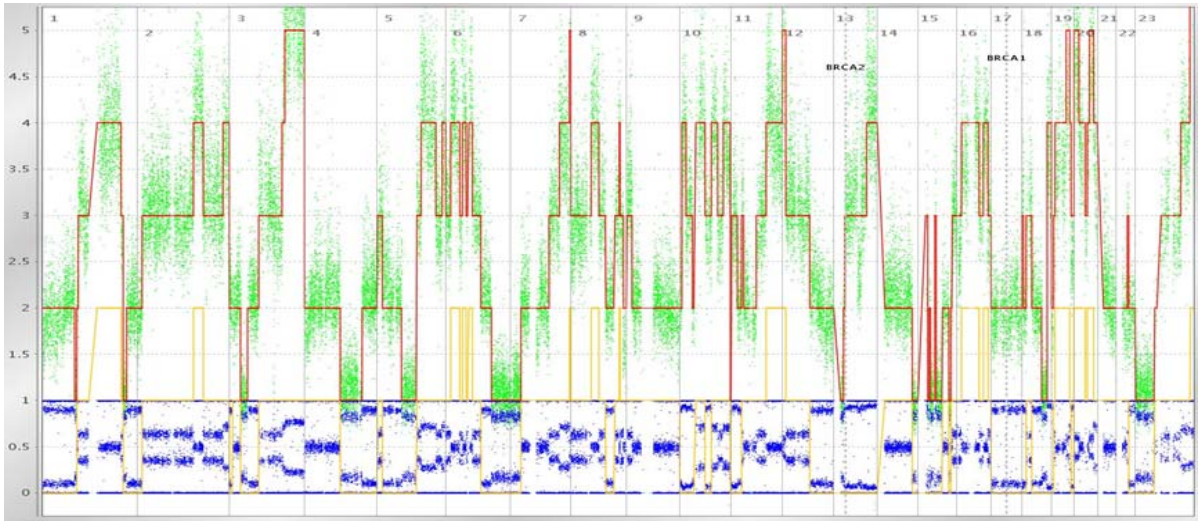
Example of myChoice HRD Genomic Profile



HRD Score = 3
HRD Negative



HRD Score = 81
HRD Positive

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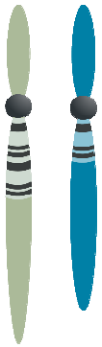
myChoice HRD Biomarkers

Loss of Heterozygosity (LOH): Presence of a single allele

Telomeric Allelic Imbalance (TAI): A discrepancy in the 1:1 allele ratio at the end of the chromosome (telomere)



Large-Scale State Transitions (LST): Transition points between regions of abnormal and normal DNA or between two different regions of abnormality

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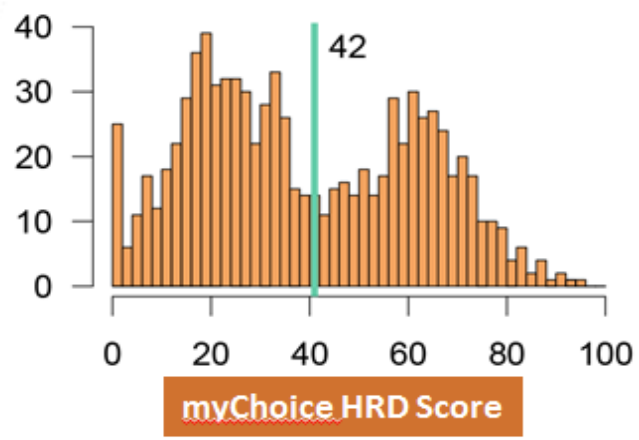
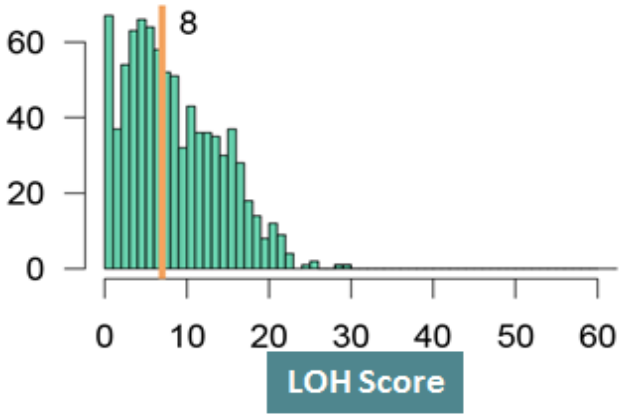
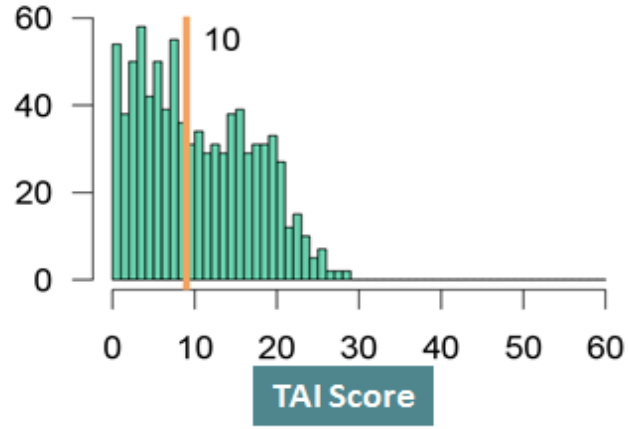
WHEN DECISIONS MATTER

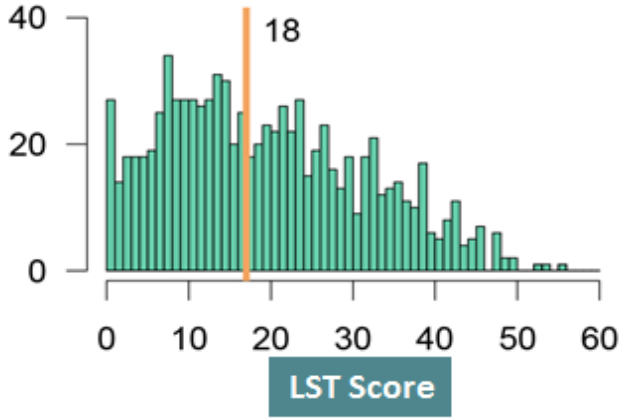
Single Measures of HRD are Insufficient



In a cohort of 859 ovarian tumors, only a combination of all three biomarkers (HRD score) yielded a clear cutoff.







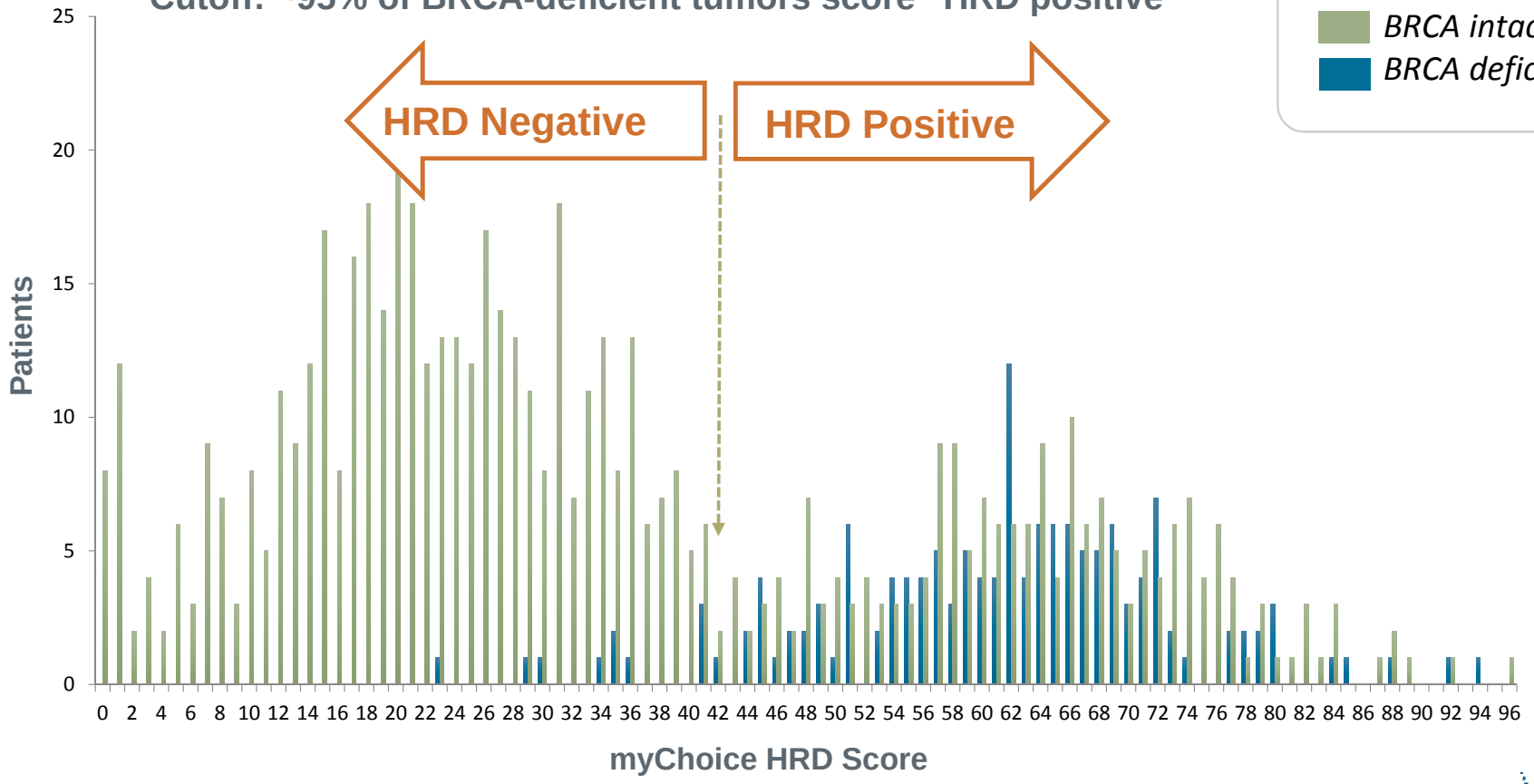
Hennessy BT, et al. *J Clin Oncol*. 2010; 28:3570.
TCGA Research Network. *Nature*. 2011; 474:6609.
Bannerjee et al. *Ann Oncol*. 2013;24(3):679.

Ovarian Cancer Score Distribution

There is a high-scoring (HRD positive) and low-scoring (HRD-negative group) represented by the two peaks.

Cutoff: ~95% of BRCA-deficient tumors score "HRD positive"

LOH + TAI + LST = HRD



Mills et al. SGO 2016

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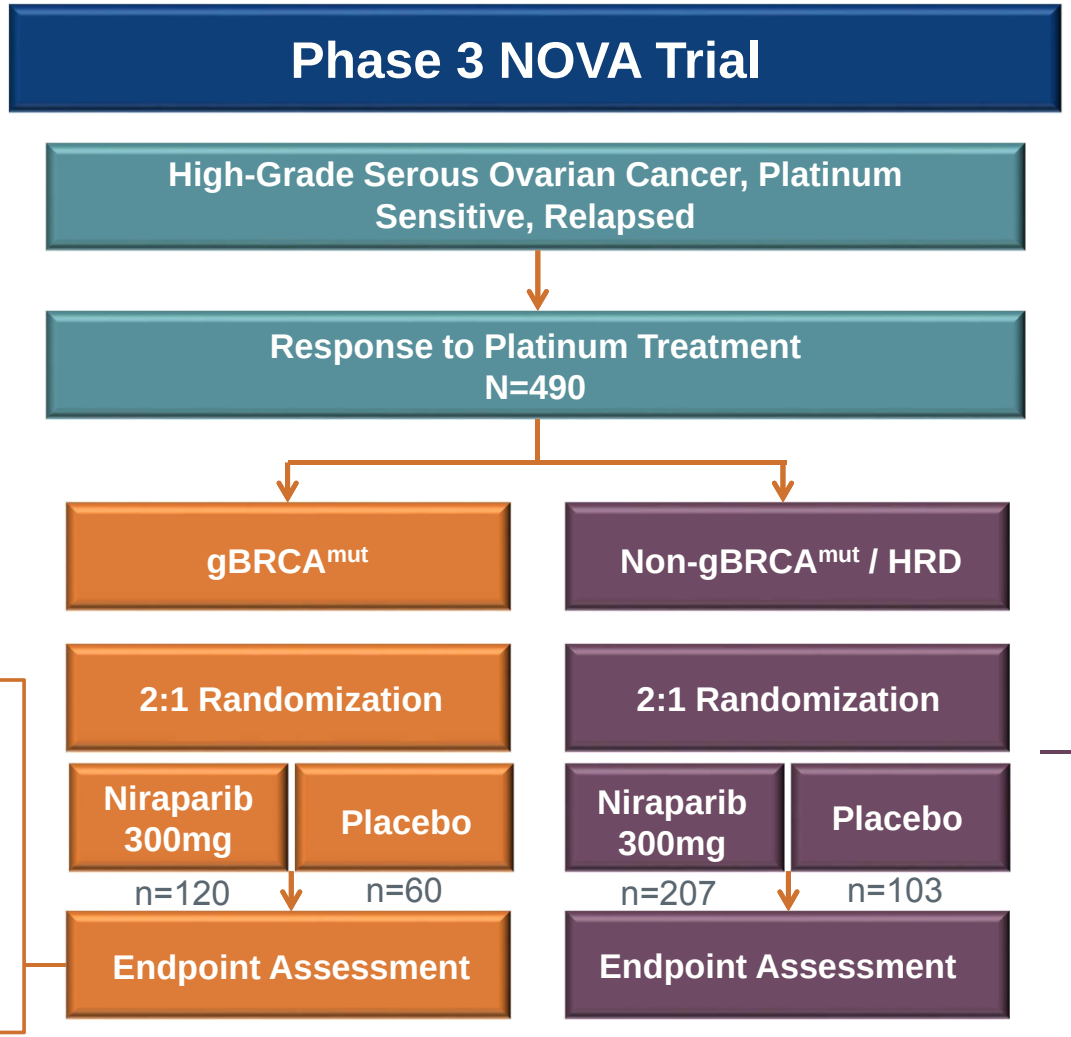
WHEN DECISIONS MATTER

Review of the NOVA Study



Primary Endpoint:

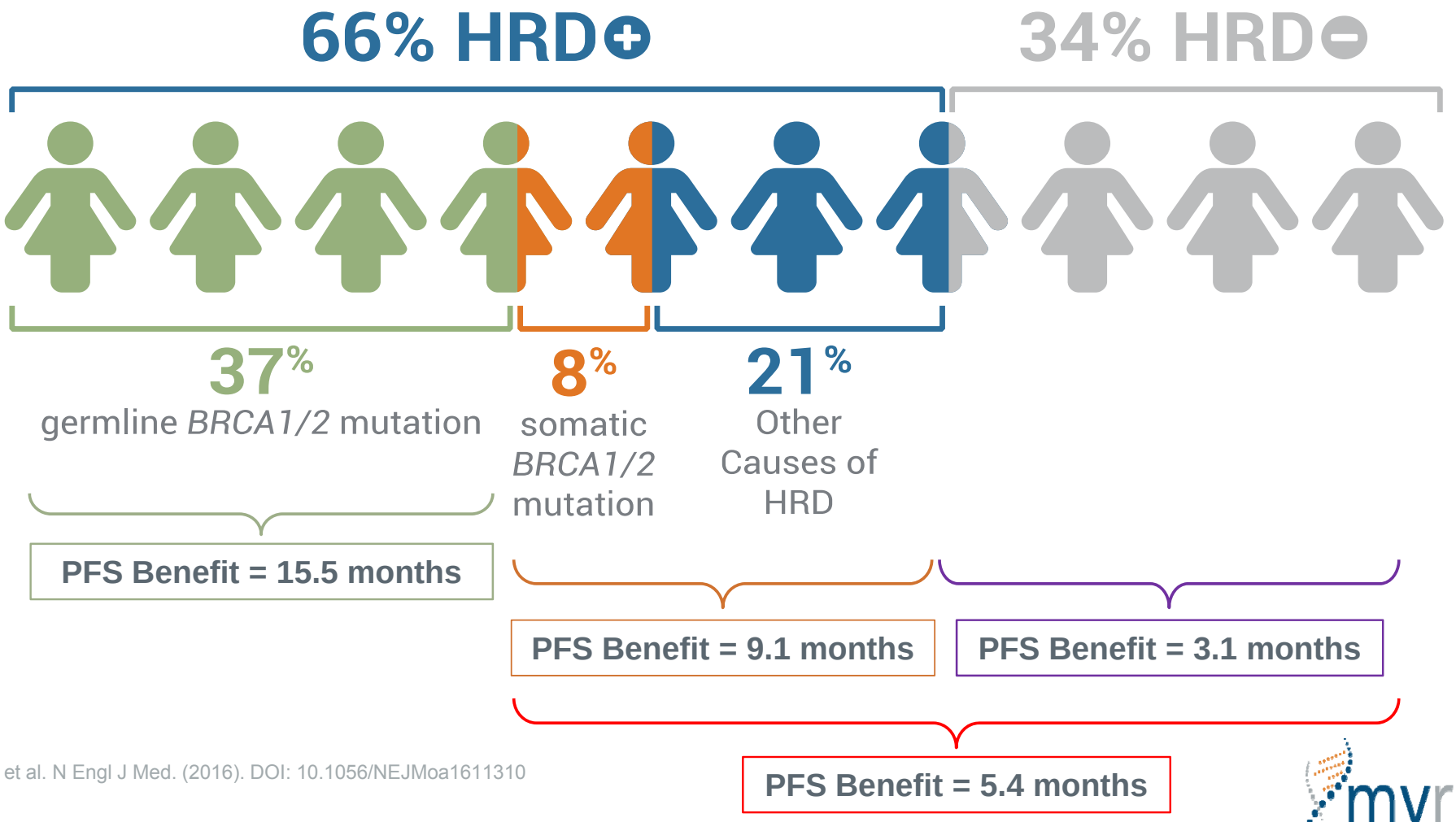
- PFS; >90% power to detect 4.8 month improvement (HR 0.50 in both cohorts)
- Assumption: 4.8 month PFS for control arms

myChoice HRD:

- First assess PFS in HRD+ subset
  - n≈165
  - >90% power to detect a HR=0.50
- If HRD+ subset has p<0.05, assess PFS for the entire cohort
  - N=310
  - >90% power to detect a HR=0.50

myChoice HRD – NOVA Study Results

All Platinum Sensitive High-Grade Serous Ovarian Cancer



Mirza et al. N Engl J Med. (2016). DOI: 10.1056/NEJMoa1611310

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Homologous Recombination Deficiency (HRD) as a predictive biomarker of response to neoadjuvant platinum-based therapy in patients with triple-negative breast cancer (TNBC): A pooled analysis

Telli ML *et al.* Presented at SABBCS, December 10, 2015.

Trial	N	Weeks of Therapy	Neoadjuvant Regimen
Gepar Sixto[1]	101	18	Paclitaxel, non-pegylated liposomal doxorubicin, carboplatin and bevacizumab
PrECOG 0105[2]	72	12-18	Carboplatin, gemcitabine, and iniparib
NCT00580333[3]	32	12	Cisplatin with bevacizumab
NCT01372579[4]	26	12	Carboplatin and eribulin
NCT00148694[5]	18	12	Cisplatin
TBCRC 008[6]	18	12	Carboplatin, nab-paclitaxel, with or without vorinostat

267 TNBC patients with multiple neoadjuvant therapies

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WHEN DECISIONS MATTER

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Telli ML *et al.* Presented at SABBCS, December 10, 2015.

HR deficiency and response					
Variable	**Category**	**Unadjusted OR**	**Adjusted OR**	**95% CI**	**P value**
HR deficiency status	Non-deficient (ref)	1.0	1.0		<0.0001
	Deficient	5.11	4.64	2.32-9.27	
Age	Increment of 10 years		0.81	0.62-1.06	0.109
Intended Therapy Duration	12 weeks (ref)		1.0		0.291
	18 weeks		2.38	0.42-13.47	
Clinical Stage	I (ref)		1.0		0.118
	II		0.41	0.16-1.09	
	III		0.31	0.09-1.08	
Trial	Gepar Sixto (ref)		1.0		0.002
	Others		0.37-2.38		

Adjusted OR of 4.64 based on analysis of ***BRCA1/2* positive or negative patients**

Other clinical parameter measurements not significant

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WHEN DECISIONS MATTER

Homologous Recombination Deficiency (HRD) as a predictive biomarker of response to neoadjuvant platinum-based therapy in patients with triple-negative breast cancer (TNBC): A pooled analysis

Telli ML *et al.* Presented at SABBCS, December 10, 2015.

HR deficiency in *BRCA* negative and response					
Variable	**Category**	**Unadjusted OR**	**Adjusted OR**	**95% CI**	**P value**
HR Deficiency Status	Non-deficient (ref)	1.0	1.0		<0.0001
	Deficient	4.37	4.55	2.12-9.74	
Age	Increment of 10 years		0.75	0.54-1.05	0.084
Intended Therapy Duration	12 weeks (ref)		1.0		0.316
	18 weeks		2.96	0.24-10.07	
Clinical Stage	I (ref)		1.0		0.600
	II		0.55	0.11-1.33	
	III		0.70	0.13-3.47	
Trial	Gepar Sixto (ref)		1.0		0.004
	Others		0.30 – 4.78		

Adjusted OR of 4.55 based on analysis of ***BRCA1/2* negative patients**

Other clinical parameter measurements not significant

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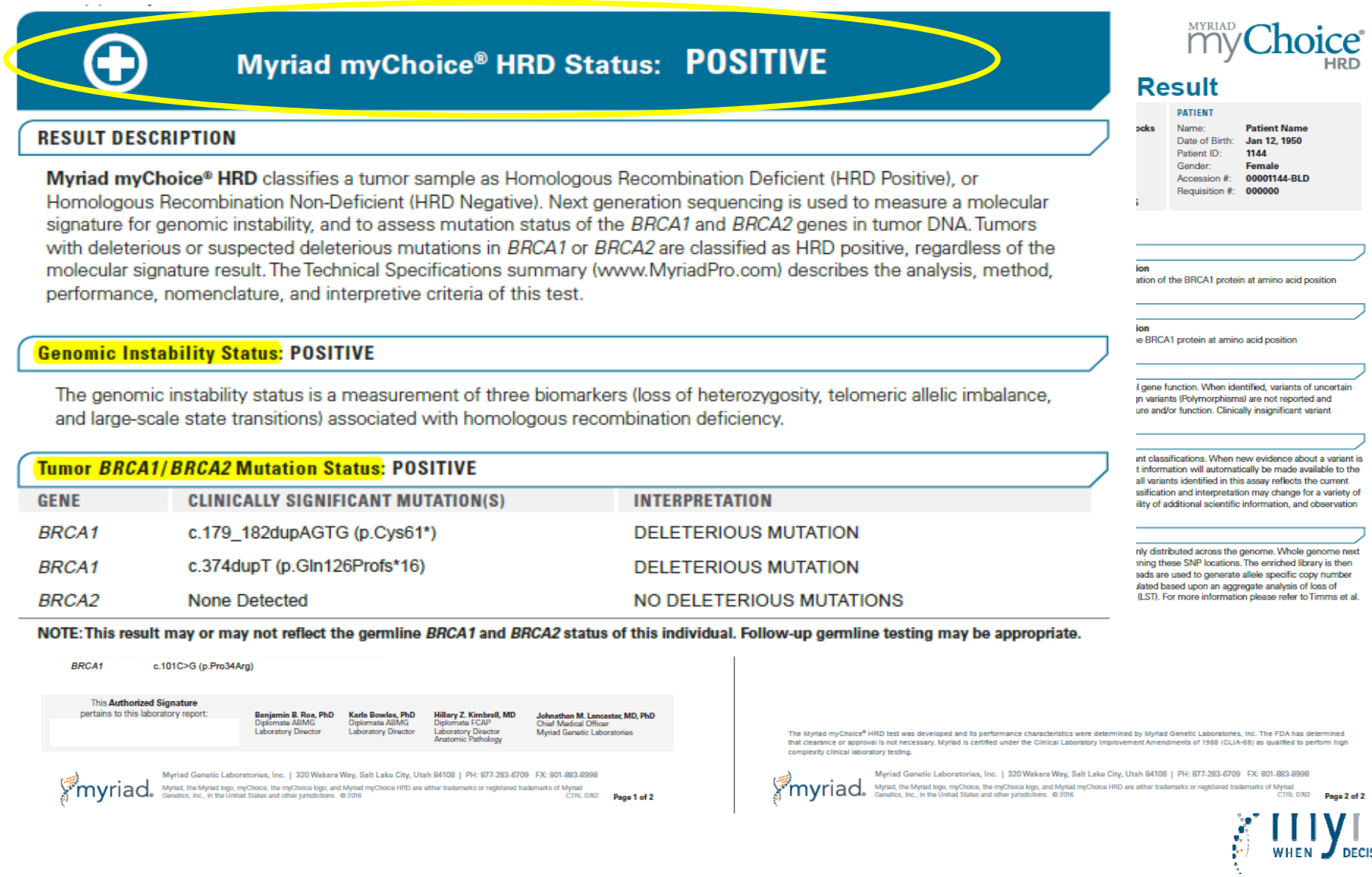
myChoice HRD Report



Myriad myChoice® HRD Status: POSITIVE

MYRIAD myChoice® HRD

Result

PATIENT

Name:	**Patient Name**
Date of Birth:	**Jan 12, 1950**
Patient ID:	**1144**
Gender:	**Female**
Accession #:	**00001144-BLD**
Requisition #:	**000000**

RESULT DESCRIPTION

Myriad myChoice® HRD classifies a tumor sample as Homologous Recombination Deficient (HRD Positive), or Homologous Recombination Non-Deficient (HRD Negative). Next generation sequencing is used to measure a molecular signature for genomic instability, and to assess mutation status of the *BRCA1* and *BRCA2* genes in tumor DNA. Tumors with deleterious or suspected deleterious mutations in *BRCA1* or *BRCA2* are classified as HRD positive, regardless of the molecular signature result. The Technical Specifications summary (www.MyriadPro.com) describes the analysis, method, performance, nomenclature, and interpretive criteria of this test.

Genomic Instability Status: POSITIVE

The genomic instability status is a measurement of three biomarkers (loss of heterozygosity, telomeric allelic imbalance, and large-scale state transitions) associated with homologous recombination deficiency.

Tumor *BRCA1*/*BRCA2* Mutation Status: POSITIVE

GENE	CLINICALLY SIGNIFICANT MUTATION(S)	INTERPRETATION
BRCA1	c.179_182dupAGTG (p.Cys61*)	DELETERIOUS MUTATION
BRCA1	c.374dupT (p.Gln126Profs*16)	DELETERIOUS MUTATION
BRCA2	None Detected	NO DELETERIOUS MUTATIONS

NOTE: This result may or may not reflect the germline *BRCA1* and *BRCA2* status of this individual. Follow-up germline testing may be appropriate.

BRCA1 c.101C>G (p.Pro34Arg)

This **Authorized Signature** pertains to this laboratory report:

Benjamin B. Roa, PhD Diplomate ABMG Laboratory Director
Karla Bowles, PhD Diplomate ABMG Laboratory Director
Hillary Z. Kimbrell, MD Diplomate FCAP Laboratory Director Anatomic Pathology
Johnathan M. Lancaster, MD, PhD Chief Medical Officer Myriad Genetic Laboratories

myriad. Myriad Genetic Laboratories, Inc. | 320 Wakara Way, Salt Lake City, Utah 84108 | PH: 877-293-6709 FX: 801-883-8998

CTRL 0762 Page 1 of 2

The Myriad myChoice® HRD test was developed and its performance characteristics were determined by Myriad Genetic Laboratories, Inc. The FDA has determined that clearance or approval is not necessary. Myriad is certified under the Clinical Laboratory Improvement Amendments of 1988 (CLIA-88) as qualified to perform high complexity clinical laboratory testing.

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