Reproductive health research

Carrier screening test consolidation: it's all about risk reduction

Most people are carriers

Most people carry at least one genetic variant associated with a severe or even lethal disorder that can manifest in subsequent generations.[1]

7,000
Rare diseases comprise roughly 7,000 disorders.[2]

~85%
About 85% of rare diseases are genetic diseases.[2]

In carrier screening research,
the focus is changing

As more causative variants are identified and ethnic diversity increases in certain regions, it is becoming increasingly important to expand carrier screening research to include more variants and diseases.

In 2021, the **American College of Medical Genetics (ACMG) adopted recommendations that shift carrier screening away from single-gene, ethnicity-based panels to a tiered approach with more ethnically inclusive and precise panels.**[3]

ACMG tiered approach
to carrier screening[3]

Tier 4
>1/200 carrier frequency (includes Tier 3)
Genes and conditions will vary by lab

Tier 3
>1/200 carrier frequency (includes Tier 2)
Includes X-linked conditions

Tier 2
>1/100 carrier frequency (includes Tier 1)

Tier 1
Cystic fibrosis, spinal muscular atrophy, and risk-based screening

ACMG recommends offering Tier 3 testing to all individuals who are pregnant or planning a pregnancy.

Consolidating multiple copy number and genotyping tests into a single molecular assay

- Saves time
- Maximizes efficiency of testing laboratories
- May yield more personalized and enhanced information

Targeted carrier screening *Often PCR-based*	vs.	Consolidated carrier screening *Microarray-based*
Small number of variants		Thousands of variants
Specific disease associations		Broad coverage of many genes and inherited diseases
Specific ethnicities		Pan-ethnic

PCR-based methods

Fragment size analysis

Test for many different types of variants, including single-nucleotide variants (SNVs), insertions and deletions (indels), and copy number variants (CNVs)

Microarrays

Detect very small duplications and deletions within chromosomes, as well as SNVs and indels in the genome

Analyze DNA of known genes from the entire human genome and known causative variants for inherited diseases in one test

Microarrays for carrier screening

SNP arrays

Identify specific locations and known "hot spots" of individual genetic variation within the genome

SNV genotyping

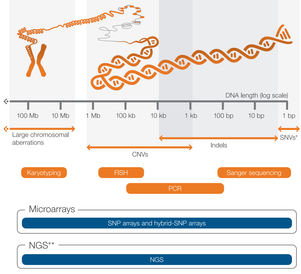
Hybrid-SNP arrays

Latest generation of DNA microarrays

Include both SNPs and high-density, high-resolution probes for genome-wide analysis of CNVs

Consolidated microarray tests may increase understanding from carrier screening for a range of challenging circumstances

- Challenging genes
- Uncertain family history
- Mixed or underrepresented ethnic background
- Inconclusive results
- Advanced maternal age
- Unexplained pregnancy loss
- Variants of unknown significance



* For SNP arrays and hybrid-SNP arrays that have probe coverage designed to detect specific SNPs.
** Specialized algorithms required for CNVs and indels.
† Size ranges are for illustration purposes in this diagram.

Genetic testing methodologies in carrier screening

Chromosomal and molecular methods enable analysis of the broad range of DNA variants important for carrier screening. High-throughput microarrays and massively parallel next-generation sequencing (NGS) have become the primary technologies for carrier screening.†

Case study

Increasing discovery yield
with a consolidated cystic fibrosis genotyping array

Linda Hasadsri, MD, PhD, Clinical Molecular Geneticist at the Mayo Clinic, presented data from a study to replace an outdated targeted cystic fibrosis genotyping assay with an updated genotyping array. The updated array contained more than 2,000 variants and over 200 genes for cystic fibrosis, as well as over 200 other disorders. It enabled detection of SNVs, indels, and CNVs with a single method.

The discovery yield using this array increased from 106 variants to over 500 variants, including CNVs. The results of this study enabled reclassification of 12 targets from pathogenic or likely pathogenic to variant of uncertain significance (VUS) or likely benign, and subsequent removal from the carrier screening test panel.[4]

Watch the webinar >

Dawning of a new era in reproductive health research

As more causative variants are identified in association with rare genetic disorders, consolidating carrier screening tests may streamline the identification of carriers of both common and rare genetic disorders. Researchers may uncover previously unrecognized correlations between mutations and specific populations, supporting the development of inclusive screening panels.

The ability to gain information from a single array that would normally require different kinds of tests may enable more cost-efficient and standardized approaches to yield better health outcomes and reduce the global burden of inherited disorders in the future.

Learn more about our carrier screening offerings at thermofisher.com/carrierscreening

References

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3. Gregg AR, et al. (2021) Screening for autosomal recessive and X-linked conditions during pregnancy and preconception: a practice resource of the American College of Medical Genetics and Genomics (ACMG) published correction. *Genet Med* 23(9):1793-1806.
4. Hasadsri L (2023) Utility of a custom targeted genotyping array for carrier screening research. Webinar. *GenomeWeb* 28 June 2023. thermofisher.com/us/en/home/global/forms/life-science/genotyping-array-carrier-screening.html