Carrier Screening: Should Evaluating More Genes Be the Standard of Care?

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BACKGROUND

Carrier screening utilization varies widely among clinicians including obstetricians (ObGyns), genetic counselors (GCs), maternal fetal medicine specialists (MFMs) and reproductive endocrinologists (REIs).[1,2] ACOG currently recommends screening for cystic fibrosis (CF) and spinal muscular atrophy (SMA), regardless of ethnicity. Ethnicity-based screening for hemoglobinopathies and Jewish genetic disorders is also recommended when appropriate. ACOG acknowledges that expanded carrier screening (ECS) has many benefits but advises that expanded panels should only include high impact disorders, disorders that are well-understood, severe, and have a carrier frequency of 1/100 or greater.[3,4]

For over five years, our laboratory has offered diagnostic testing for >1,000 genes and has recently begun offering carrier screening for up to 301 genes. These genes are available in pre-set panels or they can also be ordered as a single test or customized panel. All combinations are offered at the same out-of-pocket cost.

Pre-set panels (available with or without X-linked disorders) include:

- Core Panel (including CF, SMA, and fragile X syndrome)
- Broad Panel (including 46 high-impact genes)
- Comprehensive Panel (including 288 genes)
- Add-on genes (including 13 genes that can lead to variable clinical presentation (e.g., factor V Leiden (*F5*)) are available as an add-on to any panel

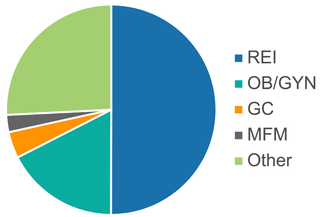
OBJECTIVE

To report ordering patterns within and outside of ACOG carrier screening guidelines.

METHODS

Testing was run for up to 301 genes in different combinations. Testing was performed by next-generation sequencing with deletion and duplication analysis. Real-time variant curation was performed and pathogenic and likely pathogenic variants were reported. Ordering patterns and positive rates were assessed.

Figure 1. Orders by Clinician Type



RESULTS

Over an eight-month period, 12,668 patient samples were tested. Orders came from 1,049 unique clinicians (20% REI, 21% ObGyn,12% GCs, 9% MFM, and 39% Other). Half of all orders came from REIs (Figure 1) and 8% of orders identified the patient or partner as pregnant.

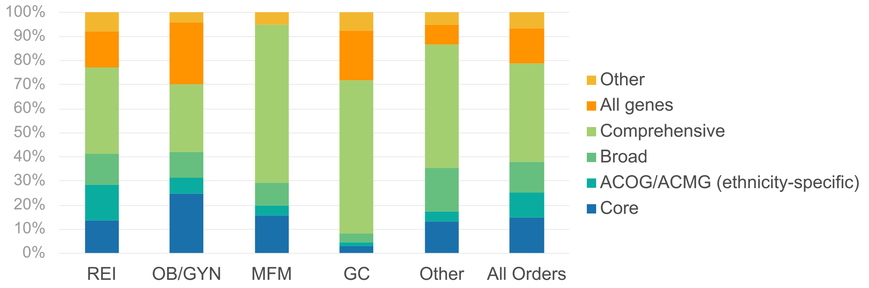
The largest pre-curated panel (288 genes) was ordered most frequently (n=5,121), followed by the Core Panel (n=1,898), all genes (n=1,865), and the Broad Panel (n=1,668). The remaining 2,116 orders were for variable combinations of genes. As expected, the positive rate increased with the number of genes tested (Table 1).

Of 2,151 opposite-sex couple orders we are aware of, 61% were sent concurrently and 39% took a tiered approach, only testing the partner when the patient was positive. When filtered for pregnant couples, 69% ordered concurrently.

Table 1. Ordering Patterns and Positive Rates

Panel	# of Genes	% Positive rate	% Concurrent	% of all orders
Comprehensive Panel with all Add-On genes (All genes)	301	77%	69%	15%
Comprehensive Panel	288	65%	68%	40%
Broad Panel	46	44%	44%	13%
Core Panel	3	15%	28%	15%
Other: ACOG/ACMG ethnicity-specific genes	4-24	22%	23%	10%
Other: All other combinations	1-300	varies	62%	7%
Total	1-301	51%	61%	100%

Figure 2: Panels by Clinician Type

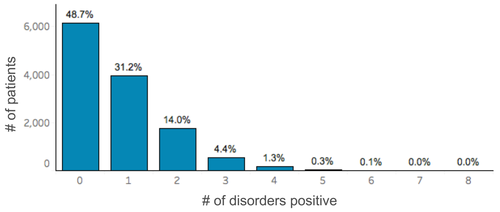


RESULTS

Guideline-based testing accounted for 25% of all orders; however, this number varied across specialties, with ObGyns having the highest adherence to guideline-based ordering (32%). Though the largest expanded panel was ordered across all specialties, MFMs were the only clinician group that did not order any add-on genes (Figure 2).

Of all tests, 31.2% were positive for 1 disorder, 14% were positive for 2 disorders, 4.4% were positive for 3 disorders, 1.3% were positive for 4 disorders, <1% were positive for 5-8 disorders, and 48.7% were negative (Figure 3).

Figure 3. Positive Rates for Multiple Disorder



The most common autosomal recessive disorders at-risk couples screened positive for (add-on genes excluded) include *CFTR*-related disorders, *HBB*-related hemoglobinopathies, phenylalanine hydroxylase deficiency (PKU), *GJB2*-related non-syndromic hearing loss, Smith-Lemli-Optiz syndrome, Gaucher disease and SMA.

Of note, at-risk couples pursued preimplantation genetic diagnosis (PGT-M) for disorders on all pre-curated panels. Approximately 25% of couples known to pursue PGT-M did so for disorders outside of ACOG / ACMG guidelines, indicating that patients use the information from expanded carrier screening to make reproductive healthcare decisions.

CONCLUSIONS

Despite current ACOG criteria, our data suggests that when given a choice, 55% of clinicians order a large panel (≥288 genes), even including frequent/variable disorders; however, 25% still follow a conservative pan-ethnic or ethnicity-specific approach.

Additional investigation is needed to understand the decision tree within and between practices including the role insurance coverage and cost plays on carrier screening ordering.

Disclosures: All authors are employees and stockholders of Invitae.

References: (1) Briggs A. et al. J Assist Reprod Genet. 2018 Sep,35(9):1631–1640. (2) Lazarin GA. et al. J Genet Couns. 2016;25:395–404. (3) ACOG Committee Opinion # 690. Obstet Gynecol. 2017 Mar;129(3):e35-e40. (4) ACOG Committee Opinion # 691. Obstet Gynecol. 2017 Mar;129(3):e41-e5.