Carrier screening clinical utility: where do you draw the line?

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Background

Gene panels for carrier screening are rapidly expanding in both size and clinical use. Currently, there is wide variability in ordering patterns, patient decision-making, and cost of testing[1,2]. Additionally, professional guidelines and approaches to testing vary among and within countries both in terms of which genes should be included on panels and in the recommended testing strategy (concurrent or sequential) for couples.

For example, the Society of Obstetrics and Gynaecology of Canada-Canadian College of Medical Geneticists (SOGC-CCMG) recommends decisions related to genetic carrier screening be based on family and/or personal medical history, ethnic background, and past obstetrical history. The current committee opinion supports direct gene mutation or expanded NGS testing being discussed as part of obtaining informed consent, and detailed genetic counselling and informed consent processes are required[3].

At the time of this study, Invitae offered carrier screening for up to 301 genes. These genes were available in pre-curated panels (3, 46, or 288 genes), or can be ordered as single test or customized panels. Thirteen additional genes (common, variable, and/or adult onset) are available as an add-on to any panel. This study aimed to assess carrier screening positivity and at-risk couple rates considering a range of panels to help clinicians and patients better understand the clinical utility of each.

Methods

Screening was performed for individual patients for up to 301 genes. Genes could be ordered in pre-curated panels (~3, 46, or 288 genes), as a single test or as customized panels. Thirteen common and/or variable genes were available as an add-on to any panel. Positive rates for individuals and known couples were assessed per panel grouping.

Several variants are routinely reported that are classified as low-penetrance or are known to have the potential to be associated with non-classic/mild disease presentation. Depending on the combination with other disease-causing alleles in the same gene, these variants may or may not increase the risk for a child to be affected with severe or classic disease. Therefore, rates for positive screens and at-risk couples were calculated with and without those variants included.

For individual carrier rates, variants associated with non-classic or mild disease were considered to be: *CFTR* (c.1210-34TG[11-13]T[5]), *GALT* (c.-199_-116del, “Duarte” variant), *GJB2* (c.109G>A, p.Val37Ile), *WNT10A* (c.682T>A, p.Phe228Ile), all variants in the 13 add-on genes (*BTD, F11, F2, F5, G6PD, GP1BA, GP9, HFE, HGD, MCCC1, MCCC2, MEFV, SERPINA1*).

For couple carrier rates, the following combinations were excluded from being considered “at-risk” in all calculations, even though both members of the couple are carriers: *CFTR* (c.1210-34TG[11]T[5]) / any variant), *GALT* (c.-199_-116del, “Duarte” variant / c.-199_-116del, “Duarte” variant), *BTD* (c.1330G>C, p.D444H / c.1330G>C, p.D444H), *FH* (c.1431_1433dup / c.1431_1433dup), *SERPINA1* (c.863A>T, “PI*S” allele / c.863A>T, “PI*S” allele), *HBA1/2* (αα/α-, “silent carrier” / αα/α-, “silent carrier”), *HBA1/2* (αα/α-, “silent carrier” / α-α-, “trait in *trans*”), *HBA1/2* (α-α-, “trait in *trans*” / α-α-, “trait in *trans*”).

For couple carrier rates, variant combinations expected to be a risk for a child with non-classic or mild disease were considered to be: *CFTR* (c.1210-34TG[11-13]T[5]) / any variant), *GALT* (c.-199_-116del, “Duarte” variant / any variant), *GJB2* (c.109G>A, p.Val37Ile / any variant), *HBB* (c.79G>A, p.Glu27Lys, “HbE” / c.79G>A, p.Glu27Lys, “HbE”), *ASS1* (c.535T>C, p.Trp179Arg / c.535T>C, p.Trp179Arg), *ASS1* (c.787G>A, p.Val263Met / c.787G>A, p.Val263Met), *ASS1* (c.1085G>T, Gly362Val / c.1085G>T, Gly362Val), *WNT10A* (c.682T>A, p.Phe228Ile / c.682T>A, p.Phe228Ile), all variant combinations in the 13 add-on genes (*BTD, F11, F2, F5, G6PD, GP1BA, GP9, HFE, HGD, MCCC1, MCCC2, MEFV, SERPINA1)*, if only a male is positive for an X-linked condition (*ABCD1, ATP7A, ATRX, CHM, COL4A5, CYBB, DMD, EDA, EMD, F9, FMR1 (premutation), GJB1, IDS, IL2RG, MTM1, OTC, PDHA1, PRPS1, RS1, SLC6A8)*, if only one member of the couple is positive for an autosomal dominant condition (*LDLR*).

Results

We evaluated 118,772 individuals who had testing with one of the pre-curated panels.
The positive carrier rates for any pathogenic/likely pathogenic variant were as follows (Figure 1):

- 13.2% for a 3-gene panel (*CFTR, FMR1, SMN1*), including variants associated with non-classic/mild disease
  - 5.6% for classic or severe variants only
- 44.8% for a 46-gene panel, including variants associated with non-classic/mild disease
  - 31.5% for classic or severe variants only
- 66.9% for a 288-gene panel, including variants associated with non-classic/mild disease
  - 57.5% for classic or severe variants only
- 72.4% for 288-panel plus at least one add-on gene, including variants associated with non-classic/mild disease
  - 57.6% for classic or severe variants only

In this cohort there were 22,832 couples.
The rates for couples to be at increased risk of having an affected child were as follows (Figure 2):

- 3.4% for a 3-gene panel (*CFTR, FMR1, SMN1*), including couples expected to be at-risk for a child with non-classic/mild disease
  - 1.2% for expected classic or severe presentation only
- 5.2% for a 46-gene panel, including couples expected to be at-risk for a child with non-classic/mild disease
  - 2.7% for expected classic or severe presentation only
- 6.8% for a 288-gene panel, including couples expected to be at-risk for a child with non-classic/mild disease
  - 3.7% for expected classic or severe presentation only
- 30.4% for 288-panel plus at least one add-on gene, including couples expected to be at-risk for a child with non-classic/mild disease
  - 4.2% for expected classic or severe presentation only

Figure 1: The positive rates for individuals to be carriers to be at increased reproductive risk based on panel size.

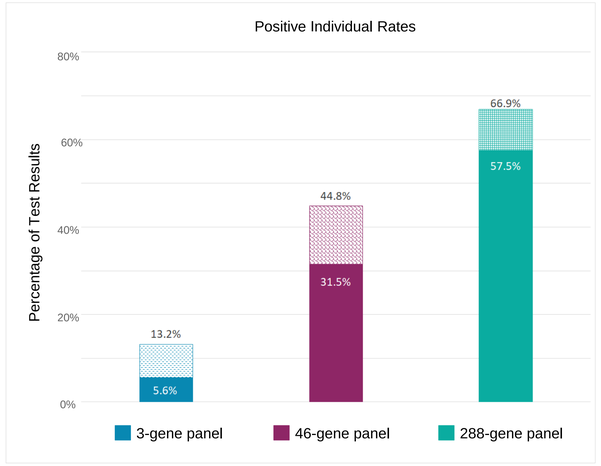
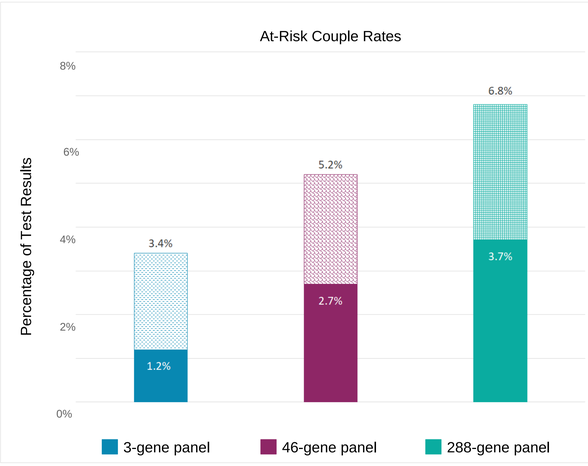


Figure 2: The positive rates for at-risk couples to be at increased reproductive risk based on panel size.



Conclusion

- Amid wide variability in carrier screening utilization and different panels being offered, results of carrier screening will depend greatly on the specific panel and the number of genes included, as well as how variants with variable presentation or reduced penetrance are reported.
- When evaluating a couple’s risk to have a child affected with one of the conditions being screened for, it is important to evaluate the specific variants involved and whether or not that combination really puts the couples at increased risk.
  - In our cohort, ~4% of couples who were tested for the largest panels were found to be at-risk to have a child affected with a classic or severe disorder, although a much larger number of couples may have received positive results.
- Clinicians and patients should be made aware of the potential findings that can come from carrier screening to be able to understand the possible utility of the results obtained prior to the testing being performed.
- Additional information is needed to better understand how patients and providers define clinical utility in carrier screening. This is particularly important in a publicly-funded healthcare system.

Disclosures: All authors are employees and/or 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) Wilson RD. et al. J Obstet Gynaecol Can. 2016 Aug;38(8):742-762.