Title:

A “Minor” Problem: Hereditary Cancer Multi-Gene Panel Testing for Individuals <18

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Description:

Genetic testing for cancer predisposition of individuals under the age of 18 (minors) is discouraged by professional statements, and should only be considered if effective medical interventions are available. At a single commercial laboratory, the majority of hereditary cancer tests ordered for minors have been limited to single site analysis for known familial mutations or single gene/syndrome tests to confirm the diagnosis of disorders that could lead to early intervention or management. However, since 2012 hereditary cancer multi-gene panel (HCMGP) testing has been available commercially to test for multiple hereditary cancer genes simultaneously. Since that time, uptake of HCMGP testing has increased due to improved time and cost-effectiveness and an increase in diagnostic yield compared to single gene testing. In contrast, concerns surrounding HCMGP testing may include higher rates of variants of uncertain significance (VUS) and, specifically for minors, incidental findings that would not lead to altered healthcare management for that child. Here, we describe a cohort of minors tested for HCMGP to identify trends and potential areas of further study.

Methods: We identified 240 minors out of a cohort of >165,000 patients tested with HCMGP at a single commercial laboratory from March 2012 through June 2016. Overall results, including rates of positive (pathogenic or likely pathogenic variants), negative, *MUTYH* heterozygotes and VUS were calculated, along with mutation rates by gene. Affected probands were defined as individuals with a personal history of cancer and/or any colonic polyps. Probands without any clinical history information provided were excluded from analyses involving affected status. A Chi-squared test was used for comparisons.

Results: Out of 240 minors tested, 62 (25.8%) tested positive, including 6 (2.5%) who carried >1 pathogenic or likely pathogenic variant and 7 (2.9%) who also carried at least one VUS. The remaining patients had VUS only (n=41, 17.1%), monoallelic *MUTYH* mutations only (n=2, 0.3%), or were negative (n=135, 56.3%). Of those who tested

positive, 9 (14.5%, 3.8% of total) carried only a gene mutation that would not be considered clinically actionable in individuals under age 18 (*CHEK2*, *ATM* + *MRE11A* contiguous gene deletion, *MSH2*, *BRCA2*, and *APC* p.I1307K). Minors were significantly more likely to test positive on HCMGP compared to probands age 18 or older (8.2%, p <0.0001). Positive rates by gene were highest for *SDHB* (22.1%), *APC* (19.1%), *TP53* (8.8%) and *VHL* (7.4%). In total, 185 (77.1%) minors tested were reported to be affected, 10 (4.2%) were reported to be unaffected, and 45 (18.8%) did not provide a personal or family history. Of affected probands, 51 (27.6%) tested positive, compared to 1 (10%) unaffected proband (not statistically significant, p=0.22). All unaffected minors tested for HCMGP had a family history of early-onset cancer (n=10).

Discussion: Our data suggests that clinicians are utilizing HCMGP testing for minors conservatively. The majority of probands under age 18 who reported personal history information were affected with cancer or polyps. Minors had a significantly higher positive rate, suggesting that clinicians apply a higher pre-test probability of a positive result before considering HCMGP testing for a minor. Further study of this cohort might include retrospective review to determine what society guidelines (if any) were met for genetic testing and if those testing positive met criteria for the genes in which they carry a mutation. Additionally, there are significant genetic counseling implications for this cohort, including: the discussion related to appropriate medical management, if any, for individuals who have unexpected results in genes in which management guidelines typically begin >18 years of age, moderate penetrance gene mutations, and gene mutations that are seemingly unrelated to the personal and/or family history which prompted HCMGP testing. Exploring the motivation for utilization of HCMGP for minors and the impact on their healthcare management is another area of further research that could potentially enhance the utility of such testing.

Keywords:
Genetic Testing

Primary Topic Focus:
Cancer Genetics

Learning Objective 1:	Estimate the likelihood of obtaining an actionable result from testing affected and unaffected minors with a hereditary cancer multi gene panel test.
Learning Objective 2:	Summarize potential testing outcomes from hereditary cancer multi gene panel testing of minors.
Learning Objective 3:	Decide if and when hereditary cancer multi gene panel testing is appropriate to use for minors in the clinic.
Learning Objective 4:	Identify genes that typically have adult onset cancer risk but may have risk for pediatric cancers.