Is Bigger Always Better? An Updated Comparison of Multi-gene Panel Results for Common Cancers

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BACKGROUND

- The increasing popularity of multi-gene panels (MGPs) has fueled debate over which genes should be analyzed.
- MGPs range in size, with varying panel designs tailored to tumor type(s), medical management and/or guideline availability, and the impact on cancer risk of individual gene mutations.

METHODS

- Patients were included if they had a personal diagnosis of breast (BC, N=67, 013), ovarian (OC, N=10,899), non-polyposis colorectal (CRC, N=7,296), or endometrial cancer (EC, N=4,214).
- The positive rate was defined as the percentage of patients with a pathogenic mutation/likely pathogenic variant (VLP), which was compared across several MGPs of increasing size (5-49 genes) for each cancer type.
- Exclusions from positive rate include: *APC* c.3920T>A (p.I1307K), *FH* c.1431_1433dupAAA (p.K477DUP), *VHL* c.598C>T (p.R200W), and all *MUTYH* monoallelic mutations.
- The authors reviewed the literature and determined which genes had associated, published medical management recommendations.

Figure 1: Panels Analyzed

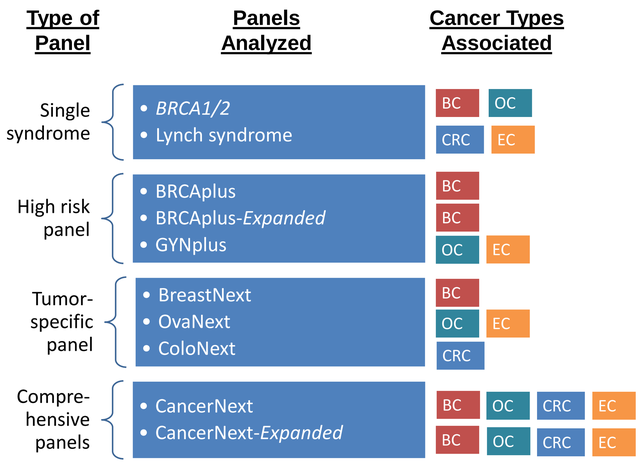


Figure 2: Gene Inclusion

Genes Analyzed on Which Panels

APC	*MSH6*	*BAP1*
ATM	*MUTYH*	*FH*
*BARD1^*	*NBN*	*FLCN*
BRCA1	*NF1*	*MAX*
BRCA2	*PALB2*	*MEN1*
BRIP1	*PMS2*	*MET^*
BMPR1A	*POLD1*	*MITF^*
CDH1	*POLE*	*RET*
CDK4	*PTEN*	*SDHA*
CDKN2A	*RAD50^*	*SDHAF2*
CHEK2	*RAD51C*	*SDHB*
EPCAM	*RAD51D*	*SDHC*
GREM1	*SMAD4*	*SDHD*
MLH1	*SMARCA4^*	*TMEM127*
*MRE11A^*	*STK11*	*TSC1*
MSH2	*TP53*	*TSC2*
		VHL

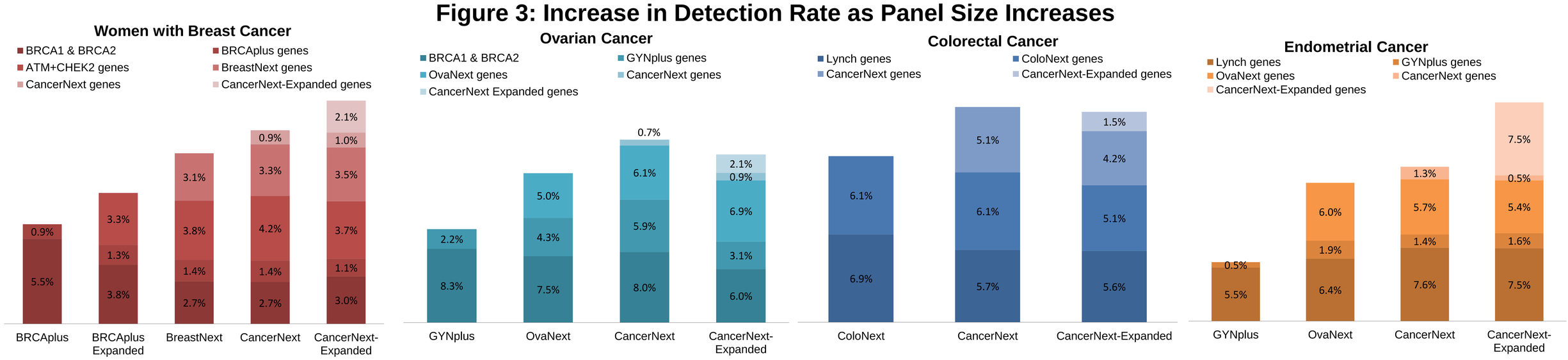
Key
- CancerNext-*Expanded*
- CancerNext
- OvaNext
- BreastNext
- ColoNext
- GYNplus
- BRCAplus-*Expanded*
- BRCAplus

^No identified management recommendations in the literature

RESULTS

- As MGP gene content increased, the positive rate increased in patients with BC (6.2%-11.3%), CRC (9.7%-13.5%), and EC (7.9-16.1%).
- OC patients showed a similar trend in positive rates increasing as panel size increased, however the highest overall diagnostic rate was seen in the second-largest panel.
- The highest positive rates in EC and CRC patients on all panels were in the Lynch syndrome genes.
- BC patients were more likely to have a mutation in *ATM* or *CHEK2* than in *BRCA1/2*.
- Out of all positive results, 6.8% of mutations were in genes without published management recommendations.

Figure 3: Increase in Detection Rate as Panel Size Increases



Explanation of Figure 3: The X Axes indicate which test was ordered. The individual shading in each bar graph represent the percentage of results where mutations were found in genes within a condition(s), or are included on specific panel types.

Figure 4: Majority of Mutations are in Genes with Published Management Recommendations

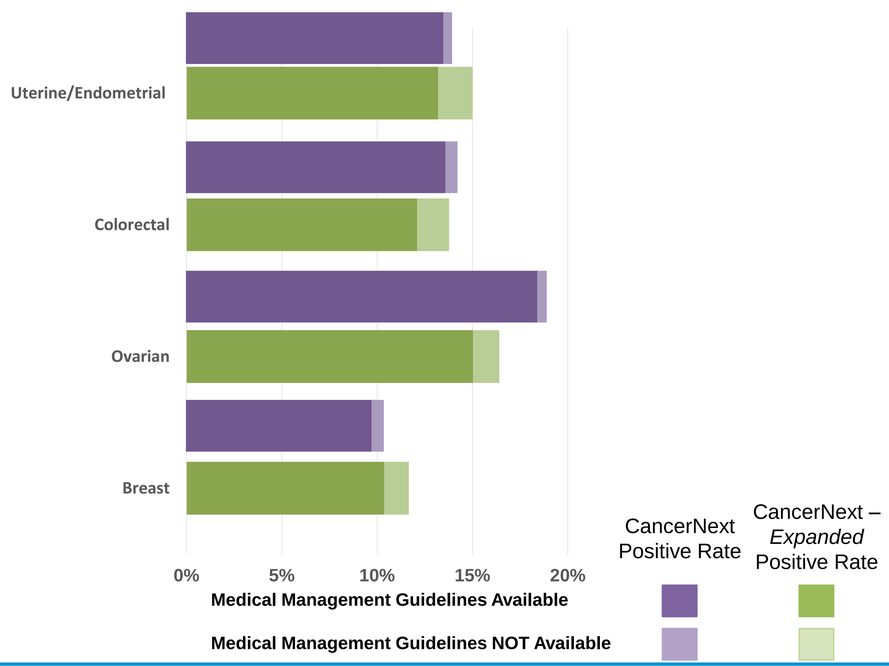
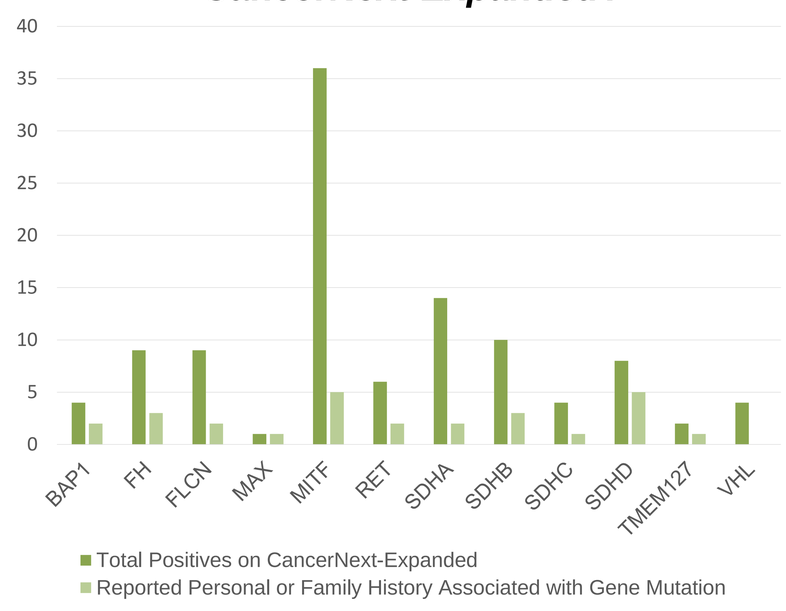


Figure 5: Does Personal and Family History Correspond to Positive Results on CancerNext-*Expanded*?



TAKE-HOME POINTS

- In the majority of cases, larger MGPs yielded an increasingly higher diagnostic rate than smaller MGPs.
- Incidental findings unrelated to the proband's phenotype were detected, though most were clinically actionable.
- More than 93% of all VLPs and mutations (2% of all results) were found in genes with published management recommendations, providing the clinician with next steps for how to manage a patient and their family.
- Further research is needed to determine the point at which maximal clinical utility of MGPs is achieved, and additional analyses regarding how factors such as family history and additional primary cancers impact panel selection and diagnostic rate are in progress.

LIMITATIONS

- Personal and family history details were limited to what the clinician provided on the test order.
- The determination of which genes have medical management guidelines was made by a small consensus regarding the availability of published literature suggesting management interventions and/or published consensus guidelines.
- Ordering providers determined which panel was most appropriate; there was no randomization.

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