Poster CAN082

Implementation and Outcomes of Standardized Germline Flagging for Potential Germline Alterations in Oncology NGS Testing

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NSGC Annual Conference
Seattle, WA | November 6-10, 2025

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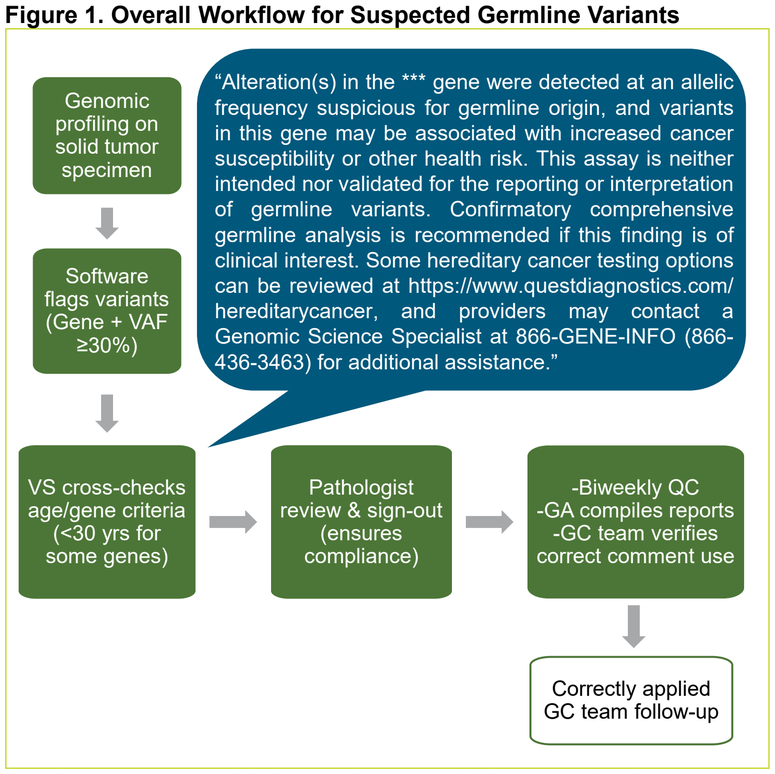
Background

- Solid tumor genomic profiling (STGP) is a tool used to help guide treatment decisions, determine clinical trial eligibility, and inform prognosis for patients with cancer.
- STGP may incidentally identify variants of potential germline origin. Consensus guidelines for laboratories do not indicate when to flag such variants with a report comment. Therefore, practices for reporting and following up with clients may not be ideally standardized.
- At this large reference laboratory, a team of genetic counselors (GCs) and key stakeholders implemented a pilot program to better standardize this process with a goal of improving patient outcomes by increasing provider awareness of these suspected variants. This study examines the implementation process and initial outcome data.

Methods

- A group of molecular pathologists, variant scientists, and genetic counselors collaborated to review available guidelines (NCCN, ASCO, ESMO, CAP, WHO) and draft a list of genes for which germline testing is recommended as follow-up to STGP when a variant is detected. A workflow and standard report comment were created to flag potential germline variants (**Figure 1**).
- Variants are flagged when the allele frequency is above 30% in genes with known germline implications (57 genes total), with 7 of these genes having an age qualifier of under 30 years.
- GCs reviewed flagged reports from STGP panels of >500 genes and 49 genes. Clinical judgment was applied to determine if ordering provider (OP) contact is indicated (**Figure 2**).
- The number of tests performed, reports with a suspected germline comment, cases called by the GC team, and cases where the OP was successfully reached were identified. Related germline test orders and results were then reviewed periodically by the GC team to determine the outcome of germline testing and efficacy of the pilot project.

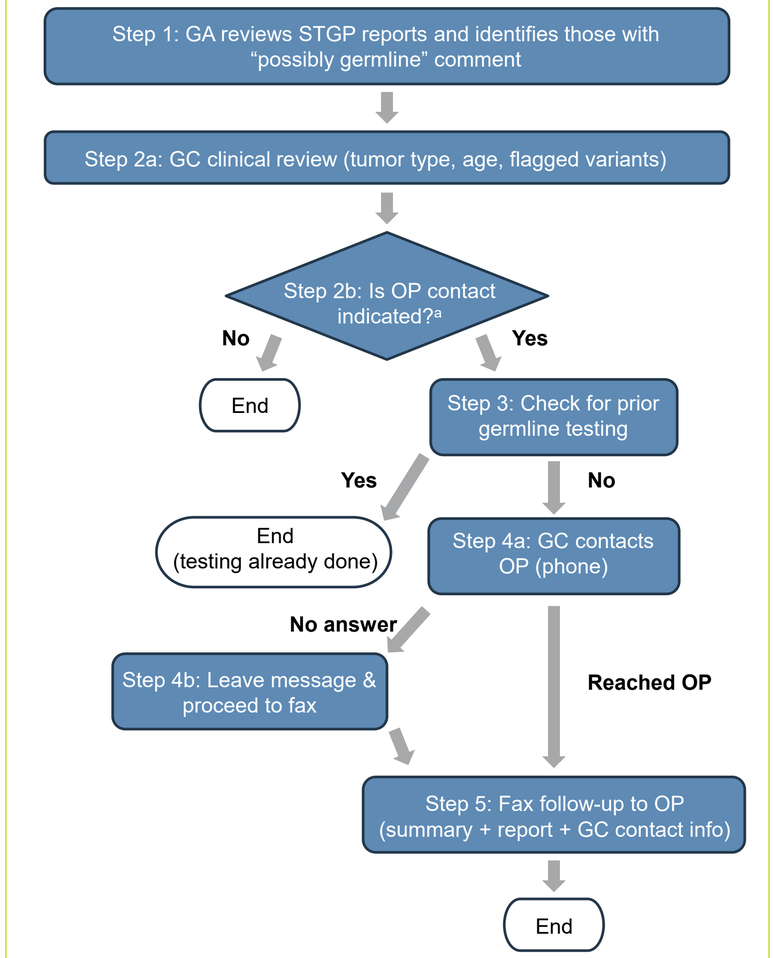
Figure 1. Overall Workflow for Suspected Germline Variants



GA, Genetic Assistant, GC, Genetic Counselor; VAF, variant allele frequency; VS, Variant Scientist.

Methods (continued)

Figure 2. GC Follow-Up Process for Flagged Variants



GA, Genetic Assistant; GC, Genetic Counselor; OP, ordering provider; STGP, solid tumor genomic profiling.
[a] Initiation of OP contact considered the following:
- Cases did not receive OP contact if the flagged gene was syndromic and identified in an elderly patient because the variant is likely somatic.
- Cases did not receive OP contact if the flagged gene is associated only with autosomal recessive phenotypes.
- If the flagged gene is not known to be associated with the tumor type in the germline setting, then a cross-check with ClinVar was performed to determine if the variant has been reported as pathogenic/likely pathogenic in the germline setting. If the variant is reported as a VUS or benign/likely benign, the OP was not contacted.

Results

- During the study period, 2,122 STGP tests were performed. Of these, 241 (11.4%) reports included the potential germline comment.
- After clinical review, the GC team called the provider in 142 cases (6.7% of total tests, 58.9% of tests with comment) and reached them in 119 cases.
  - Among the 142 reports, 165 variants of possible germline origin were flagged. The most commonly flagged genes were *BRCA2*, *ATM*, and *BRCA1* (**Table**).
- Eleven patients were known to have germline testing ordered prior to contact, including 9 with testing ordered at this laboratory.
  - Six tested positive for the variant identified on STGP, 2 had limited testing that did not include the variant identified on STGP, and 2 orders were received for prior authorization without a specimen.
- Five patients had follow-up germline testing after contact including 4 with testing ordered at this laboratory: 1 tested positive and 4 tested negative for the suspected variant.

Results (continued)

Table. Number of Flagged Variants by Gene

Gene	n	Gene	n	Gene	n	Gene	n
BRCA2	23	*MUTYH*	6	*SMAD3*	2	*SDHB*	1
BRCA1	18	*TP53*	5	*DICER1*	2	*SMARCA4*	1
ATM	16	*RET*	5	*MEN1*	2	*BARD1*	1
BAP1	8	*TSC1*	5	*APC*	1	*MSH2*	1
STK11	8	*MLH1*	4	*BRIP1*	1	*SMARCB1*	1
SMAD4	7	*PALB2*	4	*FH*	1	*TGFBR1*	1
VHL	7	*POLE*	3	*PMS2*	1	*WT1*	1
CDH1	7	*NF2*	3	*PTEN*	1		
NF1	6	*PTCH1*	2	*RAD51C*	1		
CHEK2	6	*TGFBR2*	2	*RAD51D*	1	**TOTAL**	**165**

Conclusions

- This pilot program implemented a standardized workflow for reporting and contacting clients about potential germline variants following STGP.
- Challenges included manual addition and review of the reporting comment and thorough case review to determine if OP contact was warranted due to the algorithm not accommodating every scenario. In addition, OPs were often not the most appropriate provider to facilitate additional germline testing. Obtaining contact information for the patient's oncologist, who would be a more appropriate provider, was not always possible.
- Ongoing changes to the process include updating genes of interest based on evolving guidelines, the creation and implementation of a standard fax as a second means of client communication, tailoring communication for high volume clients, and implementing case reviews to identify cases that did not need OP contact. Clinical judgement, group discussion, and ClinVar review are now used to determine if an OP is contacted.
- Limitations include small sample size and limited follow-up, which made it difficult to quantify the success of this pilot program.
- Program implementation is iterative and requires collaboration and buy-in from various stakeholders. Laboratory GCs were critical in implementing this pilot program and are well-positioned to connect OPs and the laboratory for optimal patient care.

Acknowledgments

The authors would like to acknowledge Diana Tully, Michele Basiliere, and Gina Donnini for their involvement with this pilot project, and Terra White for creating this poster.

Disclosure

All authors are employees of Quest Diagnostics.