Navigating from Somatic Tumor Testing to Germline Genetic Testing

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Somatic Testing vs. Germline Testing

• **Somatic**
  - Identifies mutations in the tumor (ie. acquired changes)
  - Performed on tumor tissue
  - Patient has cancer
  - Purpose is to identify treatment options, determine prognosis
  - Ordered by oncologist
  - Patient not often consented

• **Germline**
  - Identifies mutations in the germline (ie. mutations you are born with)
  - Performed on blood/saliva
  - Patient may be unaffected
  - Purpose is to identify patients with inherited cancer predisposition syndromes
  - Often ordered by GC, sometimes by oncologist, surgeon, PCP, etc.
  - Patient often receives counseling
What genes are analyzed?

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Genes in gray are the 94 included in the Hematologic Cancer Panel.
ASCO supports the communication to patients of medically relevant incidental germline findings from somatic mutation profiling conducted in the clinical setting. Oncology providers should communicate the potential for incidental and secondary germline information to patients before conducting somatic mutation profiling and should review the potential benefits, limitations, and risks before testing.
NGS offers promise, but poses significant challenges for oncologists who are ill prepared to handle incidental findings that have clinical implications for at-risk family members. This report underscores the need for oncologists to develop a framework for pre- and post-communication of risks to patients undergoing routine tumor-only sequencing.
### Table 3. Recommendations for screening and genetic counseling based on pre- and post-NGS probability risk

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<th>Risk group based on Pre-NGS probability</th>
<th>Description of Pre-NGS groups</th>
<th>Recommendations to the oncologist before/after ordering NGS</th>
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| High                                   | • Strong family or personal history of malignancy, per current tumor-specific genetic counseling guidelines  
• Ashkenazi Jewish heritage            | • Emphasize the implications of NGS testing, including the possibility of identifying a somatic mutation that would be suspicious for germline potential.  
• **Prior to testing:** ask the patient about their preferences regarding disclosure of this information.  
• **Prior to obtaining NGS results:** strongly consider referral to a genetic counselor. |
| Intermediate                           | • May have family history of malignancy or other high risk features (e.g. very early age at diagnosis), but does not meet current guidelines for referral to genetic counseling/testing. | • Discuss the implications of NGS testing and the possibility of identifying a somatic mutation that would be suspicious for germline potential.  
• **Prior to testing:** ask the patient about their preferences regarding disclosure of this information.  
• **After NGS testing:** Use post-NGS risk to determine whether referral to genetic counselor and germline testing is warranted.  
• When in doubt, discuss the case with a genetic counselor to clarify whether referral is recommended. |
| Low                                    | • Unimpressive family history (either no known history of malignancy or remote, isolated cases) | • Briefly mention the implications of NGS testing and the rare possibility of identifying a somatic mutation that would be suspicious for germline potential.  
• **Prior to testing:** Ask the patient about their preferences regarding disclosure of this information.  
• **After NGS testing:** Use post-NGS risk to determine whether referral to genetic counselor and germline testing is warranted.  
• When in doubt, discuss the case with a genetic counselor to clarify whether referral is recommended. |

Abbreviation: NGS, next generation sequencing of tumor tissue.
How often are germline findings identified in tumor?

• Meric-Bernstam et al. (2016)
  - 1000 advanced cancer patients offered tumor-normal sequencing with 202-gene panel (19 clinically actionable in germline) at MD Anderson
  - 422/100 (42%) had pathogenic somatic variant in one of 19 genes
  - 43/1000 (4.3%) had a likely pathogenic germline variant identified
  - Tumor types included breast, colon, brain, melanoma, sarcoma, ovary, head and neck

• Schrader et al. (2016)
  - 1566 advanced cancer patients offered tumor-normal sequencing with MSK-IMPACT panel (341-gene panel)
  - 198/1566 (12.6%) had pathogenic germline variant in cancer susceptibility gene
  - Germline findings concordant with cancer type in only 81/198 (40.9%) cases

• Seifert et al. (2016)
  - 439 unselected cancer patients offered tumor-normal sequencing of 247 genes (36 genes strongly associated with hereditary cancer) at UNC
  - 19/439 (4.3%) had pathogenic germline variant
  - 12/19 (63%) were concordant with cancer type
Percentage of Somatic vs. Germline Variants

Meric-Bernstam et al.
Suggestive of Germline Finding

- All BRCA1 and BRCA2 pathogenic variants regardless of tumor type (NCCN guideline)
- Founder mutations (ie. MSH2 exon 1-6 deletion, TP53 R337H)
- Uncommonly somatically mutated genes (ie. CHEK2, PALB2)
- Gene consistent with phenotype
- Same mutation detected in multiple primary tumors
- Underlying mutation pattern (ie. hypermutated tumor)
- High mutant allele frequency (MAF)
Mutant Allele Frequency

- Mutant allele frequency (MAF) can be suggestive of a germline mutation
- MAF >50% suggest loss of heterozygosity (LOH)
- Germline mutations in tumor suppressor genes often undergo LOH events
- High MAF also seen in normal course of tumor development without a germline mutation
Do not use MAF to rule OUT a germline mutation!
Refer If Tumor Testing Is Normal?

• Regardless of tumor results, if the patient meets criteria for germline testing (NCCN guidelines), REFER!
  • Large deletion in somatic can mask germline point mutation
  • Somatic vs. germline labs cover different areas of the genes
  • Pathogenic variant in germline may not be considered pathogenic in somatic, therefore not reported
  • Not all hereditary cancer genes are on tumor panels
Considerations for incidental findings

- Insurance coverage
- Single-site vs. full panel
- Patients confused about germline vs. somatic testing
- Patient previously declined counseling/testing
- Sick patients
  - Need to be seen relatively quickly
  - May not directly impact patient
  - Who do we disclose results to?
Questions or want to refer a patient?

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