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# GERMLINE INSIGHTS FROM NGS SOMATIC TESTING: CLINICAL CHALLENGES AND CONTROVERSIES

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# GERMLINE INSIGHTS FROM NGS SOMATIC TESTING:
## CLINICAL CHALLENGES AND CONTROVERSIES

This GenomeWeb report is based on a virtual roundtable that discussed challenges, opportunities, and controversies related to informing clinicians, cancer patients, and their families of potential germline insights after receiving somatic testing.

With the increasing use of next-generation sequencing tumor panels, labs are detecting variants that may be germline rather than somatic. Germline variants are informative for patients and their families in assessing future cancer risk, as well as treatment. However, since the goal of somatic testing is to identify molecular features of tumors that may be targeted by treatments, presumed germline findings in this context may be unexpected for patients and their doctors, and oncologists may not be prepared to address the clinical significance of such findings.

Moreover, within the lab industry, there isn't a standardized way of reporting germline findings from tumor testing, and every lab currently handles this differently.

Given this context, GenomeWeb hosted an online panel, representing stakeholders in oncology, molecular pathology, and genetic counseling, who discussed a range of issues related to a hypothetical case example in which a tumor sequencing panel revealed a pathogenic germline variant.

This report is a written summary of the panel discussion. The first part, pages 1-5, summarizes key points made by the panelists in the roundtable. The second part, pages 5-8, is a transcript of a live audience question-and-answer session that followed the roundtable.

### CASE EXAMPLE AND INTERPRETATION

Ellen Matloff, President and CEO of My Gene Counsel and the moderator for the discussion, kicked off the roundtable by introducing the case example:

**A 42-year-old patient of European, non-Jewish ancestry is diagnosed with a stage IIIA - T3N1M0 left lower lobe adenocarcinoma of the lung. She is a non-smoker and has no known personal or family history of lung or other cancers, although her knowledge of her paternal history is limited. Panel-based NGS testing is ordered and reveals a pathogenic *BRCA1* variant with a variant allele frequency (VAF) of 52 percent.**

**The patient and her husband have two teenage sons and no daughters. The patient has two sisters, ages 37 and 43, who have no history of cancer. The patient and her husband are distraught by her lung cancer diagnosis and the fact that her husband lost his job as a result of pandemic layoffs.**

**The oncologist weighs the pros and cons in this case and decides that bringing up genetic counseling and testing is not worthwhile since the family already has so much on their plate, they only have sons, and the family history is not suspicious for a germline pathogenic *BRCA1* variant.**

Jonathan Nowak, Assistant Professor of Pathology at Brigham and Women's Hospital, provided an overview of the pathology and sequencing results for the case and discussed how the germline variant was identified.

**MODERATOR:**

**ELLEN MATLOFF, MS, CGC**

President and CEO, My Gene Counsel

**PANELIST:**

**JILLIANE SOTELO, MS, CGC**

IMPACT Program Navigator and Corporate Wellbeing Champion Leader, Thermo Fisher Scientific

**PANELIST:**

**VEDA GIRI, MD**

Associate Professor of Medical Oncology, Cancer Biology & Urology, Sidney Kimmel Cancer Center, Thomas Jefferson University

**PANELIST:**

**DANIEL SILVER, MD, PhD**

Associate Professor of Medical Oncology and Cancer Biology, Thomas Jefferson University

**PANELIST:**

**JONATHAN NOWAK, MD, PhD**

Assistant Professor of Pathology, Brigham and Women's Hospital

He noted that whenever molecular assays are performed using tumor tissue, the pathologist usually marks the best region for DNA isolation on the glass slide. This ensures that DNA is isolated from the correct region and also provides the opportunity to estimate the percent tumor content. Furthermore, "this information is often quite helpful for interpreting the molecular results themselves," he said.

Nowak walked through the sequencing results for the somatic assay in detail (*see below*).

**LUNG ADENOCARCINOMA SEQUENCING RESULTS (HYPOTHETICAL)***

**Sequencing QC Metrics:** Pass
**Estimated tumor content:** 40%

**Tumor Mutational Burden/megabase**: 4.8
(This is higher than 23% of all non-small cell lung cancers sequenced by this assay)

**Mismatch Repair Status:** Proficient (MSS)

**Tier 1 variants:**
EGFR c.2236_2248delGAATTAAGAGAAGinsGAAC (p.L747_A750delinsP), exon 19 - in 34% of 468 reads

**Tier 2 variants:**
BRCA1 c.5202delC (p.F1734Lfs*31), exon 19 - in 52% of 345 reads

**Tier 3 variants:**
KMT2A c.10369C>T (p.Q3457*), exon 27 - in 14% of 666 reads
SMAD4 c.1082G>A (p.R361H), exon 9 - in 27% of 228 reads
TP53 c.742C>T (p.R248W), exon 7 - in 38% of 311 reads

**Tier 4 variants:**
ERCC6 c.2750G>T (p.G917V), exon 15 - in 47% of 408 reads
IL7R c.769G>T (p.V257F), exon 6 - in 11% of 846 reads
NTRK1 c.1621G>T (p.V541L), exon 13 - in 33% of 329 reads
SETBP1 c.4577C>A (p.P1526Q), exon 6 - in 48% of 25 reads

*Data in red sheds light on germline versus somatic origin for variants

He noted that Brigham and Women's Hospital, like most institutions, classifies somatic variants into different tiers depending upon their overall diagnostic, prognostic, and predictive value for response to therapy.

Nowak emphasized that tiering guidelines for somatic interpretation, such as the joint guidelines from the Association for Molecular Pathology, the American Society of Clinical Oncology, and the College of American Pathologists, are "very different" from the American College of Genetics and Genomics guidelines for germline variant classification, "not only in terms of their intended use, but also the way those guidelines are structured and the evidence base that they draw from."

In addition, he said, "while somatic guidelines do offer some advice for how to report potential germline variants, this can be often very difficult to put into practice in the case of somatic-only sequencing." In this particular case, he noted, an in-frame deletion in exon 19 is present and is in Tier 1 because it is predictive of response to a Food and Drug Administration-approved EGFR inhibitor.

Nowak said that the *BRCA1* frameshift mutation mentioned in the case example is classified in Tier 2 "due to suspicion on the part of the molecular pathologist that this variant in *BRCA1*, which is a gene that's known to be recurrently mutated in lung cancer, is actually germline in origin."

There were a number of factors that led to this suspicion. In addition to the fact that such variants are unusual in lung adenocarcinoma, other individual pieces of data in this case led to this interpretation (*highlighted in left table in red*).

For example, Nowak said, the *BRCA1* variant is present at an allele fraction near 50 percent, which is consistent with the germline origin, "and, of course, a frameshift alteration will be expected to be pathogenic in this case." This, along with characteristics of the *SMAD 4* mutation, the *P53* mutation, and other factors, provide "a moderate level of evidence for a *BRCA1* mutation being germline in origin and illustrate some of the challenges in relying just upon a variant allele fraction without the overall picture of the case for making such calls."

He stressed, however, that "we cannot tell for sure, with somatic-only testing, whether a variant is truly germline in origin or not, and not all cases are as apparent as this one."

Another challenge, Nowak noted, "is that different laboratories often take very different approaches to the level of detail and context provided in their reports."

For example, one lab may provide a report in which the *BRCA1* result is completely suppressed or absent; another may report the variant, but with limited information on variant allele fraction or tumor cellularity; and a third lab may report the variant along with additional contextual features, such as the allele fraction and the estimated tumor content.

## DISCUSSION OF THE CASE

Matloff posed some questions to the panelists regarding the case example. She first asked about the implications of this possible germline insight for this patient's care, as well as her family members.

Veda Giri, Associate Professor of Medical Oncology at the Sidney Kimmel Cancer Center, highlighted that germline variants that are identified via tumor NGS sequencing can inform therapeutic decision-making for the patient as well as hereditary cancer risk for patients and their families.

Based on current estimates, which are changing rapidly as new data becomes available, "actionable pathogenic germline variants range from 5 percent to … 17 percent, depending on the population and genes," Giri said.

She added that the National Comprehensive Cancer Network Guidelines now include guidance regarding tumor and germline testing[1]. In particular, this guidance states that if a pathogenic mutation or variant is reported on tumor testing, then confirmatory germline testing is needed when there is "reasonable clinical suspicion," typically based upon the patient's clinical features, family history, or allele frequency.

These guidelines note that the classification of variants can differ between tumors and germline. "So, for example, a tumor variant might be classified as a variant of uncertain significance, or VUS, whereas in the germline, that same variant could be classified as pathogenic or likely pathogenic," Giri said. "Therefore, germline testing may still be indicated if there is a VUS reported on tumor testing based on clinical suspicion."

As a result, "oncologists and other providers who are ordering tumor NGS testing really need to start developing a working knowledge of the clinical and family history features that might be suggestive of hereditary cancers."

In terms of implications for the patient's care in the *BRCA1* case example, Giri discussed two strategies for making a decision on germline testing: a generalized approach, which would perform paired tumor-germline testing automatically, and a targeted approach that would be more to assess suspicion for germline mutations *(see below)*.

| Strategies | Pros | Considerations |
|---|---|---|
| Generalized approach: Paired tumor-germline testing | Streamlined testing at one visit<br><br>Reduces need for processes involved in determination of suspicion of germline mutation<br><br>Reduces risk of missing germline mutation | May not be covered by insurance<br><br>Patient may not want to know hereditary cancer information<br><br>Adds time to clinical encounter to fully discuss germline testing and perform informed consent for germline testing |
| Targeted approach: Assess suspicion for germline mutation | Targeted use of resources and staff to those patients with highest suspicion of germline mutation<br><br>Truncated pretest informed consent regarding potential of germline findings | Need to gather further data: VAF, family history, founder mutations<br><br>Family history and VAF may not be provided or known by patient<br><br>May miss germline mutations |

In the example of the patient with the *BRCA1* pathogenic variant, the next step would be confirmatory germline testing, Giri said. If she is found to be germline positive for the *BRCA1* mutation, then there are several cancer risks to consider. "One of the things to keep in mind when addressing these cancer risks in a patient population with advanced or metastatic cancer is to think about the long-term outcomes and to perhaps prioritize some of these cancer risk discussions," she said. "However, if there are good chances for long-term survival, then it would be important to really discuss these cancer risks in detail."

For example, the patient may have heightened risk for breast cancer, in which she may need to consider a risk-reducing mastectomy or more frequent screening with breast MRI and mammogram. Similar considerations would come into play for heightened risk for ovarian cancer or pancreatic cancer.

There are also implications for blood relatives, who, in this case, would be tested for a familial *BRCA1* mutation. If any of those relatives are found to be positive for a germline *BRCA1* mutation, "there could be implications for males as well as females in these families," Giri said.

In the case example, the patient has only sons, but "there still would be cancer risk recommendations if any of them were found to be *BRCA1* carriers," such as breast self-examination or clinical breast examination starting at age 35, because of the increased risk of male breast cancer.

For the patient's sisters, "if any of them were found to be *BRCA1* positive, the recommendations would be to consider risk-reducing mastectomy or heightening cancer screening with breast MRI and mammogram and to also consider risk-reducing salpingo-oophorectomy."

Jilliane Sotelo of Thermo Fisher Scientific shared some specific strategies for discussing the testing results with the patient.

Her first recommendation was to check the patient's somatic test consent form. "What is the baseline knowledge about this possibility that the patient went into their testing with? Were there guidelines outlined in the document about the possibility of an incidental germline finding? Was there any kind of opt-in or opt-out signature required? Or maybe there is no information provided," she said.

This information indicates whether the patient was interested in learning about germline changes and "gives you a baseline for what their reaction may be," Sotelo said.

An important consideration is the patient's right to know, she added. "You should inform the patient there was a finding that may inform future cancer risks for themselves and family and allow them to identify whether or not they would like to have this information."

In addition, "it's important to explain the differences between inherited and tumor DNA. This is something that patients are very, very confused about," Sotelo said. Patients should learn about what cancers they or their family members may be at risk for, as well as general information about inheritance.

It's also important to explain whether there will be a change to treatment of the current cancer based on the germline information. For example, the patient may be eligible for a PARP inhibitor based on the *BRCA1* variant.

Sotelo said that patients should also be informed of next steps for germline confirmation and what to expect in terms of testing and the return of results. "If you're going to refer to a genetics professional, what does that referral look like? What's the possible timeline? Who will be contacting them to make that appointment? What might that visit look like?"

Documentation is another important factor, Sotelo said. "In addition to including the consent information in your consult notes, you also should include your plan in your consult note and very specific information about what was identified in the somatic test results." She noted that somatic test results are not always included in an electronic medical record, which "makes it very challenging for a genetics professional outside of your institution to find a copy of this test result."

The panel also discussed what tools might be needed to better support labs and clinicians who want to responsibly uncover and act on incidentally detected germline findings.

Daniel Silver of Thomas Jefferson University noted that it's often difficult for the clinician to understand whether the somatic tumor report includes a pathogenic germline variant. "Some reports completely bury this information, and some make it hard for a typical clinical to ferret it out."

One reason for this, he said, is that tumor sequencing labs "view their primary duty to deliver a report that captures actionable mutations in a patient's tumor." Their main concern is treating the current cancer and they are often "not set up to meet regulatory requirements to deliver germline sequencing results," Silver said.

In addition, consent documents "often omit the possibility of germline implications," he said.

In Silver's view, there should be more standardization in somatic tumor test reporting. "I think, like in most aspects of medicine, if we're going to make a mistake, we should err on the side of providing more information, not less. I think reports should probably routinely include estimate of tumor cellularity and allele frequency and these are not commonly reported in a number of commercial endeavors," he said.

He also recommended that somatic tumor test reports include sections with cautionary language, such as, "Possible germline mutation; consider confirmatory germline testing if clinically indicated."

If germline mutations are filtered out and not reported, "this should be clearly stated in the report and not left unsaid so the clinician, at least, is aware that there may be findings that aren't reflected at all in the report," Silver said.

In lieu of such standardization, Silver said that practicing clinicians should "build collaborations proactively with genetics counselors" and to engage molecular tumor boards "to provide expertise that individual clinicians my not have."

He added that clinicians should become familiar with their organization's lab of choice for somatic testing "and what their reports give you regarding germline findings and what their practices are."

## AUDIENCE QUESTIONS

*(Panelist responses have been edited for clarity and length)*

### Was germline DNA available for testing for the case you discussed? And is it possible to recognize germline mutations from the tumor sample without the analysis of any blood samples?

**Ellen Matloff:** Let's keep in mind that this was a hypothetical case. No, a blood sample was not available in this case for germline testing. Let's also remember that although we can get insights about germline mutations from somatic testing, that is not the purpose of somatic testing. So getting a definitive result on a germline finding from a somatic test is not something we should count on. That's not what that test is intended for.

### Would you consider the *BRCA1* result as an incidental finding; and would not reporting it constitute a medical liability issue?

**Daniel Silver:** I am not a lawyer and so I can't comment on liability issues. But I do have those concerns. Yes, I think it is an incidental finding. I think that there are different kinds of incidental findings. If you do a CT scan for a back problem and you find a mass, that is a simple incidental finding.

But these are much more subtle. The labs in general that do somatic tumor testing aren't set up to precisely find germline mutations and they don't necessarily have the expertise and haven't thought about germline mutations to nearly the same degree as the professional germline sequencing labs.

In my own view, I think it is a great disservice to bury the potential of a germline finding, a great disservice to the family and to the patient. But it's complicated, and I realize that there are potential regulatory and other issues that the labs must contend with, so I think it makes it a little more complicated. Nonetheless, a number of labs are beginning to make their reports a little more transparent.

**Veda Giri:** I completely agree with you, Dan. I think that this would be viewed as an incidental finding, but this is a very important incidental finding. The gravity of this particular finding, and following up with confirmatory germline testing, has huge implications for this patient. We certainly see it in patients who have [a good chance of] long-term survival from their current cancer and could develop a second cancer that would have

been attributed to a germline mutation. Also, of course, there are implications for family members.

So these findings, actually one family at a time, have population-level impact. I think what we're finding from even the recent reports at [the annual meeting of the American Society of Clinical Oncology] is that this is not an insignificant percentage of the cancer population.

So I think that, just as you said, Dan, it would be extremely important to start to think of standardizing ways for somatic testing to start to address the potential of germline findings and to make that understandable to clinicians who are ordering these tests.

### When a germline mutation is identified from tumor testing, which genes would you consider follow-on germline testing for?

**Jonathan Nowak:** That's a great question and it's not always straightforward to answer. What I can do is provide a little bit of context from the panel that we actually used here. So our current [next-generation sequencing] panel targets about 450 genes and we use it for a wide variety of solid tumor types. If you take that total set of genes that are thought to be important for solid tumors, about 150 of those actually have some degree of evidence for being involved in hereditary cancer predisposition.

There's probably another set of genes that are involved in hereditary disorders that don't relate to cancer, but that means that about every third gene that you have that has a mutation in it is one where there could potentially be some association with hereditary cancer. So you can make a list if you would like about genes that you should focus on a little bit more, but that list ends up being pretty large and it's often the genes that are most commonly altered purely in a somatic setting as well for tumors.

One of the tumor types that I work on very frequently is colon cancer. One of the best examples I can share is *APC* mutations in colon cancer. Those are some of the most common kinds of founder driver alterations in the somatic setting that give rise to colon cancer. But once in a blue moon, you'll have a patient with a germline *APC* alteration that has [familial adenomatous polyposis].

So, if you take each of those individual mutations, 99.9 percent of the time they're going to be somatic in origin and that's kind of how colon cancer works, but occasionally they will be germline. That is a little bit illustrative of some of the challenges in having hard rules for individual genes and individual variants that say whenever you see this, you're going to raise a flag and automatically reflex to germline testing.

It's really, at the end of the day, dependent on the particular tumor type that you're looking at. In this case, we had a lung cancer with a *BRCA1* alteration that was just not really a gene that's very commonly altered in lung cancer, which is extremely helpful. Also really importantly, [we had] a composition of the specimen in terms of tumor content and chromosomal changes that highlighted that *BRCA1* is probably germline in origin as opposed to somatic. It's hard to move beyond a case-by-case level for that sort of interpretation.

### Would you suggest follow-up germline testing for pathogenic, likely pathogenic, and variants of unknown significance (VUS) found in clinically relevant genes on the tumor?

**Jonathan Nowak:** There's kind of two parts to that. The first is that the genes that are found in the tumor, unless you can make the specific effort to ask how they would classified in the germline setting, won't even necessarily fall into those three categorizations. We can look at a *BRCA1* frameshift alteration and say, "Yes, that would be pathogenic most likely in the germline setting" without lot of effort.

However, to know that something would be formally a variant of uncertain significance in the germline setting, it often takes a significant amount of effort to arrive at that classification and that's not something that most labs that are reporting somatic variants are really structured to do. So, you may not even really know that something is a germline VUS in order to make a decision about confirming it or not.

I think in practice for the cases that come through our laboratory, clinicians are usually most interested in confirming pathogenic and likely pathogenic variants. Perhaps where there's a strong clinical suspicion for a variant, a VUS might be confirmed. But if you were to go to that threshold, you would probably end up doing confirmatory germline testing on many or most patients that receive somatic sequencing.

**Veda Giri:** I can add here too that it might be important to also consider the cancer type, because we know that criteria-free testing is rising in terms of NCCN guideline recommendations. So, for example, ovarian cancer patients are recommended to have germline testing across the board. Pancreatic cancer patients now, metastatic prostate cancer patients. So, thinking clinically about factoring in the type of cancer, whether that would automatically signify in your practice confirmatory germline testing based on the genes, and also knowing that there are blanket NCCN guidelines for some of those cancer types, is important to also keep in mind.

**Jonathan Nowak:** That's an excellent point. I would just say, in day-to-day practice, that it's personally almost a bit of relief to me as a molecular pathologist knowing that for some of our tumor types those patients are getting blanket germline testing upfront. It doesn't make you relax, but it makes you a little bit less worried that something that's important is not going to be missed and you're free to focus your somatic interpretation on things that are truly somatic while knowing that that patient is going to get the needed and very solid germline analysis that's indicated for the particular tumor they have.

**Daniel Silver:** I just wanted to add that there are a number of other clinical variables and molecular variables that would add to suspicion in individual cases, and there are ways to whittle down that list of 100-and-some-odd possible important germline variants. Further, there are only a small number of germline inherited mutations that are clinically actionable at the moment, so it's important to be more practical about this.

In the example that Jonathan gave of an *APC* mutation, the surgeon and the medical oncologist involved wouldn't know whether that patient had innumerable other polyps clinically. So that usually sorts itself out in a clinical way. There are other indications, as Jonathan so nicely set out, based on tumor cellularity, allele frequencies, and so one, where one could ratchet up or down one's index of suspicion. I have absolutely no problem with somatic sequencing entities couching any suggestions in very cautious terms.: "Consider if clinically indicated," for example.

**Jilliane Sotelo:** Dan, you make such a good point about using clinical discretion. I also think that it needs to be mentioned that we are talking about, in this case, the incidental finding of a possible germline alteration. Just because you don't see anything on a somatic report in a particular gene that a patient's family history and personal history is pointing to, doesn't mean that you shouldn't pursue germline testing. Somatic testing, even in that regard, is not a proxy for germline analysis.

There are a lot of reasons that a germline mutation may not be reported that have nothing to do with lab error and that have nothing to do with that lab's particular reporting policy, but have a lot to do with the unstructured nature of tumor genomes. So I think that not tossing clinical discussion aside is really, really important when looking at these results.

**Ellen Matloff:** Agreed. I'd like to piggyback on what Jilliane said and just talk about this specific case. This is a young woman with lung cancer and no known family history of breast, ovarian, pancreatic, or prostate cancer and yet still she still was a good candidate for genetic counseling and testing because of that *BRCA1* finding in her tumor.

So, if we have a finding like this, we have NCCN guidelines that say if you find a *BRCA1* or *BRCA2* finding, genetic counseling should be recommended. I purposely in this case said she had no daughters because I have heard people say, "Well, there'd be no reason to offer testing because there are no daughters." I think we can all be clear that that's not a valid reason to skip genetic counseling and testing here.

**Do you discuss with a patient before asking for a normal comparator specimen, for example, blood? In order words, do you discuss before you have confirmed the germline nature of the variant?**

**Jilliane Sotelo:** Yes. When patients have been referred to me with a somatic test result where there is some suspicion of that change, in addition to taking a family history and a clinical history, we also talk a little bit about that somatic change.

There will be times they've been referred and I can say, "If we do the germline genetic testing, this will be reported as a variant of uncertain significance. This is what it means for your family." There will be times they've been referred and I say, "If we found it in the germline, it would be pathogenic. This is what it means for you and your family." But that's definitely a discussion that I have hand-in-hand with the report.

There are some cases when patients are referred for a somatic change in a particular gene that they're worried about in the germline. Let's hypothetically say, *BRCA*, but they are also a 40-year-old with colon cancer, and so it may be that I'm also having a more extended discussion about something like Lynch syndrome and ordering a panel that encompasses all of those genes, so that in addition to what I'm worried about in the somatic setting I'm also covering what I'm worried about due to their clinical history.

**Is there an opportunity to collaborate in the standardization of genetic genomic report formats to facilitate better access to important information? For example, the [US Food and Drug Administration] has expressed interest in initiating such an effort.**

**Daniel Silver:** Yes. It's obvious that we really, really need to do this.

**Jilliane Sotelo:** There are guidelines from multiple societies actually asking for this language and putting together some language. The [National Society of Genetic Counselors] recently had a practice statement. ASCO has one. ACMG has one. I think the bigger issue has been adoption from labs that maybe haven't been in the germline spacing and understandably maybe have some concerns about the legal liability around that language; and their ability, internally, to have the knowledge and the bioinformatics to identify the possible germline alterations and communication thereof. So, I do think that there has to be a little bit of a compromise when that language is created and an agreement and adoption among all the players.

**Veda Giri:** I would just add that it really goes back to the regulatory agencies, too, to help. It sounds like FDA is making a call for such collaboration, but the professional societies weigh in and then it really comes back to the regulatory agencies as to how to implement this. So I think it's going to take cross-collaborations and conversations with multiple professional societies and agencies.

**Daniel Silver:** Another point I think it's important to make here is [the data] Dr. Giri [cited], that [as much as 17 percent] of somatic tumor sequencing yields germline mutations. Many of those are actionable and rather consistently half of those germline mutations wouldn't have come to light using standard guidelines as to who should get germline sequencing and who shouldn't, based on family history.

**Is there any type of consensus in the field on somatic and germline variant reporting formats in practice? For example, should there be one unified report or two separate reports?**

**Jonathan Nowak:** I am understanding, I guess, that that question is in relation to doing true tumor-normal sequencing where you're reporting somatic variants and then also germline variants at the same time. I guess, if that's the case, there are probably multiple ways that you can ultimately return that information to clinicians and patients to make it clear. That can be two separate reports,

or it can be one report that is very clearly labeled in terms of the different data types that it contains. I think we have noticed repeatedly here that it is extremely helpful and important to make clear at the top of your report what is being analyzed and the manner in which that testing was done.

I think for many laboratories that are doing clinical testing, the speed with which those results are returned can be a little bit different. Sometimes germline data takes a little bit longer to analyze or is operating at a little different pace than somatic testing. So I think sometimes it is acceptable to release the somatic results first and then the germline can come along as a separate report shortly thereafter. I think there are a couple ways that that can be done, as long as it's made really clear what is contained within each report.

**How can we get doctors who are ordering somatic testing more aware of the germline implications and also aware of the need to collaborate with genetic counselors?**

**Ellen Matloff:** I think one of the things we need to understand is that genetic testing, both somatic and germline, is evolving very quickly and so standards that may have been appropriate five or 10 years ago in terms of repressing or not feeding back information to the clinician may not be considered acceptable today or in the future.

I think that laboratories need to rise to the challenge and say, "Do we need to have genetic counselors or use digital genetic counseling tools to reach out to those clinicians … to make sure that they've understood the report and that they are able to follow through?" We all know that [clinicians] want to do what's best for the patient, but they may need some help, particularly if they don't have the tools onsite or the personnel onsite to aid them. So I think the laboratories would be helpful if they would proactively reach out to clinicians to make sure that this information is understood.

**Do you have any further thoughts on how we might educate oncologists on differentiating germline and somatic testing? Many oncologists, for example, have interpreted somatic tumor results to be germline without germline confirmation.**

**Jilliane Sotelo:** That's really a very, very hard question. I think it really comes down to education and experience. As a genetic counselor, we often go to genetic counseling-type conferences and oncologists stick to oncology conferences – there's only so much time. But I'd really encourage [clinicians] to sort of reach across if they can and try to add genetics into some of your formal training.

Many genetic counselors know that genetic counseling works best when we're part of a larger team. Whether you have some kind of a tumor board or some kind of patient board, if there is a genetic counselor on staff, invite them to come, or even just send them cases as you have them. Many of us do curbside consultations all day long and that's a huge part of being a genetic counselor. So, don't be afraid to send them a report and say, "What do you think?" There are many free full-access sites that will tell you whether an alteration is classified and how it would be classified in the germline setting.

If you do not have a genetic counselor at your institution, or you don't know of one in your area, call up one of the germline testing labs. They can get you on the phone with somebody in a second and you can say, "This is what I found in the somatic test results. Do you think it's something that I should be concerned about?" and they'll answer that question for you. ■

[1] *J Natl Compr Canc Netw 2020;18(4) 380-391*

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