State of Utah

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30 May 2023

[Laboratory CEO]
[Address]

Dear [Laboratory CEO],

The Utah Department of Health and Human Services Cancer Genomics Program has contracted with the Center for Genomic Interpretation (CGI) to perform a survey of laboratories offering comprehensive hereditary cancer testing for HBOC and Lynch Syndrome. Your lab was identified by genetic counselors in Utah as one which provides this type of testing. This survey is voluntary. The results will be used to help clinicians assist patients in selecting appropriate comprehensive hereditary cancer tests.

The project is funded by the Centers for Disease Control and Prevention (CDC) Cooperative Agreement Number DP19-1905. The Washington and Oregon state health departments are also endorsing the survey. Therefore, all three states collectively request that your laboratory provides the Center for Genomic Interpretation with the attached information. Further details, timeline and contact information can also be found in the attachment.

Thank you in advance for your participation.

Sincerely,

Camille Roundy

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30 May, 2023

Dear [Laboratory CEO]

Your laboratory has been identified as one that is used frequently by Utah clinicians for comprehensive hereditary cancer testing, specifically the "**[Name of Comprehensive Hereditary Cancer Test]**". The nonprofit Center for Genomic Interpretation (CGI) (www.genomicinterpretation.org) has been contracted by the Utah Cancer Genomics Program (cancerutah.org/healthcare-professionals/genomics), which is funded by the Centers for Disease Control and Prevention, to perform a survey of laboratories offering such genetic testing in Utah.

The goal of the survey is to compare the similarities and differences between laboratories' comprehensive hereditary cancer genetic tests, allowing for more transparency regarding the accuracy and quality of genetic testing. CGI is requesting that your laboratory voluntarily participate in this survey.

The information collected through this project will be publicly accessible at www.testwisely.org. Our aim is for clinicians to use this website to assist them in selecting appropriate comprehensive hereditary cancer tests for their patients. We also hope patients will use this website for their own education.

Participation in this survey is completely optional. Participation ideally entails providing answers to all questions in the survey, although partially completed surveys are acceptable. The participation of each invited laboratory will be publicly displayed on the website, including if the laboratory did not participate, or if any individual survey question(s) were not answered.

We request that your laboratory adhere to the timeline in Table 1. We thank you in advance for your time and participation in improving transparency in genetic testing.

Sincerely,
Center for Genomic Interpretation

Table 1. Participation timeline

Due Date	Activity
June 16, 2023	Laboratory liaison makes initial contact with CGI by emailing Dr. Bryan Warf at bwarf@genomicinterpretation.org, indicating their level of participation. The laboratory liaison should have sufficient authority to enable on time completion of the survey. **Dr. Warf will be able to answer any questions regarding completion of the survey and survey questions.**
July 7, 2023	If participating, the laboratory has provided all the information that they are willing to answer on the survey. All information must be emailed to Dr. Warf by the end of business day on July 7, 2023. Answers may be entered in this word document, or a different document may be prepared (whichever is easiest for the laboratory).

Section 1: Testing Validity

Clinical Validity of Genes

Comprehensive hereditary cancer panels across different laboratories frequently differ in gene composition. Some laboratories may include only genes with definitive gene-disease relationships, while others may also include genes with less than definitive evidence for disease relationships, often described as “research genes.”

Current guidance from ClinGen’s semi-quantitative framework categorizes gene-disease relationships as Definitive, Strong, Moderate, Limited, No Reported Evidence, or Conflicting Evidence.

1. Please provide a list of all genes (and the associated hereditary cancer disorders) within each genetic test and/or gene panel that your laboratory offers, listing the strength of the gene-disease relationship using the ClinGen categorizations.
    a. For each gene, it is also highly recommended to also provide references that support the gene-disease relationship(s).
    b. Please provide the transcript ID (e.g., or ENST00000357654.9)
    c. Please indicate if there are any portions of the coding region which are not covered (e.g., exons not able to be covered due to pseudogene interactions).
2. What event(s) causes your laboratory to re-review gene-disease relationships for a gene that your laboratory tests?
3. What evidence is required to:
    a. Upgrade a gene-disease relationship to a higher level?
    b. Downgrade a gene-disease relationship to a lower level?
    c. Add a new gene to a test/panel?
    d. Remove a gene from a test/panel?

Test Validation

There are currently no widely-adopted standards that laboratories consistently use for the validation of genetic testing. Furthermore, there are ongoing misunderstandings and confusion in the clinical genetics/genomics industry on the correct usage of terms for defining test performance characteristics. For the purpose of this survey, we will use terminology suggested by the FDA (www.fda.gov/regulatory-information/search-fda-guidance-documents/statistical-guidance-reporting-results-studies-evaluating-diagnostic-tests-guidance-industry-and-fda). See Table 2 below for a list of terms relevant to this survey.

Table 2: Validation terminology

Term	Abbreviation	Definition
True Positive	TP	A positive sample that is correctly identified by the test. For the purpose of this survey, your laboratory should define a single TP as an *entire* sample with at least one positive Pathogenic or Likely Pathogenic variant; each individual Pathogenic or Likely Pathogenic variant within a sample does *not* count as an individual TP.
True Negative	TN	A negative sample that is correctly identified by the test (which only contains variants classified as Benign, Likely Benign, and/or Uncertain). For the purpose of this survey, your laboratory should define a single TN as an *entire* sample without a positive variant (Likely Pathogenic or Pathogenic); each individual negative nucleotide position within a sample does *not* count as a TN.
False Positive	FP	A negative sample incorrectly identified as positive by the test.
False Negative	FN	A positive sample incorrectly identified as negative by the test.
Sensitivity		$Sensitivity = TP / (TP + FN)$
Specificity		$Specificity = TN / (TN + FP)$
Positive Predictive Value	PPV	$PPV = TP / (TP + FP)$
Negative Predictive Value	NPV	$NPV = TN / (TN + FN)$

Please note that the annotation of "Positive" or "Negative" (e.g., the classification of genetic variants) must be based upon your laboratory's normal classification testing procedures and not via other methods.

This survey will request that you provide specific numbers from your validation studies, such that CGI can similarly calculate the performance metrics across all laboratories using the same analysis criteria (see Tables 3 and 4). Laboratories will be compared mainly using the Sensitivity, Specificity, Positive Predictive Value (PPV), and Negative Predictive Value (NPV) of their tests, along with the 95% confidence intervals for each estimate.

To avoid a biased estimate of performance characteristics, validation studies should always be performed on an independent set of samples from those used in development. **We ask that your laboratory only provide information for validation samples that were not also used in test development.**

Table 3: Validation data for different variant types

Variant Type	# Variants Tested	# Samples Tested	# of TP	# of TN	# of FP	# of FN
SNVs						
Insertions (All)						
Deletions (All)						
Deletion-Insertion (All)						
Copy Number Variants (CNVs) (All)						
Complex Rearrangements						
Low Complexity						
Segmentally Duplicated / Pseudogene Associated						
Putative Mosaic						
Other (please describe)						
Please provide more granular data below, if it is known						
Insertions (1-14 bp)						
Insertions (15-49 bp)						
Insertions (50-100 bp)						
Insertions (100-1000 bp)						
Deletions (1-14 bp)						
Deletions (15-49 bp)						
Deletions (50-100 bp)						
Deletions (100-1000 bp)						
CNVs (1001-5000 bp)						
CNVs (>5000 bp)						

If a certain variant type is not reportable by your lab, such as putative Mosaic, please indicate this category as “Not Tested”. SNV, single nucleotide variant. Low Complexity regions are considered sequences with extensive repeated nucleotides, such as the polypyrimidine tract within introns (which have long stretches of pyrimidine nucleotides), di/tri-nucleotide repeat regions, or other long homopolymer or highly repetitive sequences. A “Deletion-Insertion” is considered a concurrent deletion and insertion of bases. “Copy Number Variants” (CNVs) are considered multi-exonic deletions or duplications only (without any other genetic changes); “Complex Rearrangements” are considered multi-exon deletions, insertions, inversions, or rearrangements, whereby a simple CNV designation would not suffice.

Table 4: Number of samples used for validation

	# of Samples for SNVs	# of Samples for Insertions	# of Samples for Deletions	# of Samples for Other Categories
Clinical Sample Type 1 (List Sample Type)				
Clinical Sample Type 2 (List Sample Type)				
Clinical Sample Type 3 (List Sample Type)				
Synthetic				
Cell Line				
In silico				

Please make additional “Clinical” rows as needed for each sample type that was validated (e.g., whole blood, saliva, plasma, etc.). The “# of Samples for Other Categories” column should include all other variant types listed in Table 3 beyond SNVS, insertions, or deletions (e.g., Deletion-Insertions, CNVs, or Complex Rearrangements).

Section 2: Patient Testing Procedures

Please provide the following information on how patient samples are tested in your laboratory.

General Sample Testing

4. What is your laboratory's procedure if you receive an unvalidated sample type for testing?
5. What is your laboratory's procedure if a sample is suspected of having mosaic/somatic variants?
6. What is your laboratory's current average turnaround time (TAT) (defined as sample receipt to the final and complete sample report being received by the clinician/patient)?
7. Does your laboratory have example clinical reports on its website? If yes, please provide links.

Data Processing

You may list "N/A" for this section if it is not applicable (e.g., only Sanger sequencing is used).

8. How many bases into the 5' and 3' regions of introns are variants reported?
9. Does your laboratory have a minimal read coverage, post-filtering, for reporting a result for an individual base (e.g., 30X coverage)?
10. Does your laboratory have a minimal percentage of bases within a gene that must meet the above criteria for minimum coverage before a normal report can be issued on a given gene (e.g., 99% of bases must have at least 30X coverage)?
    a. What procedure(s) do you have to report samples where minimal coverage is not met (e.g., the entire gene is reported as inconclusive, or the areas with sufficient coverage are reported with text indicating which areas did not have sufficient coverage)?

Classification of Novel Genetic Variants

In order to characterize each laboratory's approach to classification of genetic variants, this survey provides a list of variants (only some of which are currently listed in ClinVar). Please provide your laboratory's current classification and reasoning for the classification of each of the following variants in Table 5. For the variants your laboratory has not yet classified, please classify them following your current testing protocol in regards to the most relevant cancer(s).

The actual classifications will be kept strictly confidential by CGI and will *not* be displayed on the TestWisely.org website or ever disclosed in any public manner. CGI is prepared to negotiate and sign nondisclosure agreements to this effect. CGI will only use these example variants to characterize the variant classifications from your laboratory using the following categories; CGI will *not* attempt to make the determination if classifications are "correct" or "incorrect," but only estimate how sensitivity and specificity are balanced in your laboratory's classification procedures.

Variant Classification Data Sources

I. Only publicly available evidence is used to support variant classifications
II. Both publicly available evidence and internally obtained evidence are used to support variant classifications
III. Other or N/A

Variant Classification Sensitivity and Specificity

I. Variant classification prioritizes sensitivity (less of a threshold to upgrade variants to Likely Pathogenic or Pathogenic)
II. Variant classification prioritizes specificity (a higher threshold to upgrade variants to Likely Pathogenic or Pathogenic)
III. Variant classification balances sensitivity and specificity (a moderate threshold to upgrade variants to Likely Pathogenic or Pathogenic)
IV. Other or N/A

For the purposes of this survey, uncertain variants will be considered as clinically non-actionable and grouped with Benign, and Likely Benign variants when it is necessary to use a binary classification schema (as overall test Sensitivity, Specificity, NPV, and PPV inherently require a binary classification schema).

Each laboratory will have advanced access to the results of this analysis for their laboratory, and each laboratory will also have the opportunity to draft a statement regarding its classification philosophy that will be included on the TestWisely.org website if the laboratory instructs.

Table 5: Variants provided for classification

Gene	Variant	Classification	Reasoning / Reporting Text
REDACTED	REDACTED		
REDACTED	REDACTED		
REDACTED	REDACTED		
REDACTED	REDACTED		
REDACTED	REDACTED		
REDACTED	REDACTED		
REDACTED	REDACTED		
REDACTED	REDACTED		
REDACTED	REDACTED		
REDACTED	REDACTED		

Please enter a classification and rationale for classification for each variant, on context of the most relevant cancer(s), using the classification categories from the ACMG/AMP sequence variant classification guidelines: Pathogenic, Likely Pathogenic, Likely Benign, Benign, or Variant of Uncertain Significance (VUS). In the "Reasoning" column, it is strongly encouraged to list appropriate references, reporting text, and/or a detailed description of internal data (when applicable). You may enter a value of "N/A" if your laboratory does not test the gene or region in question.

[Gene and variant names have been REDACTED for this public version of the survey.]

Reclassification of Genetic Variants

Variant classifications may change over time as more data is collected, and/or as a laboratory's variant classification protocols evolve.

11. What event(s) will always trigger an updated evidence search and/or re-evaluation of a previously classified variant?
    a. For example, your laboratory may re-evaluate a variant classification every single time a clinician requests you to re-evaluate the data.
12. If the variant classification protocol is updated in your laboratory, are all previously classified variants re-evaluated? (The most common answer that is expected is "No")
13. When a clinically meaningful reclassification event occurs that has the potential to alter patient care, is there a protocol for your laboratory to proactively contact the clinician and/or patient? If yes, please describe the process.
    a. Also, please describe the situation(s) for which the clinician and/or patient are not pro-actively informed.

Amended Reporting

14. What event(s) would cause your laboratory to proactively issue an amended report, without being prompted by a clinician or patient?
15. Can a clinician request an amended report? If yes, what updates can they request that would cause you to issue the amended report?
16. Can a patient request an amended report? If yes, what updates can they request that would cause you to issue the amended report?

Section 3: Laboratory Patient Support Services- Multilingual Support & Financial Aid

One fundamental issue to address in reducing health disparities in hereditary cancer testing is accessibility to all patients. Of particular importance is accessibility for patients who are under-insured or uninsured, and/or those who are not fluent in English. Please answer the following questions about what resources are available to patients for your laboratory's genetic tests.

Financial Assistance Program Offered Directly From the Laboratory

Please complete Table 6 to indicate if your laboratory directly offers financial assistance to patients for any genetic tests and/or gene panels that your laboratory offers.

Table 6. Financial assistance programs available to patients

	Program Exists? (Yes/No)	Financial Qualification Criteria	Additional Medical Qualification Criteria
Patient does not have insurance, and meets NCCN criteria for testing			
Patient does not have insurance, but does not meet NCCN criteria for testing			
Patient has high deductible insurance, and meets NCCN criteria for testing			
Patient has high deductible insurance, but does not meet NCCN criteria for testing			

17. Is there a publicly available link or form showing the break-down of the amount of assistance provided by criteria (e.g., percent discount depending on income)? If yes, please provide any available link(s).
18. Are there any partnerships or sponsored programs that make genetic testing at your laboratory easier to access for specific populations (e.g., anyone with a specific type of cancer, a specific type of insurance, etc.)? If yes, provide link(s) to these programs.
19. Do you have a patient-pay price? If yes, what are the prices for testing?

Genetic Counseling, Multilingual, and Additional Services

20. Is pre-test or post-test genetic counseling available? If yes, is the pre-test counseling offered by an in-house genetic counselor or a third party?
21. On average, how long would patients have to wait to be scheduled for genetic counseling?
22. What is the cost to the patient for genetic counseling? Is the cost covered by insurance?
23. Are languages other than English offered either by a multilingual genetic counselor, or via an interpreter for genetic counseling? If so, what is the cost and can it be covered by insurance?
24. Are the pre-test genetic counseling sessions available only by phone, or are other methods of communication available (e.g., video call for patients that are hearing impaired)?
25. Are any of the webpages, videos, and/or resources on your laboratory's site available in a language other than English? If yes, please provide a list of languages and links.
26. Are test reports available in languages other than English? If yes, which languages?
27. What familial testing options are available (e.g., single site testing for positive or uncertain variants)? How long do relatives have to test under that program? Does this apply internationally if the patient's relatives are outside the US?

~END OF LABORATORY SURVEY~