



Repetitive Constitutional Genetic Testing

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SYNOPSIS AND RELEVANCE

Constitutional genetic testing (CGT) should only be performed once in a patient's lifetime except in very unusual circumstances. Efforts to avoid repeat CGT can:

1. Prevent performing repetitive CGT when such testing provides no added value to the patient.
2. Impact the costs for CGT to medical facilities, medical practices, and patients.

OBJECTIVES

1. Understand that repetitive constitutional genetic testing provides no value, except in unusual circumstances.
2. List the benefits of avoiding repetitive constitutional genetic testing.
3. Describe strategies that are used to eliminate repetitive constitutional genetic testing.
4. Recognize situations where duplicate genetic testing may be indicated.

BACKGROUND

The American College of Medical Genetics and Genomics, as part of the Choosing Wisely initiative of the American Board of Internal Medicine, recommends against duplicate constitutional genetic testing (CGT) for inherited conditions unless there is uncertainty about the validity of the existing test result or some rare clinical situations. Although the human genome is stable, repetitive CGT commonly occurs and adds little value to caring for patients with genetic disorders.

We now better understand why tests are unnecessarily repeated. Before electronic health records (EHR) were widely implemented, clinicians often repeated genetic and other laboratory tests because they did not know the test was already performed, or did not have access to the test results. Duplicate constitutional genetic testing may also occur when these tests are included in order panels that are built to ease ordering for healthcare providers. In these instances, the tests in the order panel that are medically-indicated at that time may obscure the genetic test that was already performed. The test will be repeated unless the ordering provider knows to remove the genetic test from that order. Of course, there are rare medical indications for repeating a constitutional genetic test, and ordering systems should allow for such circumstances.

The increasing use of the EHR to order and result laboratory tests affords the opportunity to determine the extent of repetitive genetic testing within an institution. Moreover, clinical decision support tools that exist may be adapted to reduce the ordering of repetitive genetic testing.

Evaluating ordering practices for CGT may improve the value of such testing for providers and patients by:

- Facilitating the evaluation of patients with suspected genetic disorders for your health care professionals in a collaborative manner.
- Enhancing the training and education of providers who test patients for genetic disorders.
- Ensuring that your health information technology services support the decision making of health care providers who utilize CGT by optimizing the electronic test ordering system.
- Impacting testing costs for patients being evaluated for genetic abnormalities and the health care systems that care for these patients.

INSIGHTS

1. Constitutional genetic tests are usually performed only once because an individual's genetic composition does not change within their lifetime.
2. Repeating a constitutional genetic test may be considered in the following circumstances:
 - a. The first genetic test result must be confirmed because it did not match the clinical picture (ie, phenotype/genotype mismatch).
 - b. In patients who have undergone stem cell or solid organ transplant when the donor tissue is thought to alter the 'constitutional' genetics of the patient (eg, stem cell transplant in patients with von Willebrand disease).
 - c. The previously performed test did not fully explain the patient's phenotype and was less comprehensive than the current test, which incorporates new variants and/or genes. In these cases, it may not be possible to test only for the new gene/variant targets.

INTERVENTIONS

Provide educational information to providers and/or services regarding the waste and lack of utility of repeating CGT, except in rare instances. Targeted educational opportunities can be directed towards groups with a history of ordering duplicate constitutional genetic tests. Patients can also be provided with test information. The effectiveness of educational interventions is often transient and continued communication with ordering providers is needed to sustain improvements.

Investigate how providers order CGT: Identify standing orders, order panels, etc. that contain constitutional genetic tests and confirm that they are appropriately designed. The order panels may be modified or eliminated as appropriate to improve test utilization.

Modify test ordering system: The following are interventions that may reduce the number of repetitive CGTs that are ordered:

1. Create a best practice alert (ie, a "pop-up" message) that displays at the time of order entry whenever a duplicate constitutional genetic test is ordered. Clinicians may override this alert if they believe the test should be repeated.
2. Create a best practice alert (ie, a "pop-up" message) that not only displays at the time of order entry when a duplicate constitutional genetic test is ordered, but also requires that the provider acknowledge that repeat testing is indicated. If these requests are reviewed by a pathologist or designee, then it would be helpful if the ordering provider provide a reason for the duplicate testing.
3. Create a hold (hard stop) on duplicate constitutional genetic test orders. These cannot be overridden by the provider at the point of order entry. Instructions are provided describing how to override these hard stops (eg, call laboratory or pathologist).
4. Automatically cancel repeat constitutional genetic test orders (hard-stop) with instructions for how to override order cancellation (eg, call laboratory or pathologist).
5. If constitutional genetic tests are included in panels that include non-constitutional genetic tests, consider strategies that will decrease duplicate testing if the non-constitutional genetic tests may be needed in the future (eg, offer an alternate panel without the constitutional genetic test).

INTERVENTION ANALYSIS

The intervention analysis for this module involves determining the extent of repetitive CGT. If a significant number of duplicate constitutional genetic tests are performed based upon the retrospective analysis, then interventions can be applied to decrease repetitive CGT. Post intervention analysis of repeat CGT can demonstrate improvement and value impact.

1. Review or establish consensus rules regarding when repetitive CGT might be performed (eg, an erroneous result is suspected or a result requires confirmation for clinical purposes).
2. Collect data on repetitive constitutional genetic tests performed at your institution by searching the laboratory information system for commonly ordered constitutional genetic tests (see **Appendix A** for sample calculations). These data provide a baseline of your current utilization practices and allows estimation of the value impact that may be achieved by eliminating these duplicate orders.
 - a. The analysis may include identifying individual providers and groups of providers (ie, services) that order most of the constitutional genetic tests performed.
 - b. Obtain a list of order sets and/or test panels that include constitutional genetic tests. These can be reviewed to ensure that including the constitutional genetic test is appropriate for the test set.

- c. Data is collected for a defined time period (eg, 12 months) that will vary depending on your CGT volume and ease of collection. Alternatively, one could collect data until a sufficient number is achieved to allow informed decision making.
- d. These data will serve as a baseline measure of repetitive CGT. The results will be compared to data obtained after interventions have been made to document a reduction of repetitive CGT tests.
- 3. Implement interventions to reduce the number of repeat constitutional genetic tests ordered. Follow-up data can be collected to assess the success of the interventions used to reduce the number of repeat CGT orders (see **Appendix B**).
 - a. Interventions may be focused on providers and services that order the highest numbers of duplicate constitutional genetic tests.
 - b. An example of a hard stop notification for an attempt to repeat a constitutional genetic test is provided (see **Appendix C**).
- 4. Periodic reviews can be conducted to ensure that changes in test ordering practices are maintained.
- 5. Reports can be prepared for the appropriate staff, services, and/or committees. These reports and the involvement of stakeholders are especially useful when systemic ordering patterns are identified that lead to duplicate testing.

METHODS TO DETERMINE INTERVENTION IMPACT

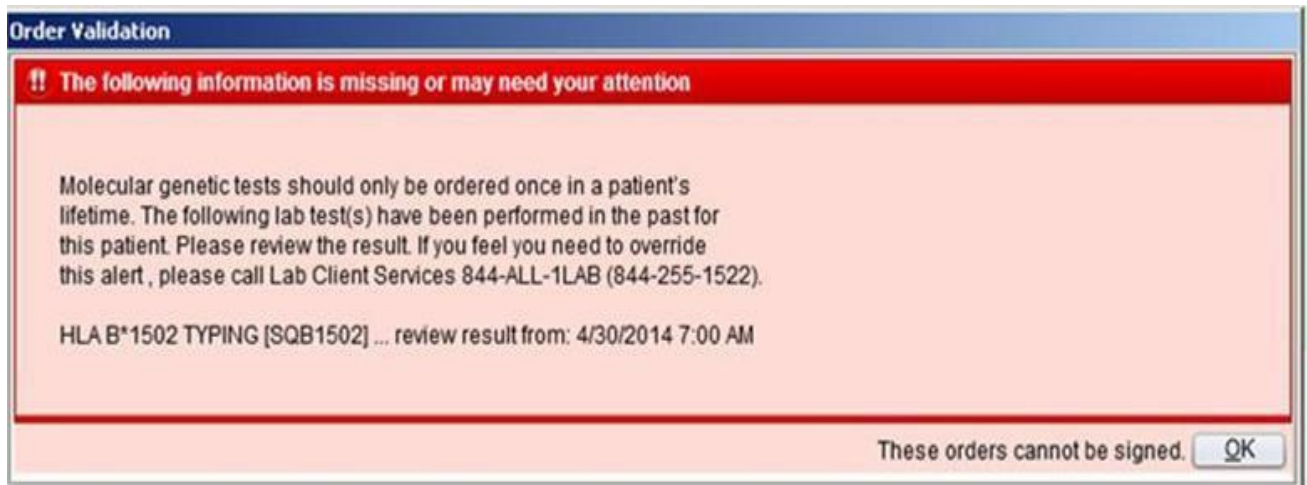
APPENDIX A: PRE-INTERVENTION DATA

<u>Constitutional Genetic Test Repeats Pre-Intervention</u>	
# Constitutional genetic tests performed over a time period (Total)	A1
# Constitutional genetic tests which were repeats	A2
Percentage of constitutional genetic test which are repeat tests	$A2/A1*100%=A3\%$
<u>Providers Who Ordered Highest # of Repeat Constitutional Genetic Tests (top 3)</u>	
Indicate the provider and # of repeat tests ordered	Provider
Provider #1 (# constitutional genetic tests)	
Provider #2 (# constitutional genetic tests)	
Provider #3 (# constitutional genetic tests)	
<u>Services That Ordered Highest # of Repeat Constitutional Genetic Tests (top 3)</u>	
Indicate the service and # of repeat tests ordered	Service
Service #1 (#constitutional genetic tests)	
Service #2 (# constitutional genetic tests)	
Service #3 (# constitutional genetic tests)	
<u>Order Sets and/or Test Panels That Contain/Include Constitutional Genetic Tests</u>	
# Order sets/panels that contain constitutional genetic tests	A4
# Order sets/panels in which constitutional genetic tests could be removed from order set	A5

APPENDIX B: POST-INTERVENTION FOLLOW-UP DATA

<u>Constitutional Genetic Test Repeats Post-Intervention</u>	
# Constitutional genetic tests performed over same time period as Appendix A. (Total)	B1
# Constitutional genetic tests which were repeats	B2
Percentage of constitutional genetic test which are repeat tests	$B2/B1*100%=B3\%$
Percent change in repeat constitutional genetic test orders	$A3\% - B3%/A3\% = A4\%$

APPENDIX C: SAMPLE INFORMATION SYSTEM ORDER PROMPT



QUESTIONS AND ANSWERS

QUESTION 1 OBJECTIVE

Recognize situations where duplicate genetic testing may be indicated.

QUESTION 1

A genetic test for cystic fibrosis (CF) is performed for a 5 year-old patient because he had a positive sweat test. The patient DOES have signs and symptoms of CF. The initial genetic test disclosed homozygosity for the $\Delta F508$ mutation. How should the laboratory handle a request to repeat genetic testing in this case?

- A. Repeat testing because the initial test result was unexpected.
- B. Repeat testing because the wrong test was initially performed ($\Delta F508$ mutation causes hemochromatosis, not cystic fibrosis).
- C. Repeat testing because there is a clear phenotype/genotype mismatch.
- D. There is no clear indication to repeat genetic testing.

The correct answer is D. The $\Delta F508$ mutation is the most common mutation associated with CF. This is consistent with the clinical signs and symptoms, and the positive sweat chloride test.

A is incorrect. The test result is actually expected because the patient has signs/symptoms of CF.

B is incorrect. The $\Delta F508$ mutation is the most common mutation associated with CF and is not associated with hemochromatosis.

C is incorrect. There is no phenotype/genotype mismatch. There were both clinical findings and a positive sweat test that warranted performing the genetic studies for CF.

REFERENCE

Newborn screening for CF. Cystic Fibrosis Foundation website. Accessed November 30, 2022.

<https://www.cff.org/intro-cf/newborn-screening-cf>

QUESTION 2 OBJECTIVE

Recognize situations where duplicate genetic testing may be indicated.

QUESTION 2

A genetic test for cystic fibrosis (CF) is performed on a 5 year-old patient because it was part of an "order set" to "rule out cystic fibrosis." It is unclear why this test was ordered because the child has no signs or symptoms of CF. A sweat test was performed because it was also included in this order set and this test was negative. Unexpectedly, the genetic test disclosed homozygosity for the $\Delta F508$ mutation. How should the laboratory handle a request to repeat genetic testing in this case?

- A. Repeat testing because blood specimens degrade rapidly, causing false positive results.
- B. Repeat testing because standard CF genetic assays are unreliable.
- C. Repeat testing because there is a clear phenotype/genotype mismatch.
- D. There is no need to repeat genetic testing because there is a high clinical suspicion of CF in this patient.
- E. There is no need to retest because many patients with homozygosity for the $\Delta F508$ mutation have a negative sweat test.

The correct answer is C. When the phenotype of the patient does not match the genotype, then repeat testing is warranted.

A is incorrect. The nucleic acids obtained from blood specimens do not rapidly degrade when properly processed and stored.

B is incorrect. The genetic tests for CF are considered highly reliable.

D is incorrect. Test results should be interpreted within the clinical context. It should not be concluded that a patient has CF based only on laboratory test results in the absence of clinical findings.

E is incorrect. Patients who are homozygous for this mutation usually have a positive sweat test.

REFERENCE

Newborn screening for CF. Cystic Fibrosis Foundation website. Accessed November 30, 2022. <https://www.cff.org/intro-cf/newborn-screening-cf>

QUESTION 3 OBJECTIVE

Recognize situations where duplicate genetic testing may be indicated.

QUESTION 3

A woman had previous genetic testing for von Willebrand disease (vWD) because of a family history of this disorder. She has no signs or symptoms of disease (ie, bleeding history) and the genetic test was negative. Later in life, she required a bone marrow transplant from a donor who was a close relative. How should the laboratory handle a request to repeat genetic testing after the marrow transplant?

- A. Repeat testing IS indicated because the transplant came from a close relative who may also have a mutation for vWD.
- B. Repeat testing is NOT indicated because genetic tests for vWD are insensitive and often must be repeated several times to detect a mutation.
- C. Repeat testing is NOT indicated because vWD cannot be transmitted to a bone marrow transplant recipient.
- D. Repeat testing is NOT indicated because vWD is caused by abnormal hepatocyte function and this patient did not receive a liver transplant.

The correct answer is A. vWD is a clotting disorder caused by genetic mutations. Thus, the disease can be transmitted through bone marrow transplant if the donor carries a vWD mutation.

B is incorrect. Genetic tests for vWD are considered sensitive.

C is incorrect. If the transplanted bone marrow elements (ie, stem cells) contain a mutated vWF gene, then the disease can be transmitted to the marrow recipient.

D is incorrect. Hepatocyte function is not directly involved in the pathogenesis of vWD.

REFERENCE

US National Library of Medicine. Genetics Home Reference website. Von Willebrand disease. Reviewed December 1, 2012. Accessed November 2022. <https://ghr.nlm.nih.gov/condition/von-willebrand-disease>

MODULE REFERENCES

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