Clinical Quality Assurance Measures at Myriad Genetic Laboratories:

Increasing the Clinical Utility and Cost-Effectiveness of Genetic Testing for Hereditary Cancer Syndromes for Patients, Healthcare Providers and Health Plans
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Executive Summary

Myriad Genetic Laboratories, Inc. ("Myriad") is a leading molecular diagnostic laboratory offering an array of genetic, prognostic and personalized medicine tests to assess a patient’s cancer risk, disease aggressiveness and manage chemotoxicity. Myriad’s testing products give healthcare providers information that helps them make medical management decisions that reduce cancer risk and ensure specific treatments are tailored for each patient. Myriad has over 900 employees in the United States, including over 140 internal and field-based specialists who perform clinical quality assurance (QA) measures on a daily basis with the goal of increasing appropriate test utilization, decreasing inappropriate utilization and increasing healthcare provider and patient knowledge. These clinical QA measures are provided as a value-added service to patients, healthcare providers, and health plans. Quality assurance measures performed by molecular diagnostics laboratories are often reported in terms of the technical performance of a laboratory test; however there is a lack of information documenting pre- and post- test clinical QA measures. Myriad is a CLIA and CAP accredited laboratory; as such, key quality indicators have been developed for all of our clinical assays and processes that meet or exceed regulatory requirements. In addition, Myriad voluntarily performs clinical QA measures both before and after performing provider-ordered testing which results in improved patient care, an increase in healthcare provider and patient knowledge and an overall cost-savings to the healthcare system. In the course of one year, Myriad’s clinical QA measures resulted in nearly 3000 cancelled, avoided or revised test orders.
Introduction/Background

The currently available clinical test menu at Myriad includes BRACAnalysis®, COLARIS®, COLARIS AP®, MELARIS®, PANEXIA®, Prolaris® and TheraGuide® 5-FU. The aforementioned tests are ordered by healthcare providers for the purpose of aiding in the medical management of individual patients. For the purpose of this publication, clinical QA measures for the BRACAnalysis and COLARIS products will be reported from a 12 month period (July 1, 2011 to June 30, 2012).

The BRACAnalysis products are tests for Hereditary Breast and Ovarian Cancer Syndrome (HBOC). From July 2011 through June 2012 the available BRACAnalysis products included Comprehensive BRACAnalysis (BRCA1 and BRCA2 gene sequence and 5-site large rearrangement analysis), BRACAnalysis All Rearrangement Test or BART (complete rearrangement analysis for both BRCA1 and BRCA2), Multisite 3 BRACAnalysis (three-mutation BRCA1 and BRCA2 analysis for individuals of Ashkenazi Jewish descent), and Single-Site BRACAnalysis (mutation-specific analysis for individuals with a known BRCA1 or BRCA2 mutation in the family). Integrated BRACAnalysis includes both complete gene sequencing and large rearrangement analysis of the BRCA1 and BRCA2 genes; however, this test was not available until January 2013 and is therefore not included in the current analysis. COLARIS is a test for Lynch Syndrome or Hereditary Non-Polyposis Colorectal Cancer (HNPCC). COLARIS includes sequencing and large rearrangement analysis of the MLH1, MSH2, MSH6 and PMS2 genes, as well as large rearrangement analysis of the EPCAM gene. Single-site COLARIS is available for individuals with a known gene mutation in the family. The COLARISPLUS test, which includes full sequencing and large rearrangement analysis of the MYH gene, in addition to the mismatch repair gene testing described above, was not available until February 2013 and is not included in this analysis.

Healthcare providers who order BRACAnalysis and COLARIS from Myriad include genetic specialists (genetic counselors and geneticists), oncologists, surgeons, gastroenterologists, obstetrician-gynecologists and nurse practitioners who specialize in women’s health and/or oncology. Multiple professional societal guidelines support any of the above healthcare providers administering genetic risk assessment and testing for patients at risk of HBOC and Hereditary Colorectal Cancer Syndromes, including Lynch Syndrome, within their own practices.2-7 Alternatively, healthcare providers may choose to identify patients at risk of HBOC and Lynch syndrome and refer them to a genetic specialist for risk assessment and testing. Clinical QA measures analyzed in this report include BRACAnalysis and COLARIS tests ordered by all types of healthcare providers.

Many employees play an important role in pre- and post- test clinical QA at Myriad including Customer Service (CS) representatives, internal Medical Service (MS) representatives, and field-based MS representatives. When a sample is received at the laboratory, a CS representative immediately enters pertinent information from the test request form into a central electronic
database. The CS representatives at Myriad handle initial review and database entry for all received test orders. Customer Service representatives review the test request form to identify potential inaccuracies or missing information. The CS representative subsequently attempts to resolve any inaccuracies directly with the ordering healthcare provider and/or patient by phone, fax, or email communication. Any case with a discrepancy that may require clinical expertise is transferred to the internal MS team for resolution. For example, all comprehensive test orders that include information indicating a possible known mutation in the family are sent to the internal MS team for clarification with the ordering healthcare provider and/or patient and the test order is revised by the ordering healthcare provider to targeted mutation testing (Single-Site testing) when appropriate. In addition, the database has specific automated clinical QA measures in place that can identify pre-test clinical factors that trigger immediate review by the internal MS team. One example of such a trigger is a COLARIS test ordered for a patient who has a personal or family history of >5 adenomas; suggesting the possibility that testing for a hereditary polyposis syndrome may be more appropriate. The internal MS team at Myriad is composed of Professional Support Specialists (PSS; board-certified and licensed genetic counselors) and Clinical Data Specialists (CDS; bachelors level employees with specialized training in all genetic tests performed at Myriad). In addition to the review of tests ordered as described above, the PSS team is available by phone or email to consult with healthcare providers and patients regarding all Myriad testing services and associated clinical risk factors.

Myriad also employs a field-based MS team of Regional Medical Specialists (RMS) who provide clinical education about hereditary cancer syndromes and serve as a resource to healthcare providers. They are available for consultation either in-person, by phone, or via email. The RMS team consists of board-certified/board-eligible genetic counselors and registered nurses with specialized training in oncology, cancer risk assessment, and cancer genetics.
Clinical Quality Assurance Measures at Myriad Genetic Laboratories

**Abbreviations**
- OHCP - Ordering Healthcare Provider
- RMS - Regional Medical Specialist
- TRF - Test Request Form
- CS - Customer Services
- MS - Medical Services
- PA - Prior Authorization

**OHCP identifies at-risk patient and provides informed consent for test**

**RMS consult with OHCP results in appropriate test selection**

**Sample and TRF arrive at Myriad; CS enters all information into central database**

**Duplicate test order** (Patient previously tested)

**Send copy of previous test result to OHCP**

**CANCEL test**

**Incomplete information**

**CS contacts OHCP and/or patient requesting missing information**

**Missing information not obtained**

**CANCEL test**

**Complete information**

**Missing information obtained/completed**

**Is MS review necessary?**

- Yes
- No

**MS discussion with OHCP confirms inappropriate test ordered**

**OHCP CANCELS test**

**MS discussion with OHCP results in confirmation of appropriate test ordered OR OHCP revises test order to more appropriate test**

**Insurance criteria review and/or PA requested by CS if required**

**Patient meets insurance criteria and/or PA obtained**

- No
- Yes

**Test released to lab**

**Patient/Provider appeal and obtain Insurance coverage or patient chooses to pay for test**

- No
- Yes

**TRF contains no personal/family history risk factors for test ordered**

**Comprehensive test ordered but possible familial mutation indicated in paperwork**

**COLARIS vs. COLARIS AP history**

**Multisite 3 ordered but no Ashkenazi Jewish ancestry indicated**

**CANCEL test**
Methods

All test orders from July 2011 through June 2012 were evaluated to determine the percentage of those orders that met the 2012 National Comprehensive Cancer Network® (NCCN Guidelines®) criteria for genetic testing and/or the Myriad Financial Assistance Program (MFAP) medical criteria. Many healthcare providers utilize the NCCN Guidelines® when assessing the appropriateness of whether or not to order hereditary cancer testing based on a patient’s personal and/or family history of cancer. In addition, a number of national and regional health insurance plans reference the NCCN Guidelines® in medical policy for coverage of genetic testing. The risk factors included in the MFAP medical criteria are based on multiple societal guidelines and peer reviewed publications. Uninsured patients who meet the MFAP medical criteria and specific financial criteria are eligible for no charge genetic testing by Myriad. A complete listing of these criteria can be found at www.myriadpro.com.

In addition, all test orders cancelled or revised during the specified timeframe were identified, including the specific reason for revision of the test order. Approximately 20% of the query results were audited and the final results were adjusted for accuracy. Test cancellations and/or revisions that could be directly attributed to clinical QA processes in place at Myriad are reported.

Some clinical QA measures are not captured by existing databases, and therefore a survey of MS employees was completed using SurveyMonkey®. The survey was completed daily from October 8, 2012-October 19, 2012 by the RMS team and results from this two week time period were used to project approximate results for a one year time period. This two week period is expected to have generalizable results for a year’s time, with no out of the ordinary campaigns or activities having taken place. The RMS team documented all instances of RMS consultation with a healthcare provider that involved any of the following: accurate test order choice (prior to the test being received by the laboratory); appropriate medical management given a patient’s clinical history in combination with the patient’s specific genetic test result for COLARIS or BRACAnalysis; and discussions with the ordering healthcare provider about the option of referral for consultation with a genetic specialist. The PSS team also completed a daily survey from October 8, 2012-October 19, 2012 in order to capture the number of discussions regarding the option of referral to a genetic specialist given to both patients and healthcare providers for those at-risk or affected with a hereditary cancer syndrome. These results were combined with those from the RMS survey and used to project the approximate number of discussions that take place with MS representatives regarding the option of referral to a genetic specialist over a one year time period.
Results

Over the one year time period, 93% of all test orders met the 2012 NCCN Guidelines® criteria for genetic testing, the MFAP medical criteria or both. Approximately 93% of the test orders meeting neither set of criteria included at least one clinical risk factor for testing (6.5% of all test orders). A clinical risk factor for testing is defined as a personal or family history of at least one syndrome-associated cancer (breast, ovarian, colorectal, endometrial) or early-onset colon adenomas (prior to age 40). To summarize, over 99% of all test orders either met at least one set of criteria or had at least one clinical risk factor for testing. The majority of test orders with no clinical risk factor for testing, representing less than 1% of all test orders, were cancelled after Myriad contacted the ordering healthcare provider and confirmed a lack of any clinical risk factor for the test ordered.

BRACAnalysis and COLARIS Tests Ordered
July 2011–June 2012

Although the vast majority of tests ordered had appropriate clinical indications, the clinical QA processes in place at Myriad identified areas of cost savings through detection of duplicate test orders and more clinically appropriate and cost-effective testing options (see Table 1). Combined, the CS and MS employees and automated clinical QA processes in place at Myriad resulted in over 2000 cancelled or revised genetic test orders for BRACAnalysis and COLARIS during the specified time period.
### Table 1: COLARIS and BRACAnalysis Tests Cancelled or Revised After Receipt at Myriad

<table>
<thead>
<tr>
<th>Test Order Type</th>
<th>Number of Tests Cancelled or Revised</th>
<th>Reason for Test Change</th>
</tr>
</thead>
<tbody>
<tr>
<td>Comprehensive BRACAnalysis</td>
<td>799</td>
<td>Duplicate Test Order (patient previously tested)</td>
</tr>
<tr>
<td></td>
<td>1050</td>
<td>Comprehensive Test changed to Single Site (targeted mutation testing)</td>
</tr>
<tr>
<td>Total</td>
<td>1849</td>
<td></td>
</tr>
<tr>
<td>Comprehensive COLARIS</td>
<td>74</td>
<td>Duplicate Test Order (patient previously tested)</td>
</tr>
<tr>
<td></td>
<td>114</td>
<td>Comprehensive Test changed to Single Site (targeted mutation testing)</td>
</tr>
<tr>
<td>Total</td>
<td>188</td>
<td></td>
</tr>
<tr>
<td>Total Combined Comprehensive BRACAnalysis and COLARIS Orders Revised</td>
<td>2037</td>
<td></td>
</tr>
</tbody>
</table>

In addition, healthcare provider consultations with field-based RMS employees assisted healthcare providers in avoiding inappropriate test orders. During the two week survey time period previously described, consultations with healthcare providers resulted in 37 cancelled or revised test orders. These consultations took place either prior to the sample being sent to Myriad or prior to the usual internal clinical QA processes. Table 2 summarizes the extrapolated annual test orders avoided or revised due to RMS consultations.
Combined survey results for both the PSS and RMS teams showed that the option of a genetic specialist referral was discussed with healthcare providers or patients in 83 MS-based interactions during the two week survey period. Extrapolation to one year’s time would suggest that over 2000 such discussions take place annually.

Table 2: Annual COLARIS and BRACAnalysis Test Orders Avoided or Revised Following RMS Consultation: Extrapolation From A Two Week Survey Period

<table>
<thead>
<tr>
<th>Test Type</th>
<th>Number of Tests Avoided or Revised Prior to Test Order</th>
<th>Reason for Test Change</th>
</tr>
</thead>
<tbody>
<tr>
<td>Comprehensive BRACAnalysis</td>
<td>416</td>
<td>Patient lacked clinical indication for BRACAnalysis</td>
</tr>
<tr>
<td></td>
<td>156</td>
<td>Single Site test ordered instead of Comprehensive BRACAnalysis</td>
</tr>
<tr>
<td>Total</td>
<td>572</td>
<td></td>
</tr>
<tr>
<td>Comprehensive COLARIS</td>
<td>286</td>
<td>Patient lacked clinical indication for COLARIS</td>
</tr>
<tr>
<td></td>
<td>104</td>
<td>Single Site test ordered instead of Comprehensive COLARIS</td>
</tr>
<tr>
<td>Total</td>
<td>390</td>
<td></td>
</tr>
<tr>
<td>Total BRACAnalysis and COLARIS</td>
<td>962</td>
<td></td>
</tr>
</tbody>
</table>

Conclusion/Summary

Ninety-three percent of test orders received at Myriad are clinically appropriate, meeting the 2012 NCCN Guidelines® genetic test criteria, MFAP medical criteria or both. This is in contrast to a report published in March of 2011, which states that inappropriately ordered tests represent “approximately 30% of all complex genetic tests ordered”. One reason for the higher percentage of clinically appropriate test orders received at Myriad may be that the current report includes only test orders for BRACAnalysis and COLARIS, tests for the two most common hereditary cancer syndromes, whereas the report published in 2011 included data for orders of 38 different “complex biochemical, cytogenetic, and molecular genetic tests.” Given the fact that both HBOC and Lynch Syndrome have established testing criteria and medical management guidelines, healthcare providers are likely more familiar with these syndromes and therefore less likely to inaccurately order these tests. In addition, Myriad employs a team of field-based MS employees who proactively provide hereditary cancer education regarding established risk factors and medical management guidelines. This educational outreach effort may increase healthcare provider interest and knowledge of hereditary cancer syndromes in comparison to rare conditions included in the aforementioned report, leading to a higher percentage of appropriately ordered tests at Myriad.

The UnitedHealth Center for Health Reform and Modernization estimates that annual spending nationally on genetic testing and molecular diagnostics will increase to $15-$25 billion by the year 2021. By providing the clinical QA measures as described above as a value-added laboratory service, Myriad is making significant efforts to control the overall spend of health plans. Myriad’s clinical QA measures result in savings to the healthcare system, either through the cancellation of tests that were not medically necessary or by revising the order to a less expensive, and more clinically appropriate, test following consultation with the ordering healthcare provider. These measures resulted in nearly 3000 cancelled, avoided or revised test orders in one year alone. In addition, healthcare providers are able to access valuable expert consultation and clinical education regarding hereditary cancers through Myriad’s MS department. This partnership between healthcare providers and the PSS and RMS teams encourages the appropriate medical management of thousands of patients annually in accordance with current societal guidelines. Medical Services employees may discuss the option of referral to a genetic specialist with healthcare providers and/or patients, based on healthcare provider preference and/or in clinically complex situations. Such discussions are projected to occur more than 2000 times per year. Some examples of situations where a genetic specialist consultation would be discussed include but are not limited to: patients at risk of rare hereditary cancer syndromes based on clinical history, patients at risk of multiple hereditary cancer syndromes and providers who do not feel that a patient’s clinical history falls within their area of expertise.
As healthcare providers and patients become more aware of the importance of personal and family history risk factors for hereditary cancer syndromes, the demand for genetic testing will continue to increase. As such, working with a diagnostic laboratory that provides extensive clinical QA measures whose goal is to support the most clinically appropriate care, while simultaneously avoiding unnecessary healthcare spending, is critical to the success of personalized medicine.
References


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