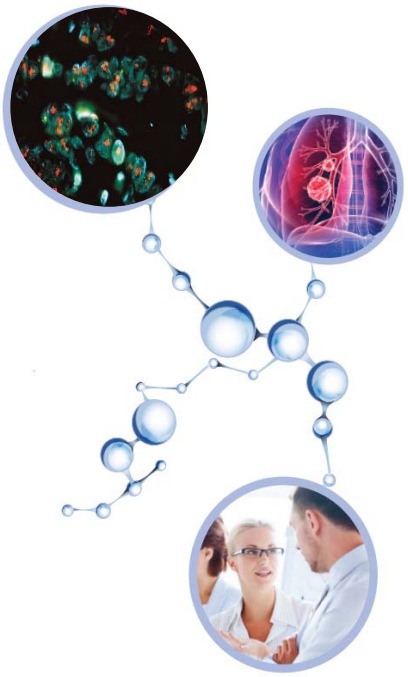
A Community Pathologist-Driven Approach to the Implementation of Best Practices in Immuno-Oncology (IO) Across the Multidisciplinary Cancer Care Team

Project Closeout Report



Project Title

A Community Pathologist-Driven Approach to the Implementation of Best Practices in Immuno-Oncology (IO) Across the Multidisciplinary Cancer Care Team

Project Partners/Collaborators

Grant organization: American Society for Clinical Pathology

Q Synthesis LLC

Project Dates

Start date: January 1, 2018
End date: December 31, 2019

Agency Support

Funded by an independent educational grant from Pfizer/Merck KGaA

Grant Award Number

34604349

A Community Pathologist-Driven Approach to the Implementation of Best Practices in Immuno-Oncology (IO) Across the Multidisciplinary Cancer Care Team

Project Closeout Report

Abstract

Purpose: The overarching aim of the project was to increase the laboratory team's critical scientific knowledge and leadership skills to build capacity and drive systems-based change in community cancer care. The intent was to address specified clinical gaps relating to understanding of the science of IO, awareness of testing and reporting guidelines, integration of pathologists and laboratory professionals in the multidisciplinary team, and developmental support for multidisciplinary and interprofessional cancer care teams.

Scope: Aligned with the multidisciplinary nature of the clinical gaps, the primary target audiences for the education were pathologists, laboratory professionals, and community pathology teams. Secondary audiences included oncologists and other multidisciplinary team members at community cancer centers.

Methods: The project comprised five sets of educational activities blending online learning and live education with a change-based approach to education and patient care. These activities include a baseline IO practice survey, a set of IO scientific core online modules, live, virtual leadership discussions, multidisciplinary live QI initiatives, and panel discussions on IO implementation.

Results: More than 3,600 learners (including pathologists, laboratory professionals, and other healthcare professionals) participated in the education. Pretest and posttest performance showed significant gain in knowledge of IO science, with overall mean scores increasing 28.8%. Follow-up also respondents rated their knowledge and confidence in several areas of IO significantly higher than respondents did in the baseline IO practice survey. Teams of cancer clinicians worked to develop and implement process improvements that increased IO biomarker testing rates and produced more effective immunotherapy symptom assessment and management.

Key Words

Immuno-oncology, checkpoint inhibitors, biomarkers, pathology, laboratory professional, quality improvement, multidisciplinary team, IO diagnosis, immunotherapies, pan-tumor

Introduction

While breakthroughs in immuno-oncology (IO), which engages the body's natural defenses to fight cancer, have revolutionized cancer therapy, they have also posed challenges for cancer care teams and medical laboratory personnel. The Association for Cancer Immunotherapies (CIMT) 2014 Annual Report highlighted significant diagnostic and clinical knowledge gaps about immunotherapeutic antibodies and treatments currently approved by the FDA.[1] The report also indicated that rapid breakthroughs in immunotherapy require new models for scientific exchange, collaboration, and education. To address these gaps and related needs in the pathology and laboratory medicine communities, ASCP developed a comprehensive IO Education Strategy,[2] and this project ("A **Com**munity **Path**ologist-Driven Approach to the Implementation of Best Practices in Immuno-Oncology [IO] across the Multidisciplinary Cancer Care Team") was a part of this strategy. The project, summarized in this report, supported the learning of foundational IO scientific concepts and promoted integration of learning into practice among the cancer care team.

Purpose

The overarching aim of the project was to increase the laboratory team's critical scientific knowledge and leadership skills to build capacity and drive systems-based change in community cancer care. The intent was to address the following four clinical gaps identified by ASCP's IO Workgroup and existing IO literature.

- **Clinical gap 1:** Pathologists and laboratory professionals lack awareness about the core science of IO and the implications of biomarkers, checkpoints, and clinical pathways in the identification, diagnosis, and treatment of pan-tumor cancer. There is also a lack of understanding of how complex combinations of various therapeutic agents, disease states, and thresholds affect diagnostics and treatment plans.
- **Clinical gap 2:** There is suboptimal awareness among laboratory team members about current IO testing and reporting guidelines as well as emerging protocols. This includes understanding clinical indications for and analytical processes related to biomarker and pathway testing.
- **Clinical gap 3:** There is suboptimal integration of pathologists and laboratory professionals in the multidisciplinary team, which adversely affects patient care and safety.
- **Clinical gap 4:** Development of and support for pathology and laboratory leadership is needed on the multidisciplinary and interprofessional[i] cancer care team.

This report summarizes the outcomes of the educational activities designed to address these gaps.

[i] The term *interprofessional* in this document refers to teams of advanced practitioners (e.g., physicians and clinical laboratory scientists), other cancer care providers (e.g., nurses, laboratory professionals), and/or support staff (e.g., quality improvement data specialists) on the cancer care team.

COMPATH IO Project Goals

- Increase the knowledge, skills, and competence of pathologists and laboratory professionals responsible for cancer diagnosis and management using pan-tumor IO
- Empower community pathology teams to play a greater role in shaping and implementing institutional IO policies/protocols within cancer centers
- Promote pathologists and laboratory professionals as leaders in the multidisciplinary team who can guide medical oncologists and other team members in the safe and effective implementation and delivery of IO
- Disseminate best practices and lessons learned to enhance capacity to ensure proper diagnosis and inform therapeutic decisions among the broader IO multidisciplinary patient care team

Scope

Pathologists and laboratory professionals (e.g., clinical laboratory scientists, administrators, and laboratory technicians) are key members of the multidisciplinary team[ii] with roles in the diagnosis, testing, and management of IO-related cancers. As key health care providers responsible for the testing and identification of biomarkers and immune checkpoints, the laboratory team must understand the scientific foundations and procedural considerations of IO diagnostics and treatment. However, there has been confusion among the laboratory team about IO testing and diagnosis, which could lead to significant loss of patient lives if not addressed. For instance, advancements in IO have created new—and nonintuitive—diagnostic paradigms and testing protocols for cancer, contributing to clinical gap 1. Thus, pathologists and laboratory professionals must develop their basic scientific knowledge as well as the testing and diagnostic skill sets associated with IO and immunotherapeutics. In addition, private-practice and community pathologists may find it challenging to keep up-to-date with rapidly changing knowledge in the management and treatment of multiple cancers and the complex combination of therapeutic agents, disease states, and thresholds affecting IO diagnostics. The project addressed these needs by providing educational activities aimed at increasing scientific understanding of IO and improving IO-related skills.

Educational Needs Addressed

- Understanding the science of immune biomarkers, checkpoint molecules and their pathways, and their implications for the identification, diagnosis, and treatment of multiple types of cancers
- Understanding complex combinations of therapeutic agents, disease states, and thresholds affecting IO diagnostics
- Need for IO diagnostic approaches that extend beyond traditional evidence-based guidelines
- Keeping up to date with the latest advances in IO
- Need to trengthen pathologist and laboratory leadership on multidisciplinary clinical care teams

Pertaining to clinical gap 2, current practice guidelines that include IO diagnostics tend to focus on specific disease states. There is currently no established guideline for immunotherapy testing and diagnostics, and there is a profound need in pathology for IO diagnostic approaches that extend beyond traditional evidence-based guidelines. Moreover, pathologists and other members of the laboratory team have lacked the knowledge and skills necessary to implement appropriate disease-specific guidelines. The educational activities described in the Methods

[ii] *Multidisciplinary* refers to physicians from multiple specialties (e.g., pathologists and oncologists).

section address these needs by increasing awareness and highlighting evidence-based practices. The project also addressed communication-related gaps, as suboptimal knowledge hinders multidisciplinary communication and teamwork that advances appropriate patient care.[3,4]

Although pathologists and laboratory professionals are critical members of the IO care team, they are often underutilized as members of tumor boards or cancer care teams in clinical settings, as reflected by clinical gap 3. Pathologists who do not regularly attend tumor boards may miss key opportunities to provide valuable input regarding the pathologic features that are characteristic of cancers, beyond their basic gross and histomorphologic aspects. This valuable information may impact how clinicians develop treatment plans and monitor care for their patients with cancer.[5] Due to the growing complexity of biomarker testing and interpretation, the role of pathologists is becoming more central to safe and effective delivery of precision medicine in cancer care. Their unique perspective on disease processes and access to tissue specimens allow pathologists to guide cancer clinicians who are developing treatment plans and monitoring response to selected therapies.[6]

This need also pertains to clinical gap 4, as the emerging science of IO provides an opportunity to strengthen pathologist and laboratory leadership on multidisciplinary clinical care teams. Physician leadership is an important component of the delivery of modern health care, and the American Hospital Association has identified several emerging competencies for physicians in the next generation of health care delivery, including leadership, systems theory and analysis, cross-disciplinary cooperation, and interpersonal and communication skills. Engaging pathologists and laboratory professionals in leadership training can improve the quality and delivery of health care services, reduce costs, and improve health outcomes.[7] The project addressed these needs through educational activities that promoted pathology leadership and enhanced communication within multidisciplinary care teams.

Aligned with these needs and the multidisciplinary nature of the clinical gaps (refer to p. 3), there were two target audiences for the education. The primary target audiences were pathologists, laboratory professionals, and community pathology teams. Secondary audiences included oncologists and other multidisciplinary team members (e.g., pulmonologists, urologists, surgeons, radiologists, radiation oncologists, nurses, navigators, pharmacists, and administrators) at community cancer centers. The geographic scope of these audiences included the United States and Europe, whereas the local educational activities, such as Activities 3 and 4 (described in the Methods section) focused on US practices because of distinct differences in US and international health care delivery.

Primary Target Audiences

- Pathologists
- Laboratory professionals
- Community pathology teams

Methods

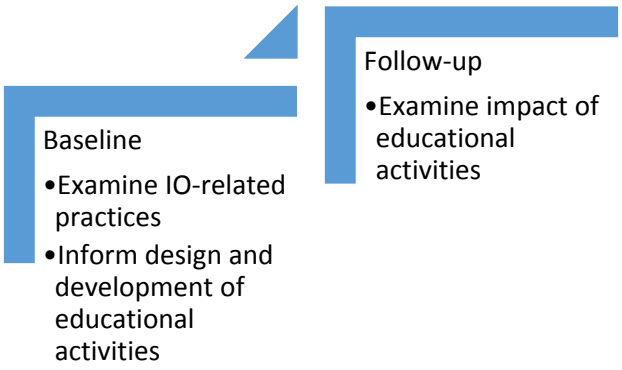
The COMPATH IO project comprised five sets of educational activities designed around the clinical gaps:

- Activity 1: IO Practice Survey
- Activity 2: IO Scientific Core Online Modules
- Activity 3: IO ChangeMakers: Virtual Leadership Discussions

- Activity 4: Multidisciplinary Live QI Initiatives
- Activity 5: IO Implementation PBL Live/ Enduring Panel Discussions

Activity 1: IO Practice Survey

At the start of the project, the baseline IO practice survey was deployed online to a national and international sample of medical laboratory personnel drawn from ASCP's databases. The overall purpose was to assess the state of IO testing, reporting, and associated performance gaps across the laboratory, such as:



- Determining what cancer care providers and laboratories were currently doing in the context of IO
- Identifying the needs of cancer care centers
- Identifying potential implications for future practices in IO

The results of the baseline survey highlighted the state and prevalence of various IO-related practices among pathologists and laboratory professionals, including:

- The need for timely communication across departments
- The need for education across the spectrum of health care providers (including laboratory staff and oncologists)
- The logistics of conducting biomarker testing (including when testing was needed, who should order it, and ways of standardizing testing processes and procedures)

Formatively, these themes informed the development and delivery of subsequent educational activities, including the IO ChangeMakers (Activity 3) and the panel discussions (Activity 5). The practice survey also served a summative role through the deployment of a condensed follow-up version to participants in the online educational activities to examine the intermediate-term impact of the education. Deployed approximately 9 months after the launch of the online modules, the follow-up survey primarily focused on the participants' self-reported understanding of key aspect of IO science and practice, as well as their confidence in their ability to perform various IO-related tasks.

Activity 2: Scientific Core Online Modules

The scientific core modules comprised three 1-hour online, CME-accredited modules designed to increase pathologists' and laboratory professionals' core scientific knowledge and skills in IO.

- **Understanding the Importance of Mismatch Repair Deficiency and Microsatellite Instability in Pathology:** This module discusses the basic biology of mismatch repair deficiency (MMRd) and microsatellite instability (MSI), emphasizing the application of these tests to tumor samples. Participants learn how the tests were developed, the types and limitations of the tests, and how they are currently utilized.
- **Basic Concepts in Predictive Biomarkers for Immuno-Oncology:** This case-based module focuses on how tumor samples can be used to guide patient therapy. The module discusses general concepts of the predictive nature, cellular location, and reporting of programmed cell death ligand 1 (PD-L1) expression, and introduces ideas on future predictive biomarkers for IO.
- **Tumor Biology 101: Detecting Genomic Targets and Mutation Patterns:** This module provides participants with an understanding of the basics of genomics, MSI, genomic instability, tumor mutational burden (TMB), homologous repair defects, and related concepts, including their interplay and indication. In addition, participants learn how next-generation sequencing (NGS) can detect different types of genomic targets in tumor specimens, how to recognize patterns of tumor mutations for monitoring clonal evolution and treatment response, and how to recognize mutational patterns associated with TMB, MSI, and homologous repair deficiency.

Learning Objectives by Module

Understanding the Importance of Mismatch Repair Deficiency and Microsatellite Instability in Pathology

- Describe how MMRd and MSI tests were developed
- Discuss the limitations of MMRd and MSI tests
- Describe the current utilization of MMRd and MSI tests

Basic Concepts in Predictive Biomarkers for Immuno-Oncology

- Describe basic concepts of immune-based therapy, including immunosurveillance and immunosuppression of the tumor microenvironment
- Describe general concepts of predictive biomarkers, cellular location, and reporting of PD-L1 expression in various cancer types.
- Explain the advantages of immune checkpoint therapy and the types of patients who respond

Tumor Biology 101: Detecting Genomic Targets and Mutation Patterns

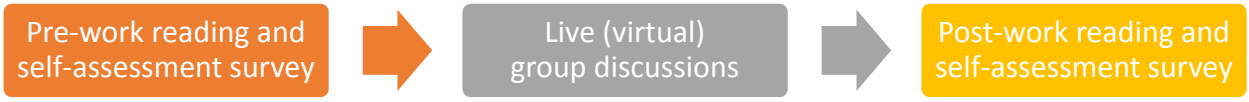
- Describe how NGS can detect different types of genomic targets in tumor specimens
- Recognize the patterns of tumor mutations for monitoring clonal evolution and treatment response
- Recognize mutational patterns associated with TMB, MSI, and homologous repair deficiency

Accessible to both US and international learners via ASCP's learning management system, each module promoted learning through the use of authentic, engaging patient cases and scenarios. Knowledge gain from the education was measured via a pretest and posttest

administered before and after each module, respectively. Each test contained 5 to 8 items targeting declarative knowledge and procedural knowledge. An evaluation administered at the end of each module also provided indirect insights into the participants' learning, based on their comments, as well as indications of the participants' perceptions of the quality and value of the education.

Activity 3: IO ChangeMakers: Virtual Leadership Discussions

The IO ChangeMakers activity consisted of CME-accredited group discussions aimed at educating and empowering community pathologists, senior laboratory professionals, and laboratory administrators to serve as effective change agents in their institutions. The sessions were led by an expert facilitator and incorporated a combination of pre-work, team-based case studies, and post-work.



These activities actively engaged participants around the role of physician leadership, the application of change management strategies, and the leadership skills needed for the navigation of IO care delivery in community settings. Via case-based scenarios, the participants discussed techniques to guide the delivery of IO among their interprofessional and multidisciplinary teams.

Aims of the IO ChangeMakers Activity

- Assess current practice patterns around the use of IO biomarker testing and checkpoint inhibitors
- Discuss the evolving landscape of IO biomarker testing, tumor biology and immune pathways, and the use of checkpoint inhibitors
- Apply leadership skills to navigate complex clinical and operational issues surrounding institutional IO policies and procedures
- Discuss how to lead organizational change and implementation efforts in the setting of a multidisciplinary cancer care team environment

Similar to the results of the baseline practice survey, the results of the IO ChangeMakers activity helped inform the design of subsequent educational activities, such as the panel discussions (Activity 5). Thematic analyses of the discussions, as well as the post-work, helped identify key challenges and obstacles to optimizing biomarker testing.

Activity 4: Multidisciplinary Live QI Initiatives

Three US community cancer centers accredited by the American College of Surgeons Commission on Cancer participated in intensive QI initiatives, centered on implementation science principles and the critical role of pathology in IO-based patient care, to help the centers implement process and care improvements and incorporate new scientific knowledge about the utility of IO agents for solid tumors and hematologic malignancies.

Through a series of live CME initiatives with follow-up activities, each cancer center used the Active Implementation Framework to develop site-specific performance improvement plans based on its unique educational needs.[8] This framework incorporates the Plan-Do-Study-Act cycles for quality improvement.[9]

Activity 5: IO Implementation PBL Live/ Enduring Panel Discussions

Two 1.5-hour CME multidisciplinary panel discussions were conducted live at ASCP's 2018 and 2019 Annual Meetings.

- **Overcoming Common Barriers Around the Application of Immuno-Oncology in Community Settings:** This panel featured interactive problem-based learning (PBL) with a focus on common barriers to implementing and delivering IO in community pathology settings, including a practical discussion around overcoming some of those barriers.
- **Advancing the Application of Immuno-Oncology to Improve Patient Care:** This panel reviewed the evolving landscape of IO biomarker testing and highlighted practical examples of quality improvements that could be implemented in cancer centers. Discussion topics included multidisciplinary perspectives around IO biomarker testing, the role of standardized processes and protocols, and the need to continuously evaluate and apply the latest evidence when diagnosing cancer and treating patients with immune checkpoint inhibitor (CPI) therapy.

Learning Objectives by Panel

Overcoming Common Barriers Around the Application of Immuno-Oncology in Community Settings

- Outline pathology-driven processes that can improve the use of appropriate IO diagnostics and therapies based around the latest clinical evidence
- Discuss ways that pathologists can actively engage members of the multidisciplinary cancer care team around the selection and use of IO therapies in community settings
- Describe how to strengthen pathology leadership on multidisciplinary teams as they guide their institution around complex and evolving IO trends

Advancing the Application of Immuno-Oncology to Improve Patient Care

- Review recent clinical evidence around IO biomarker testing and the use of immune checkpoint inhibitor therapy
- Outline pathology-driven processes that can improve IO biomarker testing
- Describe how members of the multidisciplinary cancer care team can implement new processes to improve the care of patients treated with immune checkpoint inhibitor therapy
- List specific examples of quality improvements directed around the use of IO biomarkers and immune CPI therapy

The session at the 2018 ASCP Annual Meeting, which featured interactive PBL, focused on overcoming common barriers to implementing and delivering IO in community pathology settings. At the session at the 2019 ASCP Annual Meeting, faculty and members of the multidisciplinary teams involved in the QI initiatives shared best practices and lessons learned. Both sessions were

recorded and subsequently offered as enduring materials to extend the reach of the sessions to other learners and broader laboratory medicine community.

Results

The following sections summarize the project outcomes using the framework of Moore's model for evaluating continuing medical education.[10] As shown in Figure 1, the model covers a variety of outcomes ranging from participation (level 1) to patient health and community health (level 6 and 7, respectively). The project produced outcomes through level 6.

Figure 1. Moore's model for evaluating continuing medical education.[10]

Outcomes: Participation

For the complete set of educational activities, there were a total of 7,233 participants. Across the online modules, IO ChangeMakers, and IO Implementation Live/Enduring Panel Discussions, there were 3,678 unique[iii] learners. Table 1 summarizes the number of participants by educational activity.

Table 1. Summary of participant counts by educational activity.

Educational Activity	Launch Date	Total Participants	Total Credits Awarded[iv]
IO Practice Survey	February 15, 2018	3,555	N/A
IO Scientific Core Online Modules	June 29, 2018	4,407	3,679
IO ChangeMakers Discussions	April 18, 2018	39 (4 groups)	66
IO Implementation Live / Enduring Panel Discussions (ASCP 2018, ASCP 2019)	October 3, 2018 / December 1, 2018 September 11, 2019 / October 15, 2019	1,460	1,650
Multidisciplinary Live QI Initiatives	March 6, 2019	41 (3 sites)	36

[iii] *Unique* indicates that learners who participated in multiple activities were counted only once.
[iv] CME/CMLE and SAMs credits

Demographic data from the baseline IO practice survey indicated that approximately 87% of the respondents were laboratory professionals and approximately 5% were physicians. The professional roles of the respondents also included the secondary target audiences for the education, including nurses, nurse practitioners, and other health care professionals. The target audiences were also represented in the online education. Approximately 11% of the total respondents who completed the module evaluation were physicians, and at least 75% were laboratory professionals. Among the 39 participants in the IO ChangeMakers activity, there were 26 physicians and 13 laboratory professionals.

The QI initiatives involved 3 cancer centers across the United States (in San Mateo, CA; Memphis, TN; and Richmond, VA) that were comprehensive community cancer programs accredited by the Commission on Cancer. Pathologists, cancer clinicians, and administrators at those centers had expressed a strong desire to improve IO biomarker testing and care coordination for patients treated with immunotherapy.

Outcomes: Satisfaction

Indications of the participant's satisfaction with the education included their perceptions of the overall quality of the content as well as the value and benefit they perceived. Ratings showed that at least 77% of the evaluation respondents rated the quality of the online modules as good or excellent (refer to Figure 2). Comments from several respondents also praised the quality of the education:

- "Excellent content, well presented"
- "Excellent info on biomarkers and potential pitfalls"
- "Excellent introduction to MMR and MSI"

Ratings of the live panel sessions, obtained via a paper evaluation deployed at the session, were also favorable. At least 75% of the respondents rated the sessions as good or excellent.

Examples of what participants in the online education found valuable

- "Gave me a better understanding of tumor biology, which I regularly interact with in my lab."
- "Great discussion on practical issues related to immuno oncology related lab testing"
- "I found the calculations needed to determine whether a patient will likely benefit from treatment or not valuable and interesting."
- "… This was a great introduction to some of the newer choices our clinicians are exposed to and have to decide on for research for the future, and treatment of current patients."

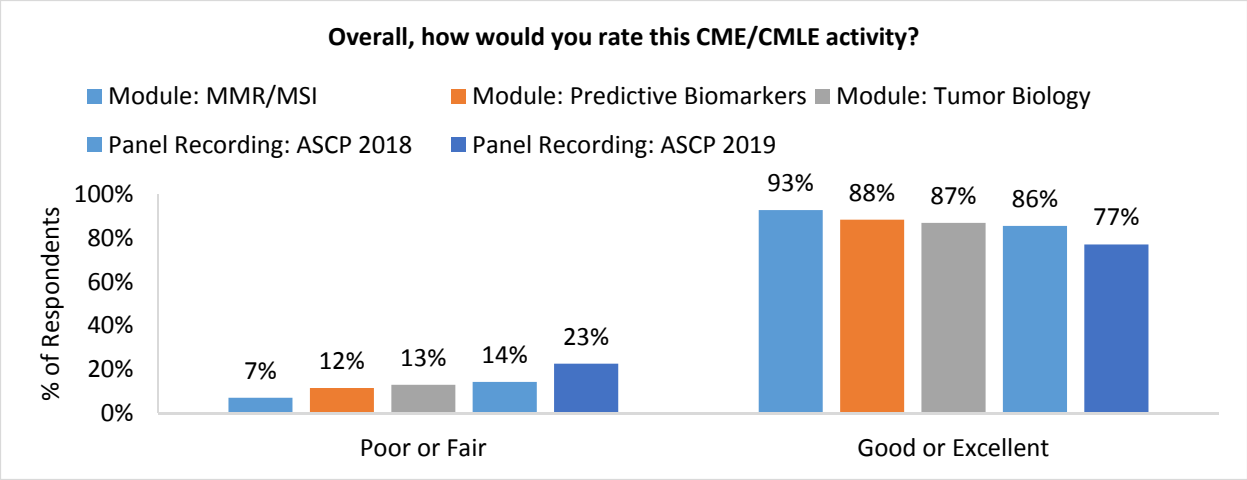
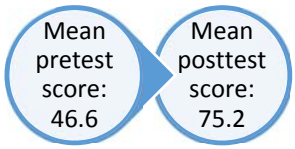


Figure 2. Ratings of the overall quality of the online education. (N = 833 MMR/MSI; N = 1,930 Predictive Biomarkers; N = 956 Tumor Biology; N = 600 ASCP 20199 Panel; N = 534 ASCP 2019 Panel).

Outcomes: Learning and Competence

Results of a dependent-means *t*-test of the overall pretest and posttest scores from participants in the online education indicated a significant increase in general knowledge of IO science: 28.8%, t(4,954) = 90.3, p < .01. Each module also showed a significant increase in the participant's understanding of IO science (refer to Figure 3).



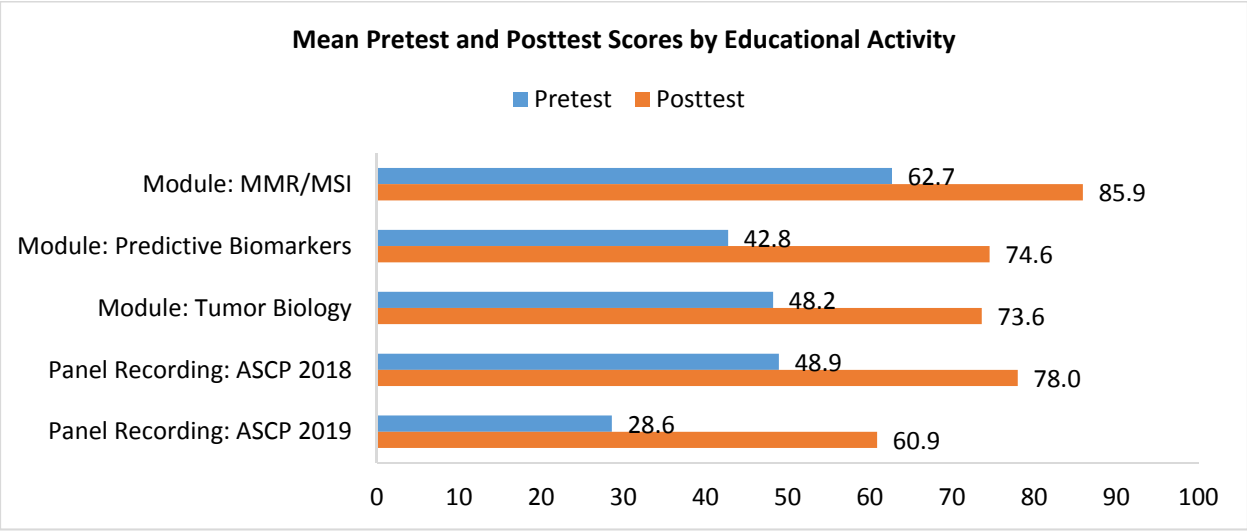


Figure 3. Mean pretest and posttest scores from the online education. (N = 4,955 pre; N = 4,955 post).

In addition to the direct measures of learning, there were also self-reports of learning via the module and panel evaluations. At least 75% of the evaluation respondents from the panel

sessions agreed or strongly agreed that they had gained or reinforced their knowledge/skills by participating in the session. More than half of the respondents (58% to 81%) also agreed or strongly agreed that the session had increased their confidence in their ability to do their job.

The results of the follow-up IO practice survey also provided longer-term indicators of increased knowledge and confidence. A total of 109 participants in the online education responded to the follow-up survey, and comparative analyses of matching indicators from the baseline survey and follow-up survey showed knowledge gain in several areas. Respondents rated their understanding of their IO knowledge in several areas significantly higher than respondents did in the baseline survey (refer to Figure 4):

- Knowledge of the requirements for PD-L1 expression testing, $t(2,605) = 12.2$, $p < .01$
- Knowledge of requirements for MMR vs. MSI testing, $t(2,620) = 11.9$, $p < .01$
- Knowledge of clinical mechanisms that differentiate IO therapies, $t(2,509) = 12.2$, $p < .01$

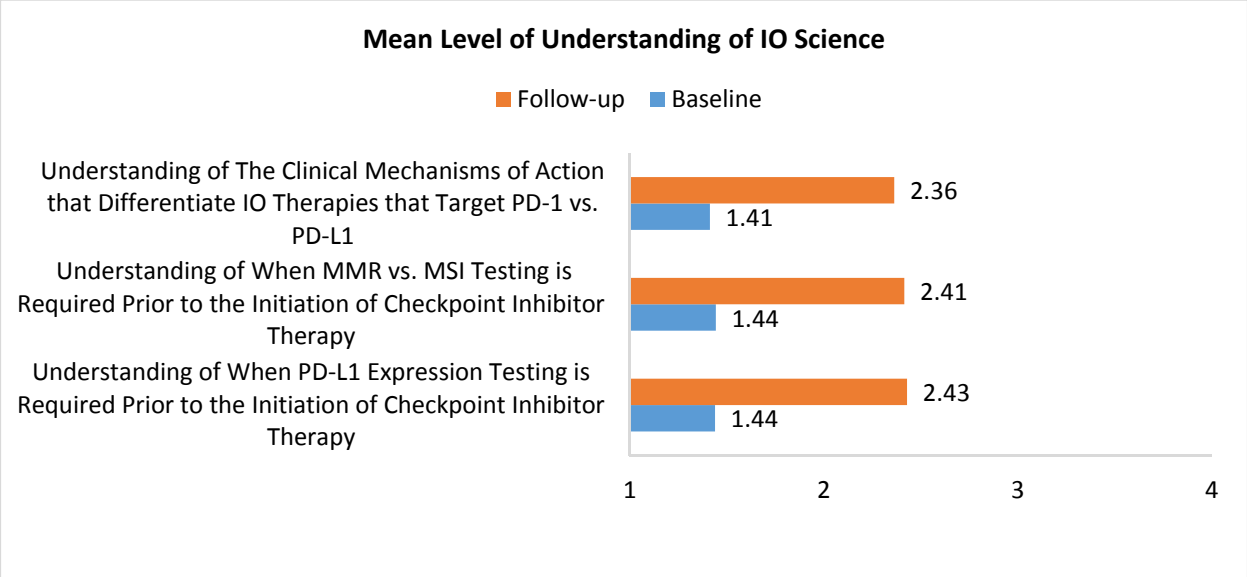


Figure 4. Participants' ratings of their understanding of IO science. 1 = Not knowledgeable, 2 = Somewhat knowledgeable, 3 = Moderately knowledgeable, 4 = Very knowledgeable. (N = 2,516 baseline, 91 follow-up).

Comparisons of baseline and follow-up ratings of confidence in ability to perform various IO-related tasks showed similar gains. Using a 4-point scale from "not confident" (1) to "very confident" (4), follow-up respondents rated their confidence in their ability to suggest an IO treatment based on pathologic testing and patient history significantly higher than respondents did in the baseline practice survey, $t(1,987) = 8.9$, $p < .01$. Mean ratings increased from 1.5 ($SD = 0.8$) on the baseline survey to 2.3 ($SD = 0.8$) on the follow-up survey. Furthermore, follow-up respondents also rated their confidence in their ability to recognize immune-related adverse events (irAEs) significantly higher than respondents did in the baseline practice survey (refer to Figure 5):

- Gastrointestinal: $t(1,989) = 8.4$, $p < .01$

- Pulmonary: $t(1,967) = 8.8$, $p < .01$
- Dermatologic: $t(1,962) = 7.7$, $p < .01$

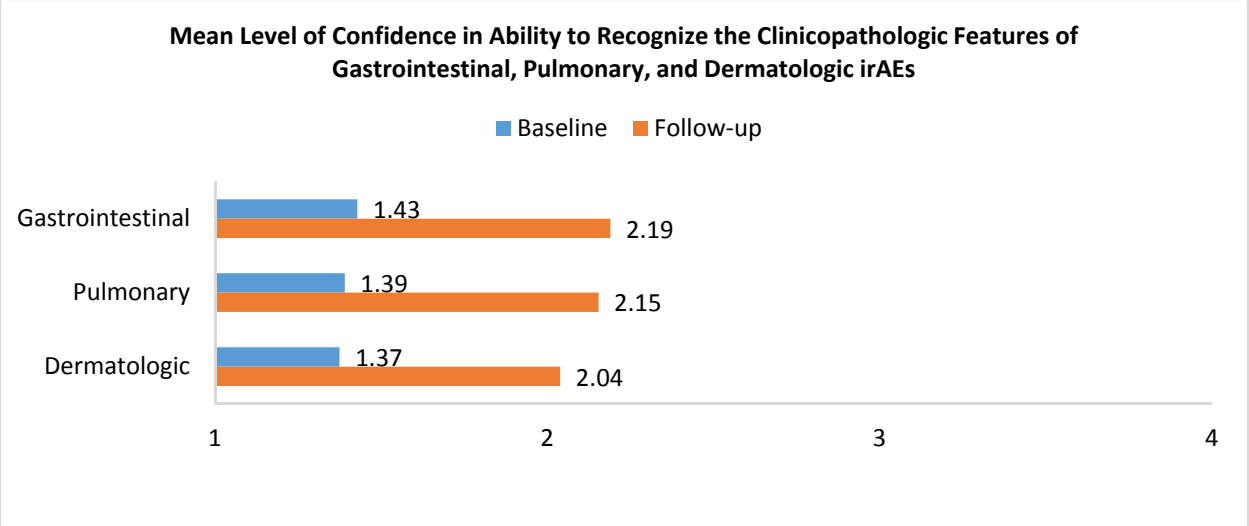


Figure 5. Participants' ratings of their confidence in their ability to recognize irAEs. 1 = Not confident, 2 = Somewhat confident, 3 = Moderately confident, 4 = Very confident. (N = 2,516 baseline, 91 follow-up).

Comments conveyed on the follow-up survey also provided insight into how the respondents had applied their learning. Examples of changes that the follow-up respondents had already made in their practice (at the time of the follow-up survey) due to the education included:

- Extending and/or sharing their knowledge
- Improving communication with members of the cancer care team, including tumor boards
- Revising testing procedures

In addition, qualitative analyses of the IO ChangeMakers discussions and pre- and post-work yielded insight into increased competence among the participants. Discussion within the groups focused around addressing key challenges and barriers to biomarker testing, including:

- Communication of test results to inform clinical action
- Navigating disagreements about testing policies/procedures
- Ensuring that clinicians understand test results
- The financial implications of biomarker testing

Examples of changes made in practice due to the online education

- "Able to guide others about what IO test is most appropriate and if it can be performed."
- "I have a better understanding of the tests and can discuss the tests with other physicians"
- "I shared my knowledge in tumor boards. I also improved in the selection of paraffin blocks for tumor testing."
- "Practicing and teaching with more confidence and experience; making appropriate test recommendations."
- "…there were several subjects touch[ed] upon in the IO educational series that were helpful in discussion and problem solving with pathologist and ordering oncologists."

In the post-work, participants identified numerous opportunities and ways to improve IO processes at their institutions. As shown in Figure 6, the top opportunities pertained to how team members communicated about the tests, how PD-L1 and MMR/MSI testing were conducted, and how results were used to inform treatment decisions. Only 5% of the participants indicated that their current processes were already optimized.

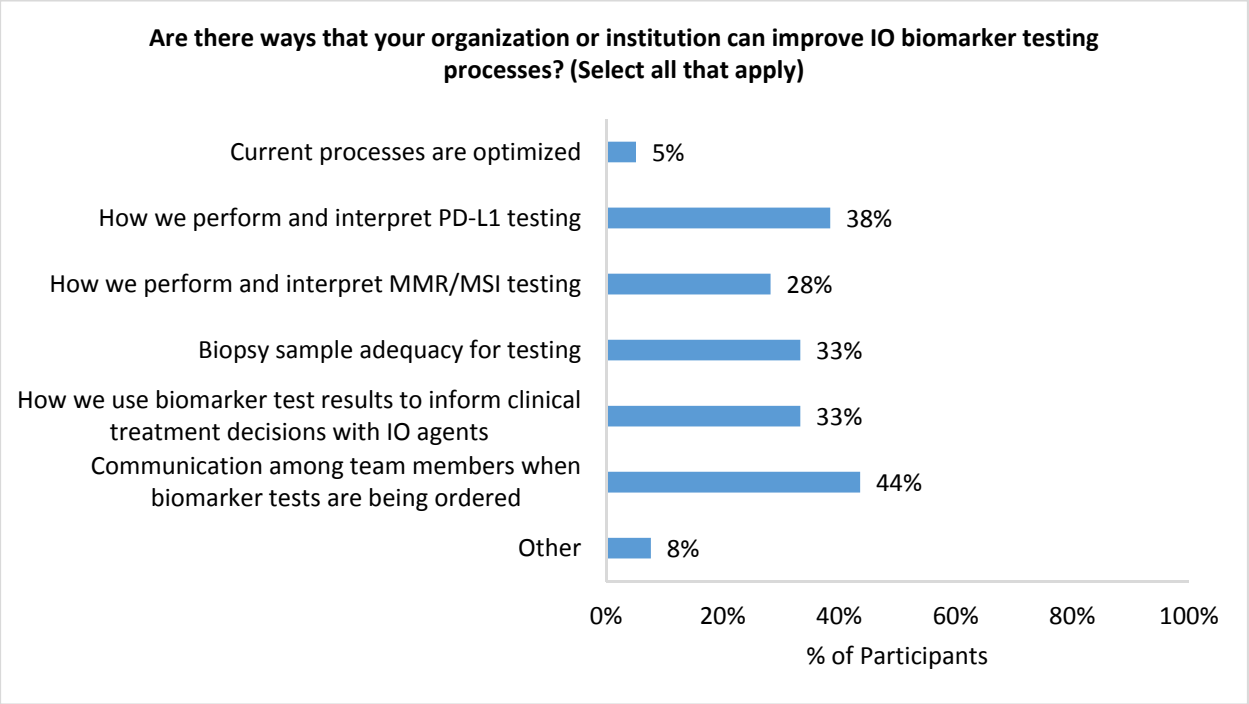


Figure 6. Prevalence of opportunities to improve IO processes at the institutions of the participants in IO ChangeMakers. (N = 39)

In the post-work, participants also reported exploring some of the potential improvements at their institution, including the possibility of performing more IO biomarker testing in their own laboratory (n = 16, 41%) and/or sending more samples out to other labs for IO biomarker testing (n = 4, 10%). At the completion of the IO ChangeMakers activity, one-third of the participants (n = 13, 33%) expressed strong interest in leading and implementing a systems-based QI project at their own institution. However, most of these participants were not decision-makers at their respective organizations and were not able to get approval from their colleagues at their cancer center or from their administrative leadership.

Outcomes: Performance and Patient Health

Both the processes and results of the QI initiatives (Activity 4) showed evidence of performance improvement. During the baseline assessment process, each cancer center reviewed patient charts and their processes of care. Collectively, the cancer centers reviewed 90 patient charts and found that:

- Patients had advanced cancers and were evaluated for treatment with an immune checkpoint inhibitor.
- PD-L1 tests were ordered for 85 of the patients, and the average turnaround time for obtaining the test results was 5.7 business days.

Across the charts, numerous types of cancer were represented, with non-small cell lung cancer (NSCLC) being the most prevalent (n = 75). Other types of cancer included gastric or gastroesophageal junction cancer (n = 6), melanoma (n = 3), cervical cancer (n = 2), colorectal cancer (n = 2), urothelial cancer (n = 1), and pancreatic cancer (n = 1).

Table 2. Summary of results from the baseline assessments from the QI initiatives

Baseline Indicator	Baseline Results	
PD-L1 tests performed	• 22C3: TPS (n = 80) • 22C3: CPS (n = 3)	• 28-8 (n = 2) • Not tested (n = 5)
Prevalence of "quantity not sufficient" (QNS)	QNS was noted in 3 cases (lung cancer biopsies)	
Testing site (in-house or outside lab)	All PD-L1 tests were sent out to different reference labs; none of the centers are performing PD-L1 tests in-house.	
Average turnaround time for test results	Average turnaround time for PD-L1 results = 5.7 business days • 5 occurrences where results exceed 14 business days	

During the QI workshops, the pathologists, cancer clinicians, and administrators on each QI team reviewed their baseline data and formulated a set of problem statements reflecting the obstacles and challenges to optimizing patient care. The participants discussed root causes that contributed to these problems and explored ways to make improvements in each of these areas. Table 3 summarizes the collective improvement ideas that were generated by the learners during the QI workshops across all the cancer centers.

Table 3. Summary of collective improvement ideas generated during the QI workshops

Area of Improvement	Description of Improvement
Ordering PD-L1 tests	• Improve communication by providing more clinical information when ordering PD-L1 tests; specify the type of tumor; indicate the type of therapy that the patient may be receiving; example: clarify how PD-L1 test ordering for triple-negative breast cancer (SP142) is different from ordering other PD-L1 tests (eg, 22C3 or 28-8) • Develop or update reflex biomarker testing pathways or protocols for specific indications (e.g., advanced NSCLC) • Update PD-L1 test ordering forms and processes to improve efficiencies; include more clinical information about the patient when ordering these tests • Develop processes to ensure that all eligible patients are considered for immune checkpoint inhibitor therapy; pathology may suggest PD-L1 testing when clinically indicated • Improve biopsy sample quantity and quality for biomarker testing (especially for lung cancer)
Timely access to PD-L1 test results	• Evaluate different processes that may improve turnaround time for test results • Assign a coordinator or navigator to check lab portals for test results • Utilize automation to streamline how test results appear in a coordinated fashion on multiple electronic health record (EHR) systems • Perform PD-L1 testing in-house; train pathologists on scoring and interpretation
Identifying and managing immune-mediated adverse events	• Improve communication between emergency/urgent care clinicians and medical oncology groups • Develop a process for proactive symptom assessment and monitoring • Integrate clinical decisions support tools into the EHR • Develop new patient education materials, wallet cards, etc. • Educate patients specifically about these risks • Extend oncology clinic hours to offer expanded access to patients

Following the workshop, the learners reviewed their ideas and assessed them for clinical impact versus feasibility (ease of implementation) using a priority matrix (e.g., low vs. high impact and easy vs. difficult to implement). Each team then selected two projects that had the highest clinical impact:

- Reflex Biomarker Testing Protocols (Cancer Center 1)
- Biomarker Tracking Dashboard (Cancer Center 1)
- PD-L1 Ordering Reference Card (Cancer Center 2)
- Proactive Symptom Management (Cancer Center 2)
- Extended Oncology Clinic Hours (Cancer Center 3)
- IO Journal Clubs (Cancer Center 3)

Upon implementing the selected interventions, the teams collected data to measure the corresponding outcomes and examine who well they had addressed the underlying aim of the intervention. Collectively, the QI initiatives achieved the following outcomes:

- Increased the use of PD-L1 and MMR/MSI testing in patients with advanced NSCLC, colorectal, gastric, cervical, urothelial, and triple-negative breast cancer
- Increased the likelihood that the correct PD-L1 test would be ordered based on the type of cancer and the intended therapy
- More timely and proactive detection and management of irAEs
- Increased patient access to cancer clinicians by extending clinic hours to manage irAEs
- Held ongoing education meetings as "IO journal clubs" to review the latest advances in IO biomarker testing and therapy

Summary and Conclusions

The education reached the target audiences, including pathologists, laboratory professionals, and other members of multidisciplinary care teams. Across the online modules, recorded panel discussions, and the IO ChangeMakers discussions, there were 3,678 total, unique learners. Participants rated the quality of the online education highly, and their comments touted the benefits and value for increasing their understanding of IO concepts. Pretest and posttest performance also provided direct indicators of significant knowledge gain among the participants in the online education. Overall mean scores increased from 46.3% correct to 75.2% correct, a 28.8% increase, $t(4,954) = 90.3$, $p < .01$.

Results from the follow-up survey also indicated knowledge gains, based on comparisons with the baseline control data. Follow-up respondents rated their knowledge in several areas significantly higher than respondents did in the baseline survey, such as:

- Knowledge of the requirements for PD-L1 expression testing
- Knowledge of requirements for MMR vs. MSI testing
- Knowledge of clinical mechanisms that differentiate IO therapies

The results also showed that the education had helped increased the participants' confidence in their ability to perform various IO-related tasks. Follow-up respondents rated their confidence in several areas significantly higher than respondents did in the baseline survey:

- Ability to suggest an IO treatment based on pathologic testing and patient history
- Ability to recognize gastrointestinal, pulmonary, and dermatologic irAEs

Participants in the IO ChangeMakers identified opportunities to improve biomarker testing at their institutions, and some of the ways were reflected in the types of improvements underscored by the QI initiatives. Across the QI initiatives, the project teams achieved numerous improvements in their IO processes and patient outcomes, such as:

- Increasing the use of PD-L1 and MMR/MSI testing in patients with advanced NSCLC, colorectal, gastric, cervical, urothelial, and triple-negative breast cancer
- Increasing the likelihood that the correct PD-L1 test would be ordered based on the type of cancer and the intended therapy
- Detecting and managing irAEs in a more timely proactive, manner

- Increasing patient access to cancer clinicians by extending clinic hours to manage irAEs
- Holding ongoing education meetings to review the latest advances in IO biomarker testing and therapy

Collectively, the outcomes provide evidence toward addressing the clinical gaps targeted by the project. For clinical gaps 1 and 2 (refer to p. 3), the knowledge gains imply improvement in the participants' understanding of IO concepts and the core science of IO (including biomarkers, checkpoints, and clinical pathways). The results of the follow-up survey also show improvements in the area of understanding implications that the results of IO testing in conjunction with patient history can have for the selection of specific IO treatments. In addition, the results of the follow-up survey suggest improvement in the participants' understanding of the importance of monitoring patients treated with CPI therapy for irAEs.

Pertaining to clinical gaps 3 and 4 (refer to p. 3), the processes engaged in the QI initiatives demonstrate site-based examples of integrating pathologists, laboratory professionals, cancer clinicians, and other member of multidisciplinary cancer care teams to improve IO processes and ultimately patient care. Furthermore, the interventions designed and implemented by the cancer care teams show examples of the clinical gaps being addressed in a local context. For example, the Reflex Biomarker Testing Protocols intervention provides an example of applying knowledge gains around IO testing to making improvements in testing protocols (e.g., establishing criteria around when the tests should be ordered, which labs would perform the testing, and how the results would be communicated, and implementing a process for updating the protocols based on significant emergent updates in IO science). Similarly, the Biomarker Tracking Dashboard intervention also provided examples of improvements in testing protocols, particularly around the availability and communication of test results. Also related to biomarker testing, the PD-L1 Ordering Reference Card intervention reflects improvements in the ordering of appropriate types of PD-L1 tests based on the type of cancer and the intended IO therapy, which can ultimately help reduce the need for repeat testing and associated delays in treatment planning. Both the Proactive Symptom Management and Extended Oncology Clinic Hours interventions show improvements in proactively addressing the types of irAEs that can occur in patients who are being treated with CPIs. Furthermore, the IO Journal Clubs intervention not only helps improve awareness of the core science of IO, as well as current IO testing and reporting guidelines, but also helps members of the cancer care team stay abreast of the latest advances and developments in IO that could impact patient care. These projects also add to the outcomes of the IO ChangeMakers activity in providing developmental support for pathology and laboratory leadership on multidisciplinary and interprofessional cancer care teams, addressing clinical gap 4 and supporting the overall project goals.

Future Educational Needs

Although the results show progress towards addressing the clinical gaps, the results also imply areas of continued and future educational needs. These needs include continuing efforts to:

- Improve communication between oncologists and pathologists as more patients undergo IO biomarker testing

- Cultivate a deeper understanding of biomarker testing as the science becomes more complex
- Promote understanding the role of NGS when selecting patients for IO therapy
- Provide safe and appropriate care as clinicians expand the use of IO to treat many other types of cancers
- Increase awareness of emerging biomarkers such as TMB
- Proactively identify and manage severe irAEs

Acknowledgements

The project was funded by an independent educational grant from Pfizer/Merck KGaA.

References

[1] Huber C. *Association for Cancer Immunotherapies 2014 Annual Report*. Mainz, Germany: 2014. http://www.cimt.eu/about. Accessed June 10, 2017.
[2] Feldman M, Milone M; ASCP Immuno-oncology Workgroup. IO Educational Strategy: Meeting Notes. May 1, 2017.
[3] Betrand A, Kostine M, Barnetche T, Truchetet ME, Schaeverbeke T. Immune related adverse events associated with anti-CTLA-4 antibodies: systematic review and meta-analysis. *BMC Med*. 2015;13:211.
[4] Blood bank issues in targeted therapy interference. Interview with Richard Kaufman, MD, Brigham Young University. May 24, 2016.
[5] Strobel SL. Enhancing the pathologist's role at hospital tumor boards. *Ann Clin Lab Sci*. 2006;36(3):243-247.
[6] Perl DP. The role of the pathologist in translational and personalized medicine. *Mt Sinai J Med*. 2007;74(1):22-26.
[7] Combes JR, Arespacochaga E. *Lifelong Learning Physician Competency Development*. Chicago, IL: American Hospital Association Physician Leadership Forum; 2012. http://www.ahaphysicianforum.org/files/pdf/physician-competency-development.pdf. Accessed July 24, 2017.
[8] Fixsen DL, Naoom SF, Blasé KA, Friedman RM, Wallace F. *Implementation Research: A Synthesis of the Literature*. Tampa, FL: National Implementation Research Network; 2005.
[9] National Implementation Research Network. *Active Implementation Networks*. Chapel Hill, NC: NIRN; 2013.
[10] Moore DE Jr, Green JS, Gallis HA. Achieving desired results and improved outcomes: integrating planning and assessment throughout learning activities. *J Contin Educ Health Prof*. 2009;29(1):1-15.