PMC PERSONALIZED MEDICINE COALITION

Dear Colleague:

Personalized medicine — linking therapies to molecular diagnostic tests to ensure that the right treatments are targeted to the right patients — is still more aspiration than reality.

Although we have made enormous progress in developing a new scientific appreciation of human heterogeneity, as evidenced by the rise in the number of personalized treatments on the market from five in 2008 to over 250 today, significant obstacles remain.

In brief, we need more evidence that personalized medicine works — that it can improve clinical outcomes while making health care more efficient and therefore less costly.

The proposals in this *Sponsorship Prospectus* are designed to help us do that. They tackle issues across a wide spectrum of topics from early stage discovery to clinical adoption.

Four of this program's initiatives are in progress, but the other five proposals are not fully funded.

We therefore request your thoughtful consideration of the *Prospectus*, which calls on organizations from multiple sectors of the health care ecosystem to provide support, in addition to membership dues, for the Personalized Medicine Coalition's *Research Program Studying the Clinical and Economic Utility of Personalized Medicine in Multiple Disease States*.

Sincerely yours,

Edward Abrahams, Ph.D.
President

Jay G. Wohlgemuth, M.D.
Chairman, Board of Directors

Summary of Research Portfolio

IN PROGRESS

1. ***Defining the Clinical Utility of Genomic Testing in Cancer Care*** will advance a more comprehensive definition of clinical utility in cancer care that can prompt more widespread clinical adoption of genomic testing technologies by highlighting underappreciated benefits of testing. *

2. ***The Integration of Personalized Medicine into US Health Systems:* A Landscape Analysis** will explore through survey research and interviews the extent to which providers throughout the U.S. health care system are already integrating personalized medicine in clinical settings. *

3. ***The Cost-Effectiveness of Next-Generation Sequencing (NGS)-Based Diagnostic Tests for Cancer Patients*** will inform efforts to integrate personalized medicine into clinical work streams by providing evidence about the cost-effectiveness of NGS in melanoma. *

PARTIALLY FUNDED

4. ***Evaluating the Clinical and Economic Value of Sequencing-Based Diagnostic Tests for Patients With Rare and Undiagnosed Diseases*** will provide evidence about the clinical and economic utility of sequencing-based diagnostics when applied to patients with rare or undiagnosed diseases. *

5. ***Understanding Genomic Testing Utilization and Coverage in the US*** will analyze the extent to which health systems utilize genomic tests in various contexts related to coverage and access. *

NOT YET FUNDED

6. ***Pharmacogenomics in Clinical Guidelines and at FDA*** will benchmark clinical progress in personalized medicine by providing a list of the circumstances in which current clinical guidelines combined with the labels of FDA-approved therapies support the use of personalized medicine strategies that tailor care based on scientific knowledge about drug-gene interactions. *

7. ***Improvements in Clinical Care Associated With Personalized Medicine (Phase 2 of the Integration of Personalized Medicine into US Health Systems)*** will develop a model to compare the clinical and economic outcomes at institutions that have incorporated personalized medicine strategies to those of institutions that are still tied to one-size-fits-all approaches. **

8. ***Addressing Practice Gaps in the Implementation of Personalized Medicine in Cancer Care*** will examine barriers that are discouraging the clinical integration of personalized medicine in cancer care. *

9. ***The Library of Personalized Medicine: An Online Resource*** will educate policymakers, journalists, and the public about personalized medicine's scope and significance. *

* An explanation of the purposes, methodologies and planning supporting the project is enclosed.

** The findings from "2.) *The Integration of Personalized Medicine into US Health Systems*: A Peer-Reviewed Research Article" will inform the development of a forthcoming summary of this project's purposes and methodology. More details are available upon request.
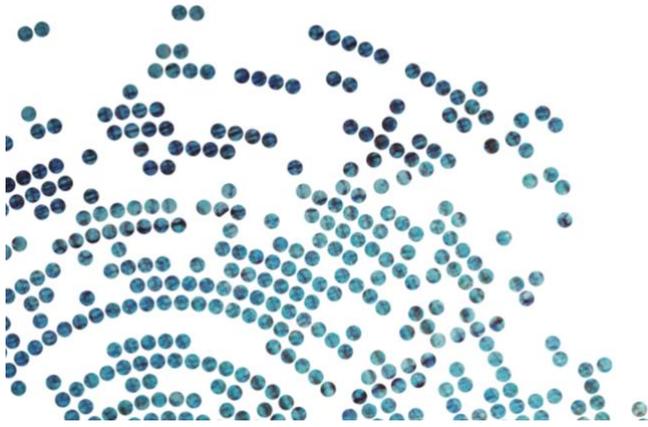
1. Defining the Clinical Utility of Genomic Testing in Cancer Care

In Progress

BACKGROUND

The use of advanced diagnostic tests to detect predictive and prognostic biomarkers is a cornerstone of personalized medicine, providing a way to guide treatment and prevention strategies based on individual patient characteristics. However, despite varying levels of evidence supporting the clinical utility of many biomarker-based strategies, advanced diagnostic testing is often not appropriately or effectively used in clinical practice. The consistent use of biomarker testing faces implementation challenges related to insufficient awareness and education, a lack of recognition by payers and providers of the clinical value of testing, and outdated practices, policies and processes. A firm understanding among all health care stakeholders of all the ways in which biomarker testing has clinical utility will be instrumental to overcoming implementation challenges and providing the most efficient and effective personalized health care.

Developing this expanded definition of clinical utility will require a better understanding of current provider and payer perspectives on biomarker testing along with a comprehensive examination of how testing strategies can benefit patient care. This, in turn, can inform further efforts to address challenges associated with personalized medicine implementation.

OBJECTIVES

PMC will examine current perspectives on the use of personalized medicine strategies in health care delivery and identify all of the factors that can help determine the clinical utility of multiplex genomic testing in clinical practice, such as for use in patient screening, prognosis, treatment decisions, clinical trial recruitment, and to inform potential off-label uses. Based on these findings, PMC will develop recommendations to broaden the definition of the clinical utility of multiplex genomic testing in patient care. The recommendations will be made to key personalized medicine stakeholders, including health care providers, payers, clinical guideline developers, clinical laboratories, and patients, to help inform their policies and processes and support their educational efforts.

PROJECT OUTLINE

The project will involve examination of current perspectives on the use of multiplex genomic testing and the subsequent development of recommendations to key personalized medicine stakeholders for the inclusion of a comprehensive set of value factors within a broadened definition of clinical utility.

1. Phase 1: Stakeholder Roundtable Event
   a. Objectives:
      i. Bring together health care providers and payers to identify the components of what an expanded definition of clinical utility could and should consist of
      ii. Align on recommendations for how expanding the definition of next-generation sequencing clinical utility can be implemented in the community to enhance patient care
         - To do this, PMC envisions the experts discussing their clinical practice (case studies), responding to pre-prepared topics/questions related to utility factors, and describing how their practical experience could inform the development of recommendations on an expanded definition of clinical utility
   b. Format:
      i. Moderated roundtable discussion to examine case study examples and respond to pre-prepared topic points related to different elements of the clinical utility of advanced genetic tests
      ii. Roundtable participants will discuss how recognition of clinical utility can help address practice gaps and develop recommendations on how to broaden the perception of utility and value amongst providers
   c. Who:
      i. 10-20 experts
         - 4 academics (representing multiple tumor types)
         - 6 community (mix of hospital system and stand-alone practice)
         - 2 - 3 payers (1 - 2 attached to practice also in the room — commercial, CMS)
         - 2 - 3 molecular pathologists/lab directors
         - Representatives from AACR (GENIE)/ASCO/NIH (*All of Us* and NCI Lung-MAP)
   d. Pre-meeting materials may include:
      i. Prepared document with discussion topics, considerations, and potential suggestions for review by roundtable participants
      ii. PowerPoint presentation for roundtable discussion
      iii. Press release
      iv. Blog, website and social media content
   v. Email to membership and other identified partners

2. Phase 2: Report/Recommendations
    a. Value data
    b. Clinical recommendations
    c. Operational recommendations
    d. Influence on guideline development bodies (such as NCCN) and payers
    e. Willingness of attendees to kick off studies at their institution
    f. Request attendees to advocate for this topic during future speaking engagements

CONCLUSION

Many organizations within the personalized medicine community have emphasized the importance of driving a better understanding of the clinical utility of genomic profiling in cancer care amongst all stakeholders, including payers and providers. This project is PMC's answer to that call.
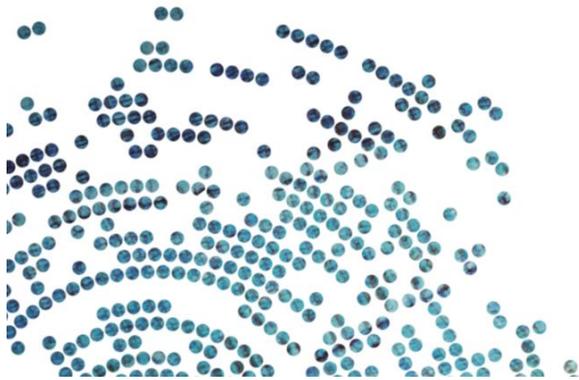
BACKGROUND

Providers are increasingly working to integrate personalized medicine into their health care delivery systems. Led by several pioneering institutions, academic health centers and community hospital systems across the U.S. are adopting strategies and processes to overcome clinical implementation challenges. By examining the experiences of these personalized medicine programs, the broader health care community is developing a better understanding of how to integrate personalized medicine into clinical practice. It is not clear, however, what impact the move towards personalized medicine within these pioneering institutions has had so far on the health care system in general. A better understanding of the current landscape for implementation within the U.S. health care delivery system will help clarify the extent to which personalized medicine has penetrated health care and help identify remaining needs. This, in turn, will inform efforts to address the most critical outstanding integration challenges.

OBJECTIVE

This project will examine varying perspectives and practices in order to capture a holistic picture of the clinical adoption of personalized medicine strategies and technologies within the U.S. health care system by querying provider institutions about baseline community, institutional, and service delivery details as well as practice patterns and viewpoints related to personalized medicine and its utilization. This, in turn, can help inform efforts to address the most critical outstanding integration challenges. The landscape analysis will include a representative sample of U.S. health care delivery institutions and could include both quantitative and qualitative results to ensure that a U.S. health system-wide picture of the integration of personalized medicine is captured.

PROJECT OUTLINE

The project, to be completed in 4 - 6 months, will involve a short survey and/or a series of interviews of U.S. health care delivery systems and subsequent analysis that will help demonstrate the current landscape of personalized medicine integration.

PMC's health care working group will guide the project, review survey questions, track progress at various milestones, and ensure an appropriate sample of survey respondents.

Survey respondents will include a representative sample of U.S. health care delivery institutions including academic health centers; urban, suburban, and rural community hospital systems; and integrated payer/provider systems.

CONCLUSION

Many organizations within the personalized medicine community have called for an analysis of the current landscape for personalized medicine implementation in the U.S. This project is PMC's answer to that call.
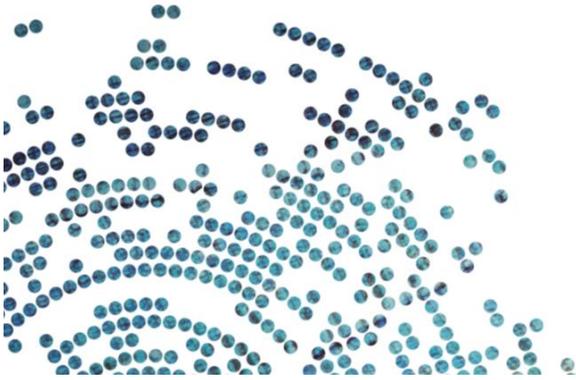
BACKGROUND

Introducing new technologies in health care, especially ones that propose to transform medical practice, can be a daunting exercise because, as Machiavelli explained, most people "do not believe in anything new until they have actual experience of it."

While the rapid decrease in the cost of next-generation sequencing (NGS) has opened up new opportunities to analyze cancer tumors to determine what therapies may be most effective, most payers and providers have had too little experience with the proposed new approach to take the lead in the introduction of a new paradigm that links the choice of therapy to the information that can be derived from sophisticated molecular diagnostics.

Without evidence that it works both for patients in better clinical outcomes and for the health systems that employ it in lower systemic costs, "medicine's next step," as President Obama has called it, will come much more slowly than we would like.

OBJECTIVE

With a planning grant of $150,000 from Quest Diagnostics, PMC organized a steering committee to develop a proposal that would demonstrate the clinical and economic value of NGS-based diagnostic testing in cancer care. The proposal outlines research that will evaluate the value, both clinical and economic, of solid tumor NGS-based diagnostic testing to guide targeted therapies. Developed by Scott Ramsey, M.D., Ph.D., at the Fred Hutchinson Cancer Research Center, it will lead to a peer-reviewed publication whose purpose is to provide evidence for developers, payers, and providers that NGS-based diagnostic testing is both clinically useful and economically efficient. As the research proposal states, "The primary hypothesis of this study is that, based on current evidence, multiplex NGS testing can be cost-effective from a payer perspective, when compared to the current standard in diagnostic testing (i.e. no testing or selected mutation testing")."

RESEARCH OUTLINE

The project will be broken into two phases. The first phase, to be completed in 6 - 9 months, will consist of the development of a value model validated with existing real-world data on NGS-based testing in non-small cell lung cancer, given the growing importance of targeted therapies in this cancer type.

The second phase, to be completed in 18 months, will include an expansion of the value assessment in other major carcinomas for which mutational analysis is prevalent, such as colorectal cancer and/or melanoma, and will also involve a value of information analysis and the identification of factors that significantly impact the cost-effectiveness of NGS-based diagnostic testing.

The project will aim to assess the value of tumor mutation profiling in general, rather than compare technology platforms.

A project advisory committee will be formed to guide the project, review progress at various milestones, and to ensure the use of appropriate and up-to-date data.

Research will utilize existing data sets and/or ongoing studies to the extent possible, supplemented with data from health systems and medical records.

In the first phase of the study, PMC will coordinate a meeting with the research team, advisory committee members, and other partners, to determine what data sets should be explored for use in the study and how we will gain access to these data sets.

A payer advisory committee will also be formed to provide guidance so the project results will be useful in informing the coverage and payment process.

Results of the study will be published in a peer-reviewed journal and disseminated through a robust communications plan to increase awareness and become a resource for decision-makers in government, industry, and health care.

CONCLUSION

Many organizations within the personalized medicine community have called for assessments of the value of NGS-based diagnostic testing. This project is PMC's answer to that call.
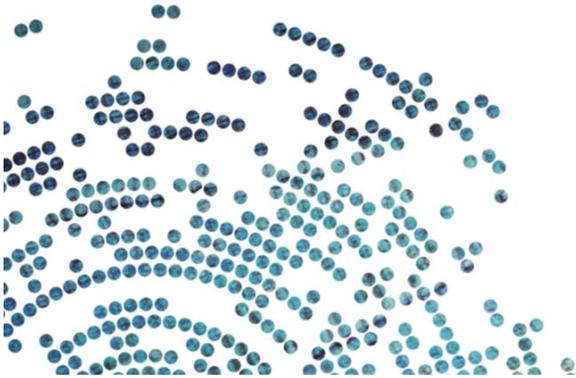
4. Evaluating the Clinical and Economic Value of Sequencing-Based Diagnostics for Patients With Rare and Undiagnosed Diseases

Partially Funded

BACKGROUND

For patients with rare and undiagnosed diseases, genomic sequencing — determining a patient's entire unique DNA makeup — may be an extremely valuable tool for discovering the genetic alterations that contribute to disease development, as well as for influencing treatment decision-making. Patients with rare and undiagnosed diseases are most often children who may have already undergone single-gene testing but still have not received a definitive diagnosis. They are sometimes referred to as "diagnostic odyssey" cases, as a child and family can bounce around various medical centers for years while numerous diagnostic procedures are performed and health care costs are accrued. All the while, the disease goes undiagnosed.

As they go through their diagnostic odysseys, these patients' diseases progress and they lose time during which they could potentially receive effective therapies or be enrolled in a clinical trial.

OBJECTIVE

PMC organized a project planning committee to develop a request for proposals for a study that would demonstrate the clinical and economic value of sequencing for rare and undiagnosed diseases. A research proposal developed by Peter Neumann, Sc.D., at the Institute for Clinical Research and Health Policy Studies at Tufts Medical Center was selected. The study will address the primary hypothesis as stated in the proposal: "Genomic sequencing testing can speed diagnosis and initiation of appropriate care and can be cost-effective when performed early on in clinical course."

Interested partners will be included on a project steering committee that will help guide the project, review progress at various milestones, and ensure the use of appropriate and up-to-date data. The study will lead to a peer-reviewed publication whose purpose will be to provide evidence for sequencing platform developers, payers, and providers that sequencing-based diagnostic testing is both clinically useful and economically efficient when applied to the right patient population.

RESEARCH OUTLINE

The project, to be completed in 6 - 9 months, will involve the development of a clinical and economic value model validated with existing real-world data from institutions that are regularly sequencing patients (and in some cases, the child and both parents) with diseases of unknown etiology.

The project may also involve a value of information analysis and the identification of factors that significantly impact the cost-effectiveness of sequencing-based diagnostic testing.

Research will utilize existing data sets and/or ongoing studies to the extent possible — supplemented by the collection of data from health system and medical records.

As the convener of the study, PMC will coordinate a meeting with the research team, steering committee members and other partners to determine what data sets should be explored for use in the study and how we will gain access to these data sets.

The project's aim is to assess the value of sequencing rare and undiagnosed disease patients in general. The study will not compare technology platforms.

A payer and employer advisory committee to include health insurers, large employers, and employer benefits management groups will also be formed to provide guidance, especially related to cost/benefit assumptions utilized in the value model, so the project results will incorporate the perspectives of these key stakeholders, increasing the likelihood that the results will be useful in informing the coverage and reimbursement process. Results of the study will be published in a peer-reviewed journal and disseminated through a robust communications plan to increase awareness and become a resource for decision-makers in government, industry and health care.

CONCLUSION

Many organizations within the personalized medicine community have called for evidence demonstrating the value of genomic sequencing in rare and undiagnosed disease. This project is PMC's answer to that call.
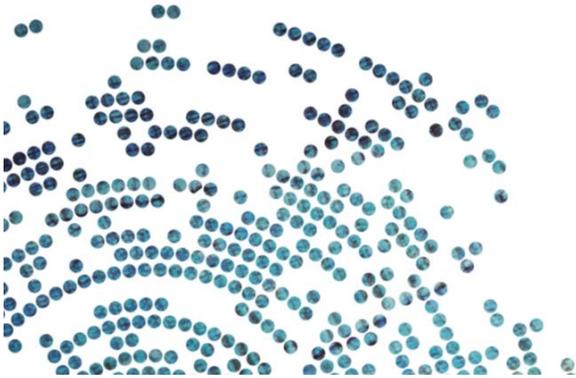
BACKGROUND

Personalized medicine rests partly on the assumption that genomic testing can aid in treatment management decisions, yielding both clinical utility and economic value. Genomic testing has the potential to improve clinical care by providing important information that can speed diagnosis, inform treatment decisions, and improve the efficiency of health care delivery in several areas, such as prenatal screening, oncology, and rare and undiagnosed disease. However, genomic testing technologies are relatively new, and providers face several barriers to the adoption of policies and procedures that will lead to widespread access of genomic testing in clinical practice. A better understanding of the utilization of genomic testing across the U.S. health system and how it relates to patient access will provide insight into genomic testing implementation trends and barriers.

OBJECTIVE

This study will examine the patterns of utilization of genomic sequencing for noninvasive prenatal testing, tumor diagnosis, and rare and undiagnosed disease in the U.S. Utilization will likely be related to a patient's distance to testing facilities, insurance coverage, and social/environmental impacts on access to testing. The results of this study's analysis will be included in a report whose purpose will be to provide key personalized medicine stakeholders, including providers, pharmaceutical and diagnostic manufacturers, payers, patients, and lawmakers with insight into genomic testing implementation and barriers so as to inform efforts to integrate and deliver personalized medicine to all patients who can benefit.

PROJECT OUTLINE

Using a U.S. clinical genetic testing market database cross-referenced to claims data, the project will involve examination of current utilization patterns of genomic sequencing-based testing as related to access factors, including coverage, distance to genomic testing facility, and social and patient-level determinants of health care.

PMC, Illumina, Concert Genetics, Blue Cross Blue Shield Association (BCBSA) and the Blue Cross Blue Shield (BCBS) Institute will work together to coordinate data collection, analysis, and development of reports.

Results of the study will be published in three separate documents:

1. A two-page analysis preview;
2. A PMC white paper detailing the findings; and

3. A manuscript focusing on implications to the integration of personalized medicine in health care to be published in a peer-reviewed journal.

The report and manuscript will be disseminated through a robust communications plan to increase awareness and become a resource for health care decision-makers.
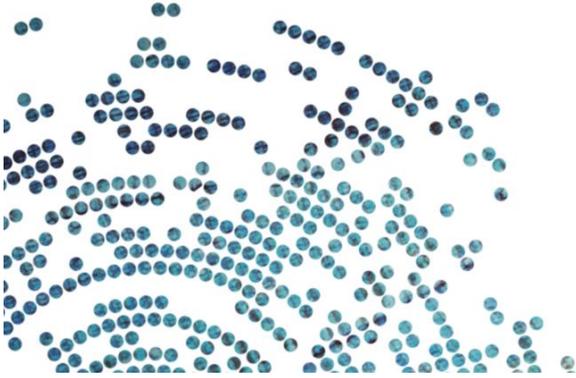
6. Pharmacogenomics in Clinical Guidelines and at FDA

Not Yet Funded

BACKGROUND

Pharmacogenomics (PGx) can play an important role in identifying responders and non-responders to medications, avoiding adverse events, and optimizing drug dosing. The use of diagnostic tests to detect PGx gene-drug interactions is a cornerstone of personalized medicine, providing a way to guide treatment and prevention strategies based on individual patient characteristics. Despite varying levels of evidence supporting the clinical utility of many PGx markers, only a select few are recommended for use in informing clinical decisions. Because of this variability in supporting evidence, PGx clinical practice guidelines formulated by panels of experts have a significant impact on the pace at which providers integrate new PGx tests and other novel technologies into their clinical work streams.

A better understanding of the current status of PGx gene-drug association inclusion in the clinical practice guidelines developed by major guideline development bodies will help clarify the extent to which personalized medicine technologies have been integrated into clinical care. An examination of biomarkers included in guidelines can also highlight areas where clinical evidence of utility is being developed but where widely recognized biomarker-based prevention and treatment strategies have not yet been included in clinical guidelines or within drug labels. This, in turn, can inform further efforts to advance personalized medicine implementation.

OBJECTIVE

PMC will catalogue the PGx-based gene-drug associations that are included in current guidelines for different health conditions and compare this to PGx associations included in drug labels. The results will be included in a report whose purpose will be to provide key personalized medicine stakeholders, including product developers, clinical laboratories, health care providers, payers, patients and policymakers with information about what PGx strategies are commonly used in practice and what strategies may require additional evidence development or provider outreach and education efforts.

PROJECT OUTLINE

The project will involve a comprehensive examination of the current clinical practice guidelines for PGx published by major guideline development organizations, including but not limited to those published by CPIC, and subsequent cataloging of included gene-drug interactions.

The clinical guideline PGx catalogue will be compared directly to PGx information listed in FDA's *Table of Biomarkers in Drug Labeling* and through a direct review of existing drug labels.

Drug-gene interactions for which there is inconsistency between inclusion in FDA labeling and clinical guidelines will be highlighted.

The results will be published in a white paper detailing the findings and policy implications.

PMC will engage with guideline development organizations and FDA to have them advise the research strategy and review results.
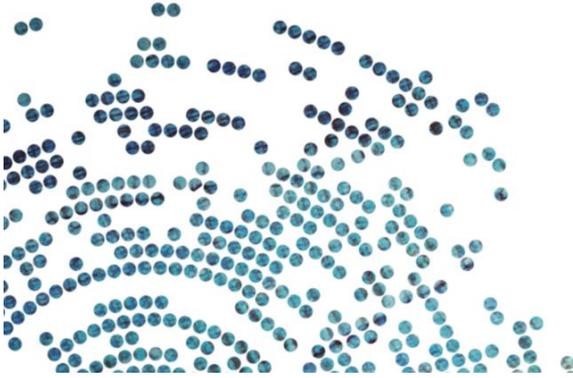
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8. Addressing Practice Gaps in the Implementation of Personalized Medicine in Cancer Care
Not Yet Funded

BACKGROUND

Predictive biomarker testing to help identify patients who could benefit from targeted therapies is a cornerstone of personalized medicine in cancer care, informing treatment decisions that can lead to better patient outcomes and improve the efficiency of the health care system. Predictive biomarker testing technologies are relatively new, however, and providers face several barriers as they seek to integrate the tests into clinical work streams. For example, although more than 30 percent of patients with non-small cell lung cancer (NSCLC) have tumors that are linked to genetic driver mutations, many NSCLC patients do not receive genomic testing. Furthermore, a recent Personalized Medicine Coalition report has estimated that only 65 - 75 percent of NSCLC patients with an actionable mutation as determined by genomic testing actually receive targeted therapies.

A recent analysis by Diaceutics estimated that more than 30 percent of cancer patients in the U.S. never receive targeted therapies that they may have benefitted from. The practice gap between patients that are eligible for targeted therapies and those that receive them is attributed, in part, to:

1. Limited access or availability of predictive biomarker tests;

2. Sample processing constraints;

3. Test performance;

4. Challenges related to reporting and interpretation of test results;

5. Limited access to targeted therapies; and

6. Lagging awareness of the rapidly evolving field of personalized medicine.

In order to help optimize the clinical use of genomic testing in cancer care and to accelerate the clinical adoption of personalized strategies, a better understanding of the associated clinical practice gaps is necessary.

OBJECTIVE

This project will utilize the Diaceutics Global Diagnostic Index (GDI) database to examine the practice gaps associated with biomarker testing-informed personalized medicine strategies in NSCLC care. The study will draw conclusions about specific practice challenges, including those related to test access and availability, sample processing, test performance, test interpretation, and utilization of results. The study will also estimate

the impact that each of these factors has on the delivery of personalized cancer care. Implementation challenges will be considered as part of a matrix of elements contributing to the overall biomarker testing practice gap. The final report will offer testing optimization recommendations.

The results will be included in a report whose purpose will be to provide key personalized medicine stakeholders, including providers, payers, clinical guideline developers, pharmaceutical and diagnostic manufacturers, and patients with insight into how biomarker testing is being implemented throughout the health care system and the impact of several potential implementation barriers. These insights can inform efforts to optimize predictive biomarker testing in clinical practice and therefore help drive the delivery of personalized medicine to all cancer patients who can benefit.

PROJECT OUTLINE

The project, to be completed in 6 - 9 months, will involve the development of a matrix of practice elements contributing to sub-optimal use of personalized medicine strategies in cancer care and will estimate the impact of each practice element toward the overall clinical practice gap.

Research will utilize existing data sets from the GDI database, which includes practice-level data for approximately 260,000 NSCLC patients who were diagnosed between October 2018 through September 2019, showing their testing rates, test performance, and treating habits.

A project steering committee will help guide matrix design and assure that results are meaningful to key audiences.

The project's aim is to assess the practice gaps related to biomarker testing and targeted therapy in NSCLC in general. The study will not compare technology platforms.

Based on the analysis, PMC will make clinical implementation recommendations, which will be published as a white paper alongside the results.
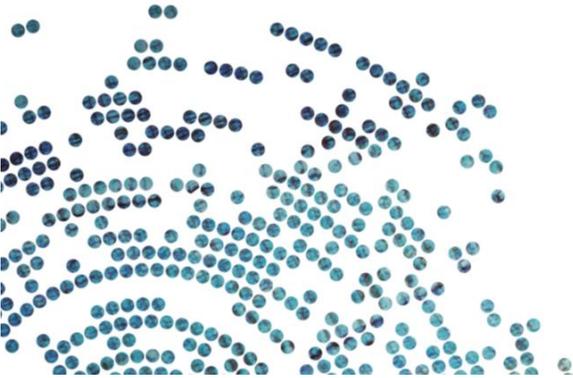
BACKGROUND

Personalized medicine seeks to target more effective prevention and treatment strategies to only those patients who need them. By recommending lifestyle changes to patients with certain molecular risk factors and matching small groups of sick patients to molecularly guided therapies that often address the root causes of their diseases, personalized medicine improves health care for patients and health systems by keeping patients healthier, longer.

But this new approach to medicine presents an unfamiliar value proposition to patients and health systems that are accustomed to treating large populations of patients with cheap daily maintenance medications. For this reason, many policymakers, journalists, and thought leaders have been slow to appreciate the scope and significance of the field, delaying the adoption of systemic changes necessary to accelerate the pace at which personalized medicine strategies are integrated into clinical work streams.

OVERVIEW

To educate policymakers, journalists, and the public about the principles, scope, and benefits of personalized medicine, PMC seeks to build a *Library of Personalized Medicine* that can serve as a resource for decision-makers in the public and private sectors. The *Library* would include:

- Information about the science underpinning personalized medicine;
- A description of how personalized medicine improves upon the standard of care;
- A summary of the existing evidence supporting the use of personalized medicine strategies in various disease states;
- An annually updated list of key diagnostic tests that can inform personalized prevention and treatment strategies, to include a description of the significance of each test; and
- An annually updated list of personalized therapies approved by FDA, to include a description of the significance of each treatment.