Precision Medicine: Adoption of Emerging Methods of Evaluation and Therapy

Introduction

Precision medicine is revolutionizing therapeutic options available for treatment and management of a wide array of pulmonary issues. Developments in both biomarker testing and treatment options are proceeding at a rapid pace, posing a challenge for frontline clinicians to stay on top of the latest developments and incorporate them into their practice. The origin of the idea behind this issue of Clinical Perspectives is rooted in exploratory research that CHEST conducted in 2018 with pulmonary fellowship program directors and current pulmonary fellows to understand the extent to which immunology, biomarker testing, and use of biologic agents for treatment of severe asthma had become part of the curriculum. Those interviews pointed to a significant need to expand this component of the curriculum. Further, it raised the question as to how frontline clinicians were learning about and deploying these emerging therapies. While precision medicine is being investigated in multiple pulmonary disease settings, we limited our survey to severe persistent asthma and non-small cell lung cancer. Biologic adoption rates are higher in these settings, and they are further along relative to “mainstream” recommendations about using precision medicine.
in clinical practice.\textsuperscript{3,4} As a result, CHEST dedicated this issue of \textit{Clinical Perspectives} to look more closely at this emerging field and how it relates to shared decision-making (SMD) with the patient.

The term “personalized medicine” was first coined in the context of genetics, though it has since broadened to encompass many types of personalization measures. Precision medicine as defined by the National Institutes of Health’s Precision Medicine Initiative Working Group, is an approach to disease treatment and prevention that seeks to maximize therapeutic effectiveness by taking into account individual genetic, molecular, environmental, and lifestyle differences.\textsuperscript{5} In this issue of \textit{Clinical Perspectives}, we examine pulmonologist’s understanding of the term within the context of their clinical practices, where personalized or precision medicine is being applied most widely in asthma, lung cancer, idiopathic pulmonary fibrosis, and cystic fibrosis.\textsuperscript{6-9} We also seek to identify the barriers and motivators that explain why some pulmonologists are quicker or slower to adopt personalized/precision medicine than their peers.

\textbf{PURPOSE}

In this issue of \textit{Clinical Perspectives}, CHEST undertook a survey study of pulmonologists to assess knowledge, attitudes, beliefs, and barriers to adoption of best practices in this emerging therapeutic environment. The objectives of this research are to:

\begin{itemize}
  \item Understand pulmonologist use of nomenclature related to the category.
  \item Assess knowledge and familiarity with key facets of precision medicine.
  \item Understand the utilization and the rate of adoption of biomarker testing and emerging therapies.
\end{itemize}
METHODOLOGY

CHEST conducted an online survey with a sample of 99 pulmonologists randomly selected from the CHEST member database. Because the focus of the study was to understand the perspectives of clinicians practicing in the community, respondents practicing exclusively in academic medical centers were excluded. Respondents were sent a link to the survey from CHEST, and data were collected during March 19 to April 15, 2019. Targeted pulmonologists in the sampling frame were contacted via email up to three times to secure their participation in the survey.

The survey included the following areas of content:

- Screening and profiling questions
- Use of language associated with precision medicine
- Exposure to definition of precision medicine
- Self-reported knowledge level on precision medicine concepts
- Current behavior, motivations, and barriers to use of precision medicine
- Experience with precision medicine under specific disease states

Descriptive statistics were used to assess distributions of the data across important behavioral variables. Inferential statistics were used to assess differences in descriptive and behavioral measures, which were cross-tabulated with patient volume and practice setting data. Depending on data type, a two-tailed independent samples t-test and a chi-square test were used to test for statistical significance ($P < .1$ considered statistically significant due to the overall sample size of the study).
Almost three-fourths of the respondents were general pulmonologists (74%), with intensivists (18%) and interventional pulmonologists (8%) making up the balance. Per inclusion criteria, all respondents practice in a community-based setting, with 84% practicing exclusively in that environment and 16% splitting time between community and academic settings. Almost all (94%) indicated they spend more than 75% of their time in clinical practice. Clinician responders were evenly split with respect to tenure: 54% had been in practice for more than 15 years and 46% reported 15 years or less post-fellowship clinical practice experience.
In order to understand the evolving and emerging nomenclature associated with the field (precision/personalized medicine), respondents were exposed to a series of different actions associated with precision medicine and were asked to indicate whether they associate the item with the term “precision medicine,” “personalized medicine,” both terms, or neither term.

**There is currently no consensus about what comprises precision medicine vs personalized medicine**

Overall, respondents have not settled on a specific nomenclature for this emerging field. For the overall descriptor of tailoring medical treatment to the individual characteristics of each patient (genetic, biomarker, phenotypic, or psychosocial), respondents are divided, with 35% associating it with “precision medicine,” 24% associating it with “personalized medicine,” and 36% saying they associate it with both terms. However, the fluidity in language at this point on the adoption curve is best evidenced by the fact that on balance, most respondents are unsure whether or not the terms “precision medicine” and “personalized medicine” are interchangeable.

While a substantial minority, ranging from 17% to 36%, uses the terms “precision medicine” and “personalized medicine” interchangeably, some tendencies emerged in how respondents apply these terms in their peer to peer and patient interactions.

**“Precision medicine” tends to be associated with core clinical actions**

Respondents were more likely to apply “precision medicine” to items that comprise the core clinical facets of patient workup, therapeutic planning, and evaluation: classifying patients into subpopulations that differ on their susceptibility to a disease (44%); classifying patients into subpopulations that differ in response to a particular treatment (45%); and using biomarker testing to evaluate response to treatment (53%).

**“Personalized medicine” tends to be associated with patient-clinician interactions**

Alternatively, respondents were more likely to associate “personalized medicine” with actions that comprise the interpersonal aspects of the patient-clinician relationship, eg, making decisions about the best course of treatment based on patient preferences (55%) and engaging in a shared decision-making process about the choice of therapy (46%).
Neither term has become part of patient-clinician conversations

The largest share of respondents (49%) say they do not use either term—personalized or precision—when in consultation with patients about this category of therapy. Among others, use of the terms is equally divided, with 27% saying they normally use the term “precision medicine” and 31% saying they use “personalized medicine.” Half (51%) also consider the terms interchangeable, regardless of whether or not they currently use them.

Not surprising given the newness of the field, respondents indicate that half of their patients (47%) are rarely familiar with this category; further, they indicate that neither term (52%) is used by patients when discussing workup and treatment options.
Which terminology do you use in consultation with your patients when discussing genetic and/or mutational testing to either establish a diagnosis, determine treatment options, and/or evaluate treatment response? PLEASE CHECK ALL THAT APPLY.

<table>
<thead>
<tr>
<th>Terminology Used by Pulmonologist When Talking to Patients About Precision Medicine</th>
</tr>
</thead>
<tbody>
<tr>
<td>I do not use either of these terms.</td>
</tr>
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<td>Personalized medicine</td>
</tr>
<tr>
<td>Precision medicine</td>
</tr>
<tr>
<td>Other</td>
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</tr>
<tr>
<td>Precision medicine</td>
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<tr>
<td>Other</td>
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Rate of adoption of precision medicine techniques varies substantially across respondents.

More than half (55%) of clinicians utilize precision medicine techniques with patients “most/all of the time.” Only 15% say they “rarely/never” employ these techniques. Early adopters—those who report using precision medicine techniques to manage patients for 3 or more years—comprise 51% of respondents, while the remainder (49%) are categorized as late adopters (using precision medicine techniques for less than 3 years).

Adoption does not vary by practice tenure or subspecialization. Not surprisingly, however, respondents who are early adopters (reported use of precision for 3+ years) report much higher levels of employing these techniques with patients (64% employ precision medicine techniques on most/all patients vs 28% on some/few).

Among your patients who are candidates for precision medicine, how often do you move forward with appropriate testing for diagnosis, treatment, and response?

What are your main objectives when utilizing a precision medicine approach to patient management? PLEASE CHECK ALL THAT APPLY.

For approximately how long have you been using a precision medicine approach to managing patients in your practice? PLEASE CHECK ALL THAT APPLY.
Clinicians primarily consider precision medicine for diagnosis and treatment.

Overwhelmingly, respondents indicate that determining the best therapeutic option (89%) is one of their objectives for employing precision medicine techniques. Establishing a diagnosis (67%) and determining treatable traits (63%) are mentioned next most frequently. Respondents are less likely to employ these techniques to evaluate the effectiveness of treatment or to determine course corrections in the treatment plan.

There is no variation in motivation for using these techniques by tenure, subspecialty, or frequency of utilization.
Limited knowledge is the single most important barrier to use of precision medicine techniques.

Limited knowledge about the effectiveness of new agents (87%) is the leading barrier to greater adoption of precision medicine techniques, and 73% identify this as the single most important barrier to use of precision medicine techniques. Barriers to access are cited next most frequently: difficulty getting insurance approval for new agents (47%); limited access to genetic/molecular testing (33%); and unacceptable turnaround times for test results (13%). Other knowledge-related issues are mentioned less frequently: concerns about patient safety (27%); outcome data are not convincing (13%); and greater confidence in current treatment approaches (7%).
Respondents were then exposed to a series of topic areas related to precision medicine and asked to indicate their level of familiarity. Respondents are most likely to express familiarity with: new biologics, use of biomarker testing alongside traditional phenotypes to establish a treatment plan, and interpreting test results. Familiarity with other topics is more mixed: using biomarker testing to evaluate treatment; identifying treatable traits, changing treatment plans based on test results; procedures for ordering tests; and application of guidelines and protocols. Familiarity with the proper progression of workup activities to ensure insurance coverage for biologic therapy is low.
### Familiarity With Precision Medicine Concepts

<table>
<thead>
<tr>
<th>Topic</th>
<th>Very familiar</th>
<th>Somewhat familiar</th>
<th>Not at all familiar</th>
<th>Not too familiar</th>
</tr>
</thead>
<tbody>
<tr>
<td>New biologics for targeting specific diseases and conditions.</td>
<td>29%</td>
<td>54%</td>
<td>2%</td>
<td>15%</td>
</tr>
<tr>
<td>Interpretation of biomarker testing results.</td>
<td>25%</td>
<td>58%</td>
<td>5%</td>
<td>12%</td>
</tr>
<tr>
<td>Which biomarker tests to order for different diseases, diagnoses, and conditions.</td>
<td>23%</td>
<td>59%</td>
<td>4%</td>
<td>14%</td>
</tr>
<tr>
<td>How to use biomarker testing to evaluate the effectiveness of treatment.</td>
<td>19%</td>
<td>52%</td>
<td>8%</td>
<td>21%</td>
</tr>
<tr>
<td>How to use biomarker testing results in concert with traditional determinants (e.g., course of disease, risk factors, comorbidities, demographic, socioeconomic, patient support) to determine treatment plan.</td>
<td>16%</td>
<td>54%</td>
<td>11%</td>
<td>19%</td>
</tr>
<tr>
<td>Procedures for ordering testing, e.g., requesting appropriate testing, where lab work/samples should be sent.</td>
<td>15%</td>
<td>48%</td>
<td>12%</td>
<td>24%</td>
</tr>
<tr>
<td>How to make changes to the treatment plan based on follow-up biomarker testing.</td>
<td>14%</td>
<td>47%</td>
<td>11%</td>
<td>27%</td>
</tr>
<tr>
<td>Identification of traits that are treatable based on phenotyping and endotyping.</td>
<td>10%</td>
<td>53%</td>
<td>8%</td>
<td>29%</td>
</tr>
<tr>
<td>Guidelines and protocols for biomarker testing and treatment planning.</td>
<td>9%</td>
<td>51%</td>
<td>13%</td>
<td>27%</td>
</tr>
<tr>
<td>Appropriate progression in patient workup to increase the likelihood that insurance will cover specific targeted therapies/medications.</td>
<td>8%</td>
<td>39%</td>
<td>20%</td>
<td>32%</td>
</tr>
</tbody>
</table>

**Q:** Please rate your level of familiarity with the following topical areas related to precision medicine:

**Clinicians rely upon a variety of resources to expand their knowledge of precision medicine.**

Respondents say they are most likely to turn to medical journals (88%) and clinical reference tools (78%) to expand their knowledge of precision medicine. Contact with other colleagues in the field is also an informative resource (72%). CHEST assets—annual meeting (43%), other communications (40%)—are also used by many, as are contacts with pharmaceutical company representatives (39%).
Clinicians with more practice experience and adopters of precision medicine techniques consider CHEST an influential education source.

CHEST assets are more influential as education sources about precision medicine for individuals who have been in practice longer (50% with > 15 years in practice cite CHEST annual meeting vs 37% with shorter tenure) and who report higher rates of adoption (49% of respondents who apply precision techniques to most/all of their candidate patients use CHEST communications for education vs 32% who report lower rates of adoption).

**Resources Used to Expand Knowledge of Precision Medicine**

- Medical Journals: 88%
- Clinical reference tools, such as DynaMed and Up-To-Date: 78%
- Contact with colleagues in pulmonary medicine, pathology, immunology, genetics, and oncology: 72%
- CHEST annual meeting: 43%
- Communications from CHEST: 40%
- Pharmaceutical company representatives: 39%
- ATS annual meeting: 17%
- AAAAI annual meeting: 2%
- ISLAC annual meeting: 2%

Q: Which resources do you use to learn more about precision medicine topics, such as targeted biomarker therapy and biomarker testing for prognosis, treatment, and response? PLEASE CHECK ALL THAT APPLY.
Asthma
Clinicians who treat patients with asthma utilize precision medicine more frequently in patients with severe persistent asthma.

Two-thirds of respondents (62%) report seeing five or fewer patients with severe persistent asthma in a typical week. Better than half (60%) say they apply precision medicine techniques to development treatment plans for these patients. Respondents are twice as likely to say they employ these techniques on all of their patients with severe persistent asthma (19%) in comparison to their estimates for their patient population as a whole (9%).

As observed in their use of biomarkers in their overall patient population, respondents are most likely to indicate that biomarker testing in patients with severe persistent asthma is for the purpose of evaluating the potential for a positive vs adverse response in patients (60%). They are less likely to indicate that they use such testing on all patients for identifying the stage/progression of the patient’s asthma (29%), setting or adjusting dosing (31%), or evaluating effectiveness of response to treatment (29%). Knowledge about the relative effectiveness of the new agents, again, is the principal barrier cited, with access issues (cost of testing and agents, insurance approvals, access to testing) also being frequently mentioned.

**Used Biomarkers in Patients With Severe Persistent Asthma**

<table>
<thead>
<tr>
<th>Purpose</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Identify patients most likely to have positive response or adverse reaction to a particular therapy.</td>
<td>60%</td>
</tr>
<tr>
<td>Evaluate effectiveness of response to treatment.</td>
<td>29%</td>
</tr>
<tr>
<td>Identify stage or progression of patient’s asthma.</td>
<td>29%</td>
</tr>
<tr>
<td>Set or adjust dosing</td>
<td>31%</td>
</tr>
</tbody>
</table>

**Non-small cell lung cancer**
Biomarker testing is commonly performed in patients with non-small cell lung cancer to help inform therapeutic decisions.

The majority of respondents (80%) report diagnosing one to five new cases of non-small cell lung cancer each month. Of these respondents, 86% report sending tissue samples for biomarker testing—a far greater rate of adoption than that reported for patients overall, eg, with severe asthma or other diagnoses.
On average, how many new cases of stage 3 and 4 non-small cell lung cancer (NSCLC) do you diagnose in a typical month?

**New Cases of Stage III/IV NSCLC Diagnosed in a Month**

- 1-5: 80%
- None: 11%
- 6-10: 7%
- 11-15: 1%
- 15+: 1%

How often do you send tissue samples from your patients with NSCLC for biomarker/molecular testing?

**Reported Frequency of Biomarker Testing of Patients With Stage III/IV NSCLC**

- All/Most of the time: 86%
- Some of the time: 9%
- Rarely: 3%
- Never: 2%

For which of the following purposes do you use biomarker testing?

Respondents are most likely to indicate that they use biomarker testing to determine cell mutation type (80%) and treatment strategy (80%). Some use it to determine eligibility for new therapies (66%), while comparatively few are using it as a means to evaluate existing targeted therapy (35%).

**Purposes for Which Respondents Used Biomarker Testing**

- Determine cell mutation type: 80%
- Determine treatment strategy: 80%
- Determine eligibility for new therapies, eg, PDL1: 66%
- Determine new resistance to previously used targeted therapy: 35%
- Determine eligibility for clinical trial: 19%
DISCUSSION

As with many fields of innovation, the development and application of language is often varied, and the emerging field of precision/personalized medicine is no different. Nomenclature in this field is not established in the professional community. Pulmonologists report their patients have little or no knowledge about precision/personalized medicine, and clinicians are not using any of the language described in the survey in discussions with patients. Clinicians use a variety of descriptors to refer to the category as a whole, as well as specific facets of the workup and treatment process, including personalized medicine, precision medicine, biomarker testing, and genetic testing, to name a few. Clinicians tend to associate “precision medicine” with frontline aspects of the process (eg, diagnosis, evaluation of candidate for therapy, identification of therapy) vs use of it later in the process, eg, evaluating the continued effectiveness of therapy and identification of new therapeutic options. In contrast, “personalized medicine” seems to go off on a variety of tangents (including shared decision-making) that have nothing to do with the topic.

Adoption of precision/personalized medicine varies widely, as might be expected in the emerging field—roughly half are moving up the curve and half are still at the lower end. Also, adoption appears to vary by clinical area. It appears that precision medicine is more widely used in NSCLC than in asthma and is used primarily for patients with persistent severe asthma. This may reflect the fact that prognostic biomarkers and actionable therapeutic targets have been identified in the areas of NSCLC and severe persistent asthma that allow for more effective treatment in specific patient populations.

Half of respondents have been in practice for more than 15 years and half for 15 years or less. It is reasonable to assume that clinicians are more comfortable with therapeutic strategies and interventions that have been part of their medical training and clinical experience. In this survey, however, tenure was not a driver of using precision/personalized medicine techniques. This makes sense given that the concept of precision/personalized medicine has evolved relatively recently based upon research and development advances; the NIH working group issued its suggested description in 2015. In fact, the majority of respondents indicate that limited knowledge about the effectiveness of new agents is the single most important barrier to greater adoption of precision medicine techniques. Discussions with clinical experts, fellows, and fellowship program directors last year indicate that in average training programs today, there is limited time to focus on biologic therapy, and many programs don’t have a “go to” faculty member who has emerged as an
expert resource within the program. Respondents do view CHEST as a source of educational content relative to precision/personalized medicine. What’s more, there’s evidence that the value extends beyond content associated with the CHEST brand. Respondents who turn to these resources are also more likely to be early adopters and heavy users of these processes and therapies. Recognizing that the respondent base comprises pulmonologists, resources from other medical societies are much less likely to be cited as sources of education.

Utilization of precision medicine techniques appear to far outpace familiarity and comfort levels with the category. This aligns with the finding that the biggest area of education relates to application of precision/personalized medicine and ongoing management application. Payment issues are a significant nonclinical factor, with precision medicine and clinicians not clear about what they need to do to ensure that payors will approve therapies associated with precision/personalized medicine.

EDUCATIONAL OPPORTUNITIES

- CHEST educational assets are utilized by clinicians who are already practicing precision/personalized medicine. Given the clinical community’s interest and the lack of medical education and training in this setting, CHEST has an opportunity to leverage its resources to expand education to community clinicians.

- Lack of knowledge about the effectiveness of new agents is a significant barrier to adoption of precision medicine techniques and represents an unmet educational need.

- Clinicians are interested in education to help them apply advances in precision/personalized medicine to their patients and practices.

- Payer issues are significant nonclinical barriers, and clinicians want to understand what they need to do to ensure coverage for precision/personalized medical therapies.
Nomenclature in this field is not established in the professional community, and clinicians are not using any of this language with patients.

Adoption of precision/personalized medicine varies widely and appears to differ by clinical area.

Utilization of precision medicine techniques appears to far outpace familiarity and comfort levels with the category.

Focus of precision medicine tends to be much more on frontline aspects of the process (diagnosis, evaluation of candidate for therapy, identification of therapy) vs use of it later in the process, eg, evaluating the continued effectiveness of therapy and identification of new therapeutic options.

REFERENCES


ABOUT
CHEST CLINICAL PERSPECTIVES™

CHEST is the global leader in advancing best patient outcomes through innovative chest medicine education, clinical research, and team-based care. This includes connecting health-care professionals to cutting-edge original research and a wide array of evidence-based guidelines through the journal CHEST, while also serving as a resource for clinicians through year-round meetings, live courses, books, white papers, and mobile apps delivering content in the areas of pulmonary, critical care, and sleep medicine.

We’ve launched this series of CHEST Clinical Perspectives studies to cover compelling issues in chest medicine, on topics ranging from the use of biologics in treatment of patients with severe asthma, to the state of practice in tissue sampling and testing for NSCLC. An expert panel of thought leaders from the Mayo Clinic, Baylor College of Medicine, Medical University of South Carolina, Walter Reed Army Medical Center, and Emory University helps to guide the content of each study and lends rich expertise and perspectives in interpreting the results.
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Medical University of South Carolina

Dr. Nichole Tanner is a lung cancer pulmonologist at the Ralph H. Johnson VA Hospital with a joint appointment as Associate Professor of Medicine at the Medical University of South Carolina (MUSC). Her research and clinical interests focus on lung cancer screening, disparities, pulmonary nodule evaluation, and the staging and diagnosis of lung cancer. She is also the co-director of the NCI-designated Hollings Cancer Center lung cancer screening program at MUSC. Dr. Tanner was integral in guiding both the research and the data interpretation components of this Clinical Perspectives™ white paper.

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