Precision Medicine 2030

FDA-MCERSI Workshop on Application of Artificial Intelligence and Machine Learning for Precision Medicine

Mike Pacanowski
Division of Translational and Precision Medicine
Office of Clinical Pharmacology
Center for Drug Evaluation and Research
U.S. Food and Drug Administration

This presentation reflects the views of the speaker and should not be construed to represent FDA’s policies
Where can AI methodologies be applied to support targeted drug development and precision patient care?

- Landscape
- Opportunities
- Challenges

*Nature 557, 555-557 (2018)*
A Brief History of Medicines
An innovative approach to tailoring disease prevention and treatment that takes into account differences in people's genes, environments, and lifestyles\(^1\)

- **Targeted therapies**: Drugs or biologics intended for use with a genomic, proteomic, or other biomarker/tool that
  - Identifies patients who are eligible for treatment
  - Aids in determining the appropriate dosage
  - Allows for monitoring of response to individualize therapy\(^2\)

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1. [Precision Medicine | FDA](https://www.fda.gov/medical-devices/in-vitro-diagnostics/precision-medicine)
2. Unofficial definition
What Can Biomarkers Tell Us?

**Susceptibility**
*Will I develop the disease?*
BRCA → breast cancer

**Safety**
*Am I having an adverse event?*
ALT → Hepatotoxicity

**Diagnosis**
*Do I have the disease?*
CFTR → CF

**Monitoring**
*Has the condition changed?*
HIV RNA → HIV/AIDS

**Prognosis**
*Will I live longer?*
17p del → CLL

**Response**
*Did treatment work?*
INR → warfarin/stroke

**Prediction**
*Will I respond to treatment?*
BRAF → skin cancer

Evolution of Precision Medicines

Pharmacogenetics
- Retrofit biomarkers of drug metabolism and response to guide dosing, patient selection, monitoring
  - abacavir/HLA-B*57:01
  - clopidogrel/CYP2C19
  - warfarin/VKORC1-CYP2C9

Reverse Translation
- Genetically informed target selection for new drug development
  - alirocumab/PCSK9
  - evolocumab/PCSK9
  - setmelanotide/MC4R

Precision Medicines v1
- Prospectively codeveloped drugs and biomarkers for patient selection
  - trastuzumab/HER2
  - afatinib/EGFR
  - ivacaftor/CFTR

Precision Medicines v2
- Tissue agnostic and other omic approaches for patient selection
  - pembrolizumab/TMB
  - larotrectinib/NTRK
  - olaparib/HRR

Genetically Targeted Therapies
- RNA interference and other modalities that target the genome
  - nusinersen/SMN2
  - patisiran/TTR
  - lumasiran/HAO-1

Individualized Therapies
- Production of drug designed to treat a very small number of patients (1 or 2)
  - milasen/MFSD8
Pathways to Integrate Technology into Drug Development and Practice

Note: These pathways do not exist in isolation and many times parallel efforts are underway within or between pathways. All share common core concepts, are data-driven, and involve regulatory assessment and outcomes based on the available data.
## Medical Products and Biomarkers
### Selected CDER Drug Approvals in 2022 (of 37 new molecular entities)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Disease or Condition</th>
<th>Biomarker</th>
<th>Use</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tebentafusp-tebn</td>
<td>Uveal melanoma</td>
<td>HLA-A*02:01†</td>
<td>Selection (subset)</td>
</tr>
<tr>
<td>Lutetium Lu 177 vipivotide tetraxetan</td>
<td>Prostate cancer</td>
<td>Prostate-specific membrane antigen</td>
<td>Selection (subset)</td>
</tr>
<tr>
<td>Futibatinib</td>
<td>Cholangiocarcinoma</td>
<td>FGFR2 gene fusions or other rearrangements</td>
<td>Selection (subset)</td>
</tr>
<tr>
<td>Mirvetuximab soravtansine-gynx</td>
<td>Ovarian, fallopian tube, primary peritoneal cancer</td>
<td>Folate receptor alpha†</td>
<td>Selection (subset)</td>
</tr>
<tr>
<td>Olutasidenib</td>
<td>Acute myeloid leukemia</td>
<td>IDH1 mutations†</td>
<td>Selection (subset)</td>
</tr>
<tr>
<td>Adagrasib</td>
<td>Non-small cell lung cancer</td>
<td>KRAS G12C mutation†</td>
<td>Selection (subset)</td>
</tr>
<tr>
<td>Abrocitinib</td>
<td>Atopic dermatitis</td>
<td>CYP2C19 variants</td>
<td>Dosage</td>
</tr>
<tr>
<td>Mitapivat</td>
<td>Pyruvate kinase deficiency</td>
<td>PKLR variants</td>
<td>Selection (diagnosis)</td>
</tr>
<tr>
<td>Vutrisiran</td>
<td>Transthyretin amyloidosis polyneuropathy</td>
<td>TTR variants</td>
<td>Selection (diagnosis)</td>
</tr>
<tr>
<td>Olipudase alfa-rpcp</td>
<td>Acid sphingomyelinase deficiency</td>
<td>SMPD1 variants</td>
<td>Selection (diagnosis)</td>
</tr>
</tbody>
</table>

The table includes 1) new molecular entities (NMEs), and selected supplements to previously approved drugs, for which the indication is restricted to a subset of patients with the disease/condition, and 2) NMEs for non-oncologic genetic diseases that mechanistically target the underlying pathophysiology

† Companion diagnostic
Trends in Targeted Drug Development

*Targeted drugs for the purpose of this figure are new molecular entities (NMEs) for which the initially approved indication is restricted to a subset of patients who are identified through molecular testing (and excludes genotype-based dosing and infectious disease subsets).
Clinical Pharmacology Fundamentals

Comprehensive Clinical Pharmacology Review Questions

To what extent does the available clinical pharmacology information provide pivotal or supportive evidence of effectiveness?

Is the proposed dosing regimen appropriate for the general patient population for which the approval is being sought?

Is an alternative dosing regimen or management strategy required for subpopulations based on intrinsic factors?

Are there clinically relevant food-drug or drug-drug interactions, and what is the appropriate management strategy?
Drug Development and Regulation: Progressive Reduction of Uncertainty

**PRECLINICAL**
- Chemical, MOA, safety characteristics
- Develop BA method
- In vitro metabolism, transporter, & DDI
- In vitro protein binding, cellular/tissue distribution
- Relevant animal/POC
- Target, mechanistic, &/or physiologic biomarker identification

**PHASE I**
- First in human
- Dose-ranging studies
- Early PK/PD
- Early food-effect

**EOP1**
- Mass balance
- Food-effect
- QTc study

**PHASE II**
- Dose identification
- PK/PD in patients
- E-R/E-S
- In vivo DDI
- Extrinsic factors
- Renal/hepatic, disease, intrinsic factors

**EOP2**
- PK/PD & E-R/E-S in target population
- Dose optimization
- Mitigation strategies in the target population

**PHASE III**
- BA/BE

**PHASE IV**
- Labeling
- PMC/PMR
- ACTION
- Surveillance

**Pharmacogenomics**

**Pharmacostatistical Modeling & Simulation**
Resolving Variability in Drug Response

Therapeutic Index

Pathobiology

Variability

Safety

Mechanism of Action

Heterogeneity
Advancing Precision Medicine Through AI

Data sources
- Clinical trials
- Observational studies
- Health records
- Claims

Sampling
- Fluids
- Cells
- Tissues
- Sounds
- Air
- Images
- Video
- Audio
- Pressures
- Electrical signals
- Outcomes

Measures
- Anthropometrics
- Protein expression
- Gene variants
- Movements
- Colors
- Voltages
- Symptoms

Impact
- Novel drug targets
- Risk assessment
- Diagnostic criteria
- Prognosis
- Dose selection
- Response prediction
- Monitoring
- Clinical decision support
## Multidimensional Profiling

### Lung Adenocarcinoma

<table>
<thead>
<tr>
<th>Drug</th>
<th>NSCLC Molecular Subgroup</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mobocertinib</td>
<td>EGFR exon 20 insertion mutations</td>
</tr>
<tr>
<td>Sotorasib</td>
<td>KRAS G12C mutation</td>
</tr>
<tr>
<td>Amivantamab-vmjw</td>
<td>EGFR exon 20 insertion mutations</td>
</tr>
<tr>
<td>Lorlatinib</td>
<td>ALK expression</td>
</tr>
<tr>
<td>Cemiplimab-rwlc</td>
<td>PD-L1 high (no EGFR/ALK/ROS1)</td>
</tr>
<tr>
<td>Tepotinib</td>
<td>MET exon 14 skipping alterations</td>
</tr>
<tr>
<td>Osimertinib</td>
<td>EGFR exon 19 deletions, L858R, T790M</td>
</tr>
<tr>
<td>Pralsetinib</td>
<td>RET fusions</td>
</tr>
<tr>
<td>Ramucirumab</td>
<td>EGFR exon 19 deletions, L858R</td>
</tr>
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<td>Erlotinib</td>
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<tr>
<td>Nivolumab</td>
<td>PD-L1 high (no EGFR/ALK)</td>
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<tr>
<td>Ipilimumab</td>
<td>PD-L1 high (no EGFR/ALK)</td>
</tr>
<tr>
<td>Brigatinib</td>
<td>ALK rearrangements</td>
</tr>
<tr>
<td>Atezolizumab</td>
<td>PD-L1 high</td>
</tr>
<tr>
<td>Capmatinib</td>
<td>MET exon 14 skipping mutations</td>
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<tr>
<td>Selpercatinib</td>
<td>RET fusions</td>
</tr>
</tbody>
</table>

(selected approvals)

DOSAGE AND ADMINISTRATION

The appropriate initial dosing of COUMADIN varies widely for different patients. Not all factors responsible for warfarin dose variability are known, and the initial dose is influenced by:

- Clinical factors including age, race, body weight, sex, concomitant medications, and comorbidities
- Genetic factors (CYP2C9 and VKORC1 genotypes)

[see CLINICAL PHARMACOLOGY (12.5)]

Select the initial dose based on the expected maintenance dose, taking into account the above factors. Modify this dose based on consideration of patient-specific clinical factors. Consider lower initial and maintenance doses for elderly and/or debilitated patients and in Asian patients [see USE IN SPECIFIC POPULATIONS (8.5) and CLINICAL PHARMACOLOGY (12.3)].

Table 1: Three Ranges of Expected Maintenance COUMADIN Daily Doses Based on CYP2C9 and VKORC1 Genotypes

<table>
<thead>
<tr>
<th>VKORC1</th>
<th>CYP2C9</th>
</tr>
</thead>
<tbody>
<tr>
<td>*1/*1</td>
<td>5-7 mg</td>
</tr>
<tr>
<td>*1/*2</td>
<td>3-4 mg</td>
</tr>
<tr>
<td>*1/*3</td>
<td>3-4 mg</td>
</tr>
<tr>
<td>*2/*2</td>
<td>0.5-2 mg</td>
</tr>
<tr>
<td>*2/*3</td>
<td>0.5-2 mg</td>
</tr>
<tr>
<td>*3/*3</td>
<td>0.5-2 mg</td>
</tr>
</tbody>
</table>

Ranges are derived from multiple published clinical studies. VKORC1 –1639G>A (rs9923231) variant is used in this table. Other co-inherited VKORC1 variants may also be important determinants of warfarin dose.

Coumadin package insert; warfarindosing.org
Where Do AI Approaches Fit?

Chronic phase CML with >3 treatments, n=157

Notes: “Discontinued” indicates that patients discontinued their last line of treatment; “On treatment” indicates that patients were still on their last line of treatment at the time of data collection.


How Can We Advance Use of AI Approaches in Precision Medicine?*

<table>
<thead>
<tr>
<th>Barriers</th>
<th>Solutions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lack of standardization and interoperability</td>
<td>Data integration and standardization</td>
</tr>
<tr>
<td>Data privacy and security</td>
<td>Improved algorithms and models</td>
</tr>
<tr>
<td>Limited data availability and quality</td>
<td>Collaboration and partnerships</td>
</tr>
<tr>
<td>Resistance to change</td>
<td>Clinical validation and implementation</td>
</tr>
<tr>
<td>Lack of regulatory guidance</td>
<td>Investment in AI research</td>
</tr>
</tbody>
</table>

* According to ChatGPT
Complex, innovative trials
Electronic health records
and real-world evidence
Telemedicine

Interventions

Targeted drugs
RNA interference
Regenerative medicine
(including cell and gene therapies)
Limited population antibiotics

Analytics

Artificial intelligence/machine learning
Modeling and simulation
Pharmacoepidemiology methods
Bioinformatics

Collection

Omics
Wearables
Surrogate endpoints
Patient-reported outcomes
Imaging
In vitro diagnostics

Measurements

Complex, innovative trials
Electronic health records
and real-world evidence
Telemedicine

PMID: 31782136
Summary

• Precision medicine approaches rely on technologies that improve mechanistic understanding of disease and drug response

• AI and complex data analytics can augment use of existing tools to further reduce biological complexity and optimize drug development

• AI tools in practice can help resolve multiple factors to support individualized therapeutic decision making