Precision Medicine 2030

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

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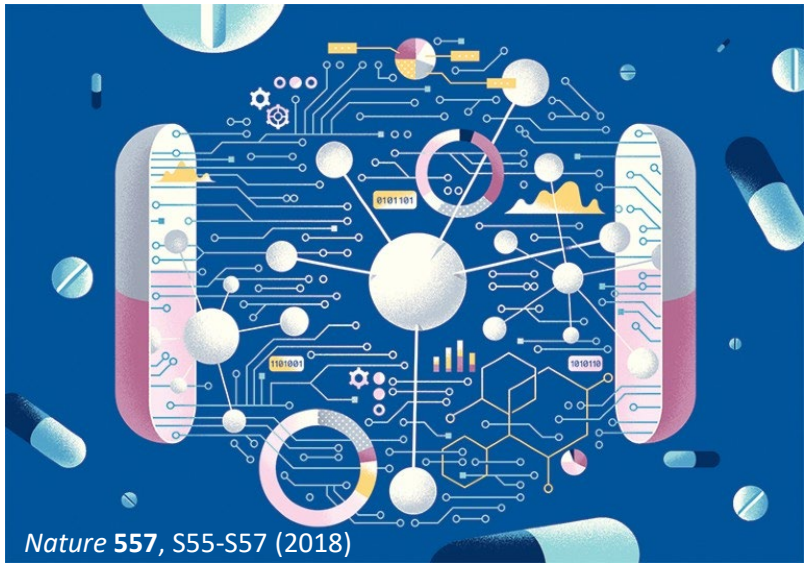
This presentation reflects the views of the speaker and should not be construed to represent FDA's policies

Agenda

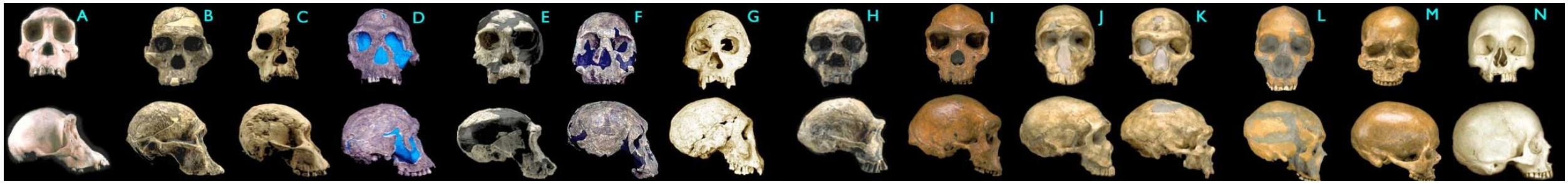
Where can AI methodologies be applied to support targeted drug development and precision patient care?

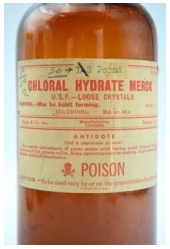
- Landscape
- Opportunities
- Challenges

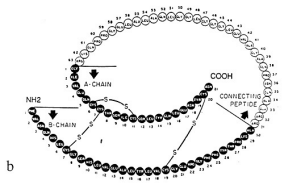


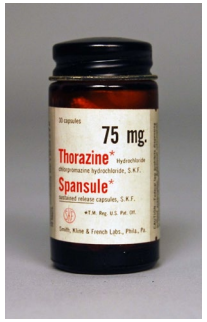
Nature **557**, S55-S57 (2018)

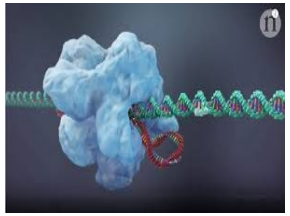
A Brief History of Medicines

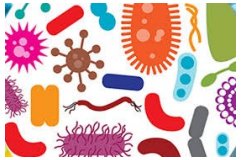


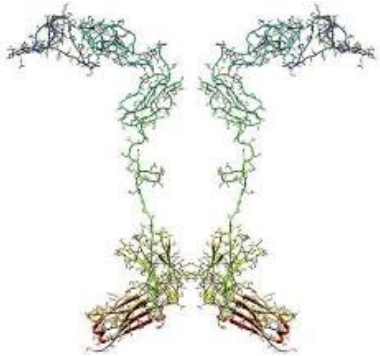


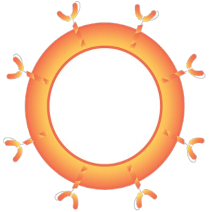


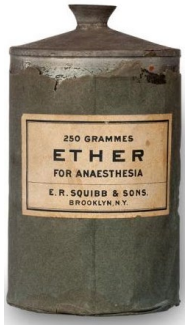


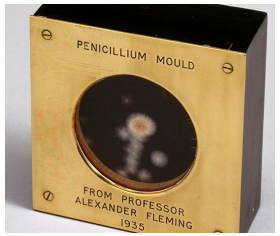












"Precision Medicine"

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]

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

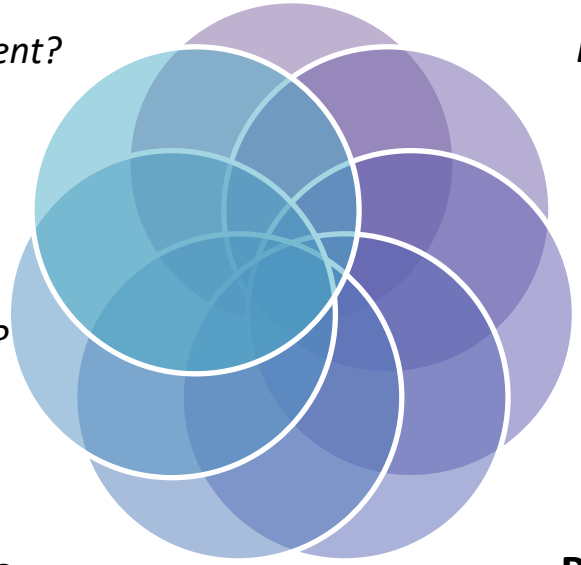
Am I having an adverse event?

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

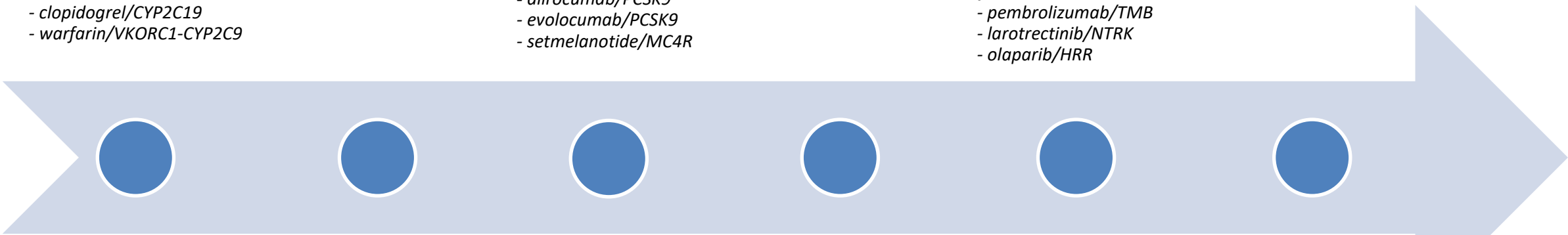
Prediction

Will I respond to treatment?

BRAF→skin cancer

https://www.ncbi.nlm.nih.gov/books/NBK326791/

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*

Precision Medicines v1

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

Reverse Translation

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

Genetically Targeted Therapies

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

Precision Medicines v2

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

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.

FDA Drug Development Tools Website

Facilitating Biomarker Development: Strategies for Scientific Communication, Pathway Prioritization, Data-Sharing, and Stakeholder Collaboration; Published June 2016, Duke-Margolis Center for Health Policy

Medical Products and Biomarkers

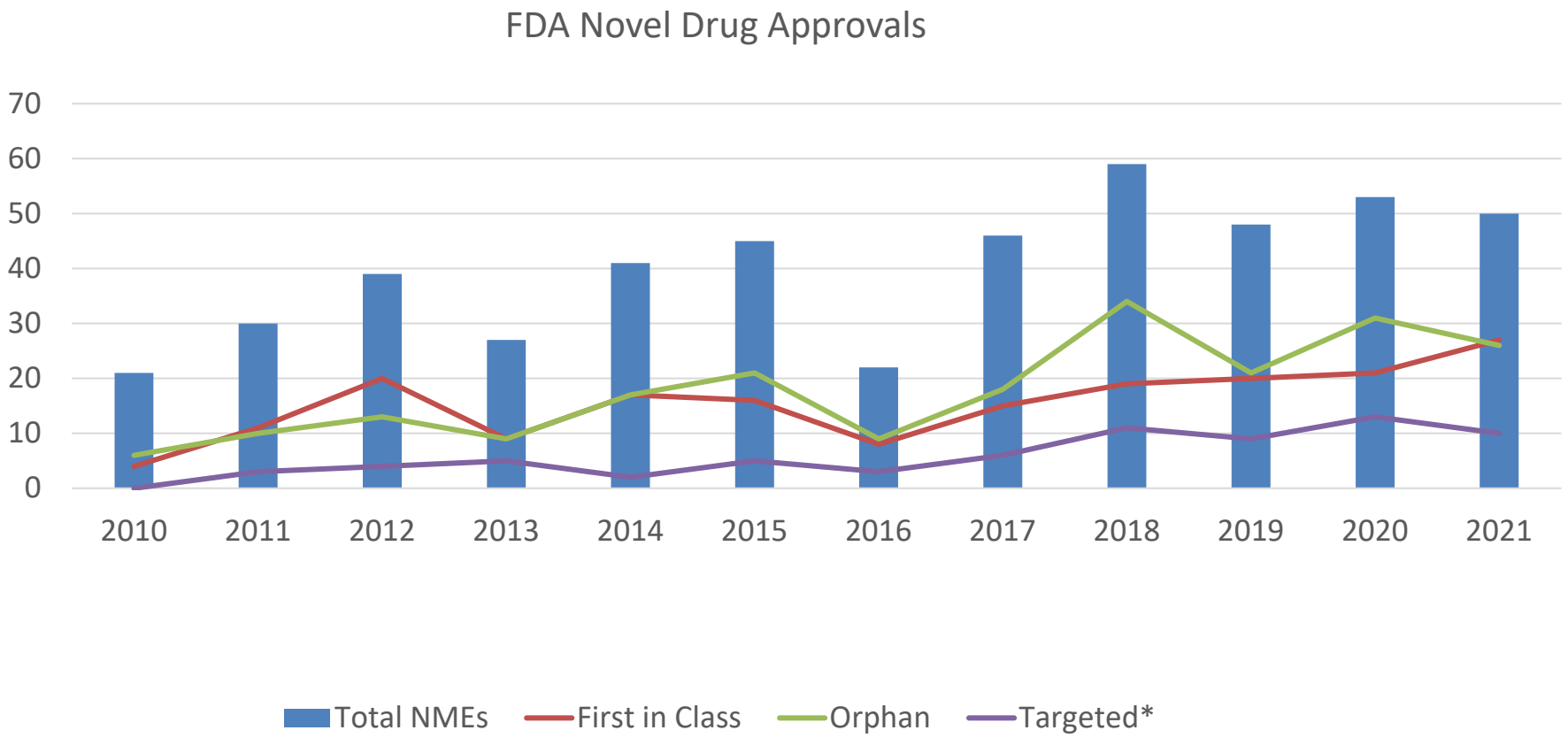
Selected CDER Drug Approvals in 2022 (of 37 new molecular entities)

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

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

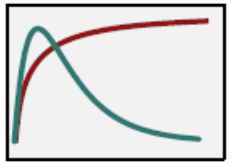
Trends in Targeted Drug Development



*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).

OPPORTUNITIES AND CHALLENGES

Clinical Pharmacology Fundamentals



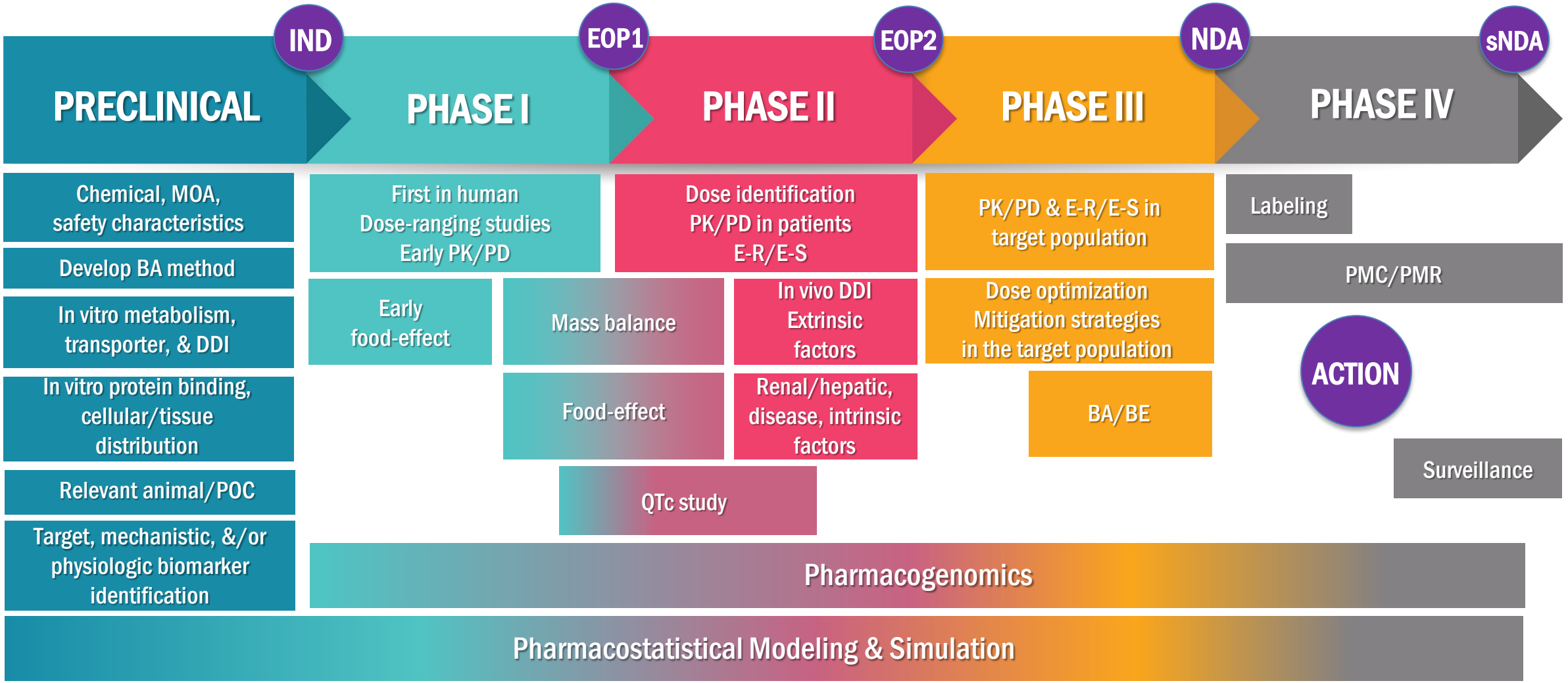
To what extent does the available clinical pharmacology information provide pivotal or supportive evidence of effectiveness?

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

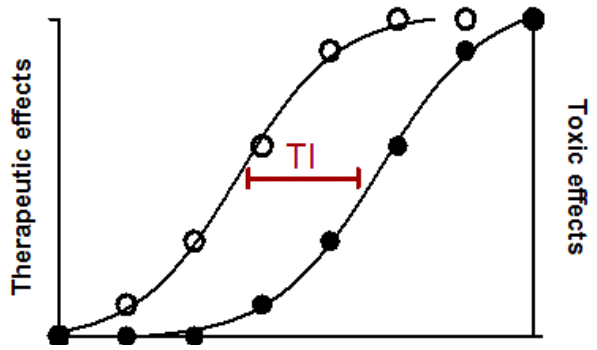
Is an alternative dosing regimen or management strategy required for subpopulations based on intrinsic factors?

Are there clinically relevant food-drug or drug-drug interactions, and what is the appropriate management strategy?

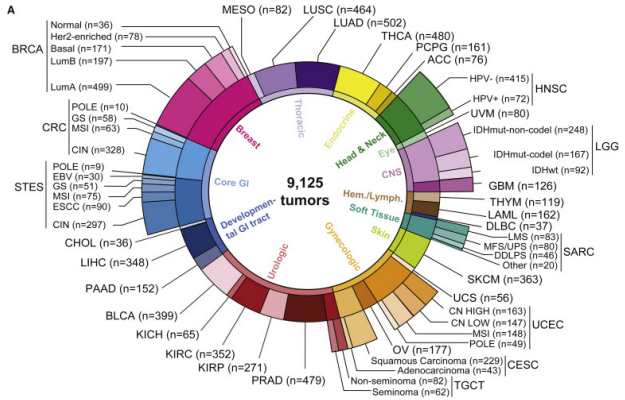
Drug Development and Regulation: Progressive Reduction of Uncertainty



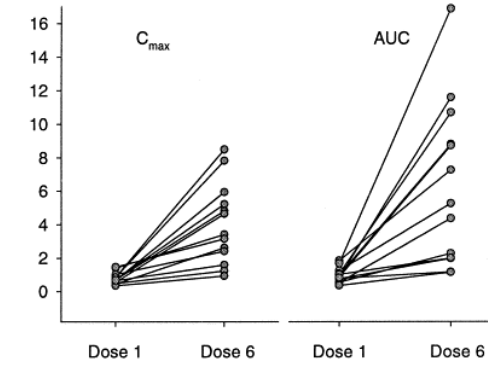
Resolving Variability in Drug Response



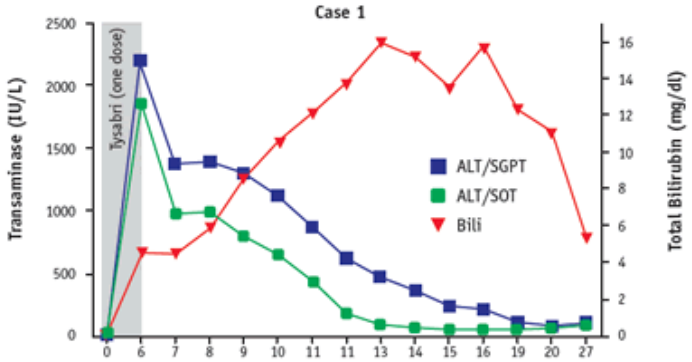
Therapeutic Index



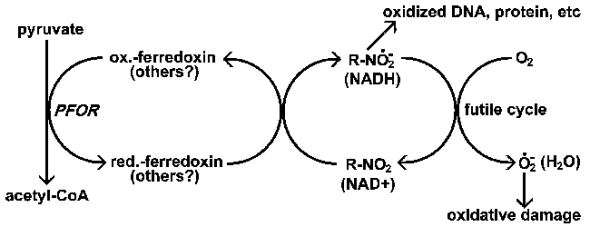
Pathobiology



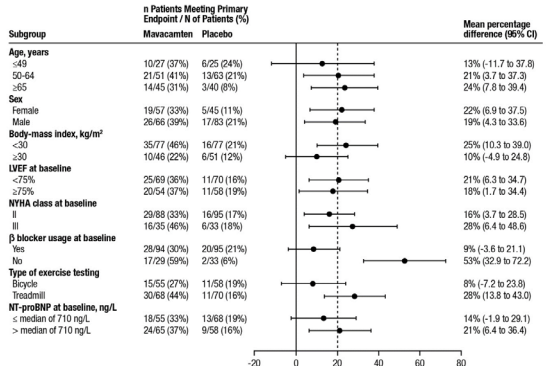
Variability



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

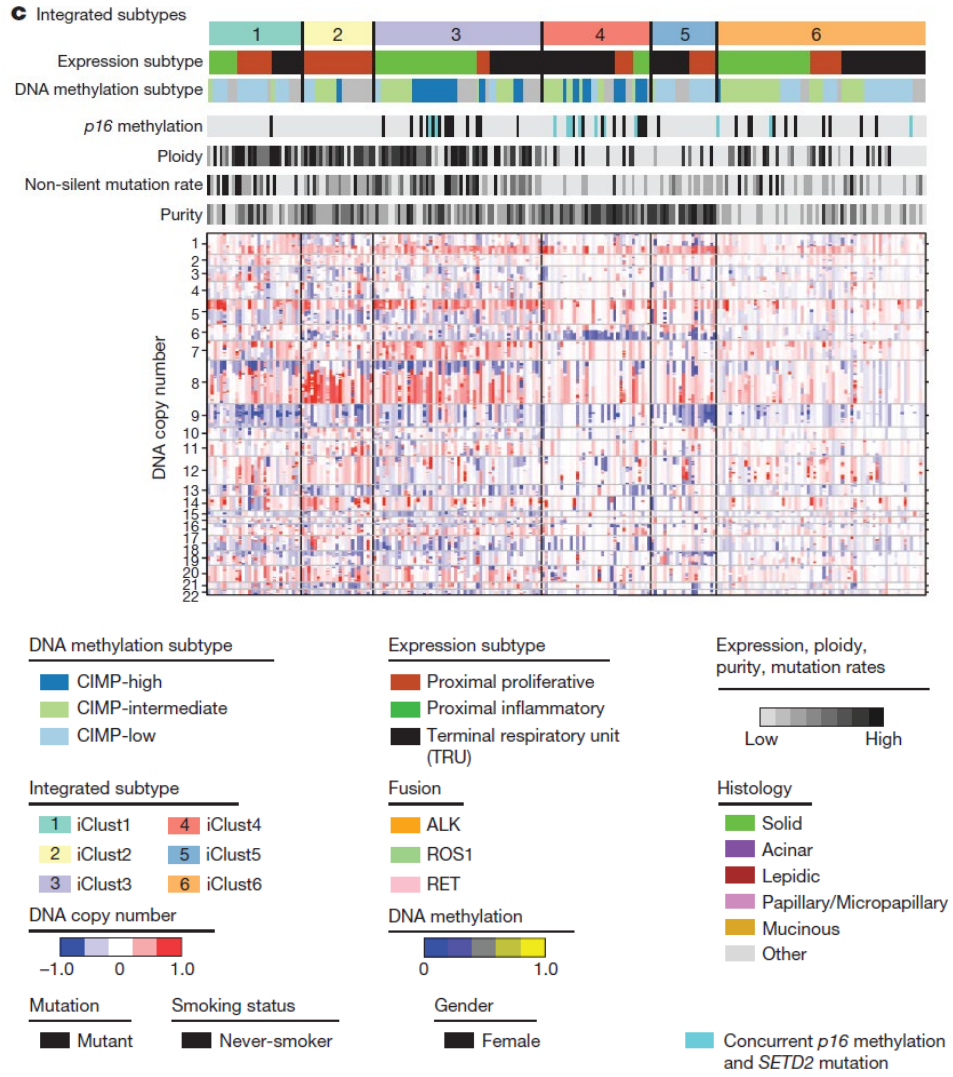
- Novel drug targets
- Risk assessment
- Diagnostic criteria
- Prognosis
- Dose selection
- Response prediction
- Monitoring
- Clinical decision support

Multidimensional Profiling

Lung Adenocarcinoma

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

(selected approvals)



TCGA Research Network. Nature 2014.

Multidimensional Profiling

Anticoagulant Dose Prediction

DOSAGE AND ADMINISTRATION

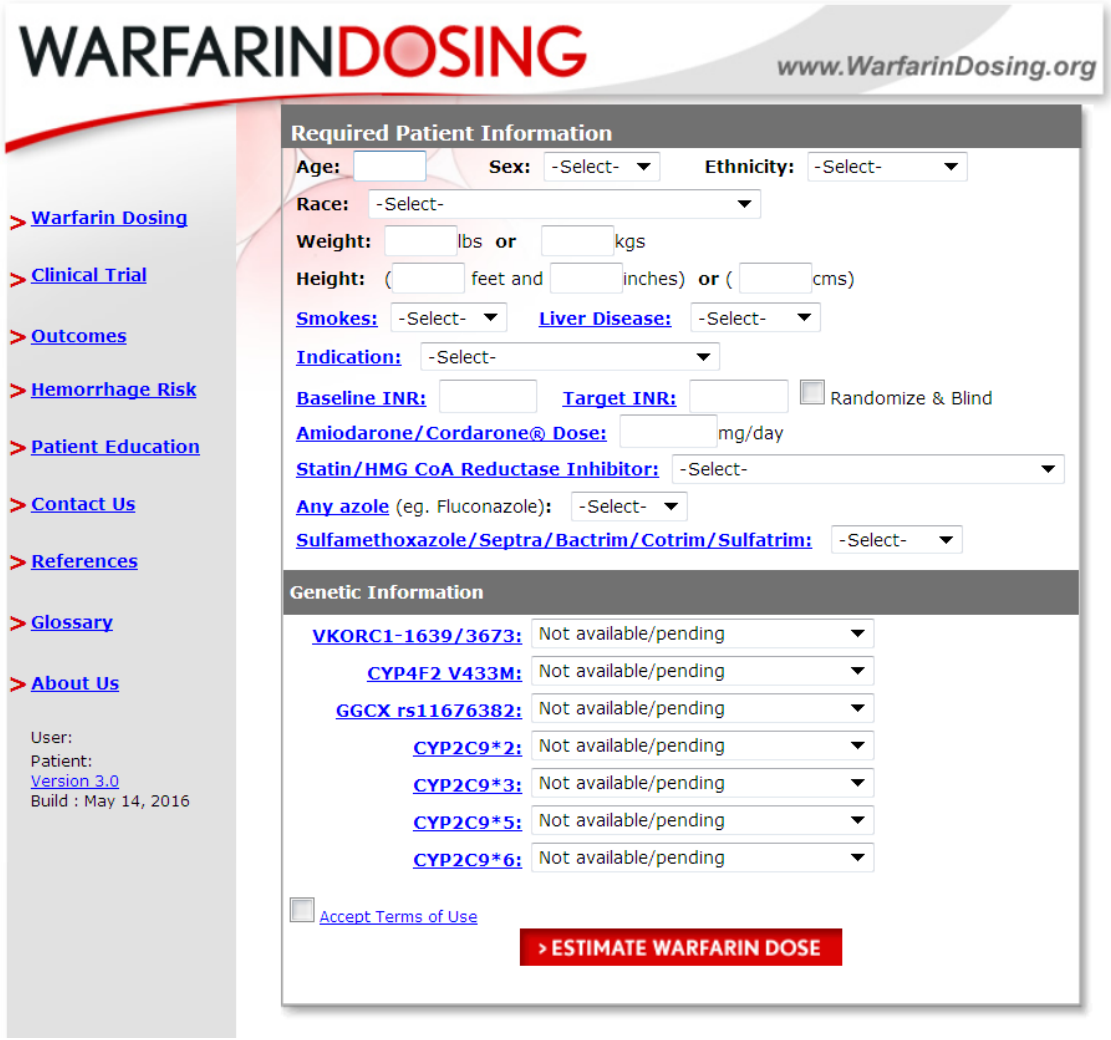
The appropriate initial dosing of COUMADIN varies widely for different patients. Not all factors responsible for warfarin dose variability are known, and the initial dose is influenced by:
•Clinical factors including age, race, body weight, sex, concomitant medications, and comorbidities
•Genetic factors (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†

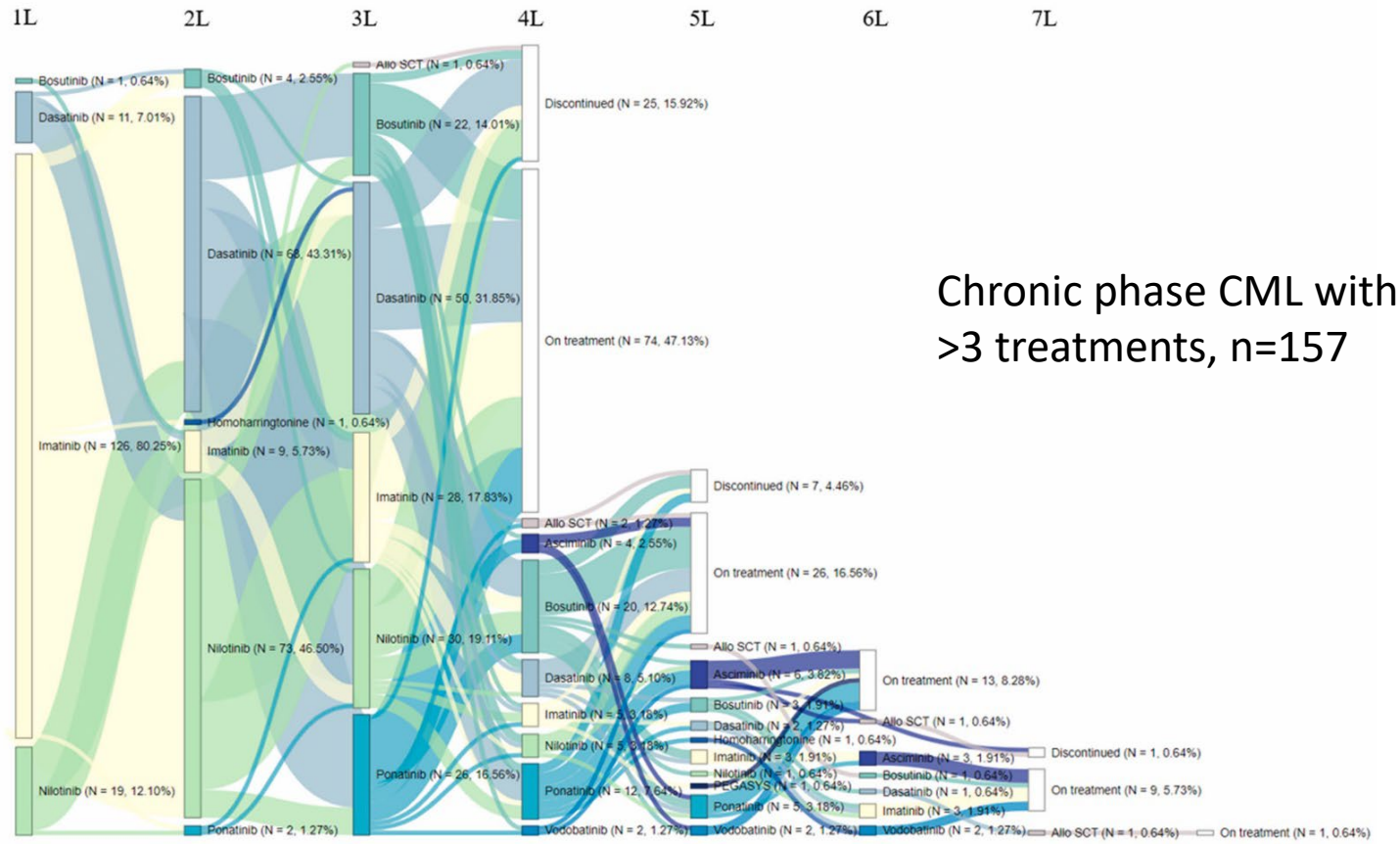
VKORC1	CYP2C9					
	*1/*1	*1/*2	*1/*3	*2/*2	*2/*3	*3/*3
GG	5-7 mg	5-7 mg	3-4 mg	3-4 mg	3-4 mg	0.5-2 mg
AG	5-7 mg	3-4 mg	3-4 mg	3-4 mg	0.5-2 mg	0.5-2 mg
AA	3-4 mg	3-4 mg	0.5-2 mg	0.5-2 mg	0.5-2 mg	0.5-2 mg

†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.

Abbreviations: 1L: first-line; 2L: second-line; 3L: third-line; 4L: fourth-line; 5L: fifth-line; 6L: sixth-line; 7L: seventh-line; Allo-SCT: allogeneic stem cell transplant.

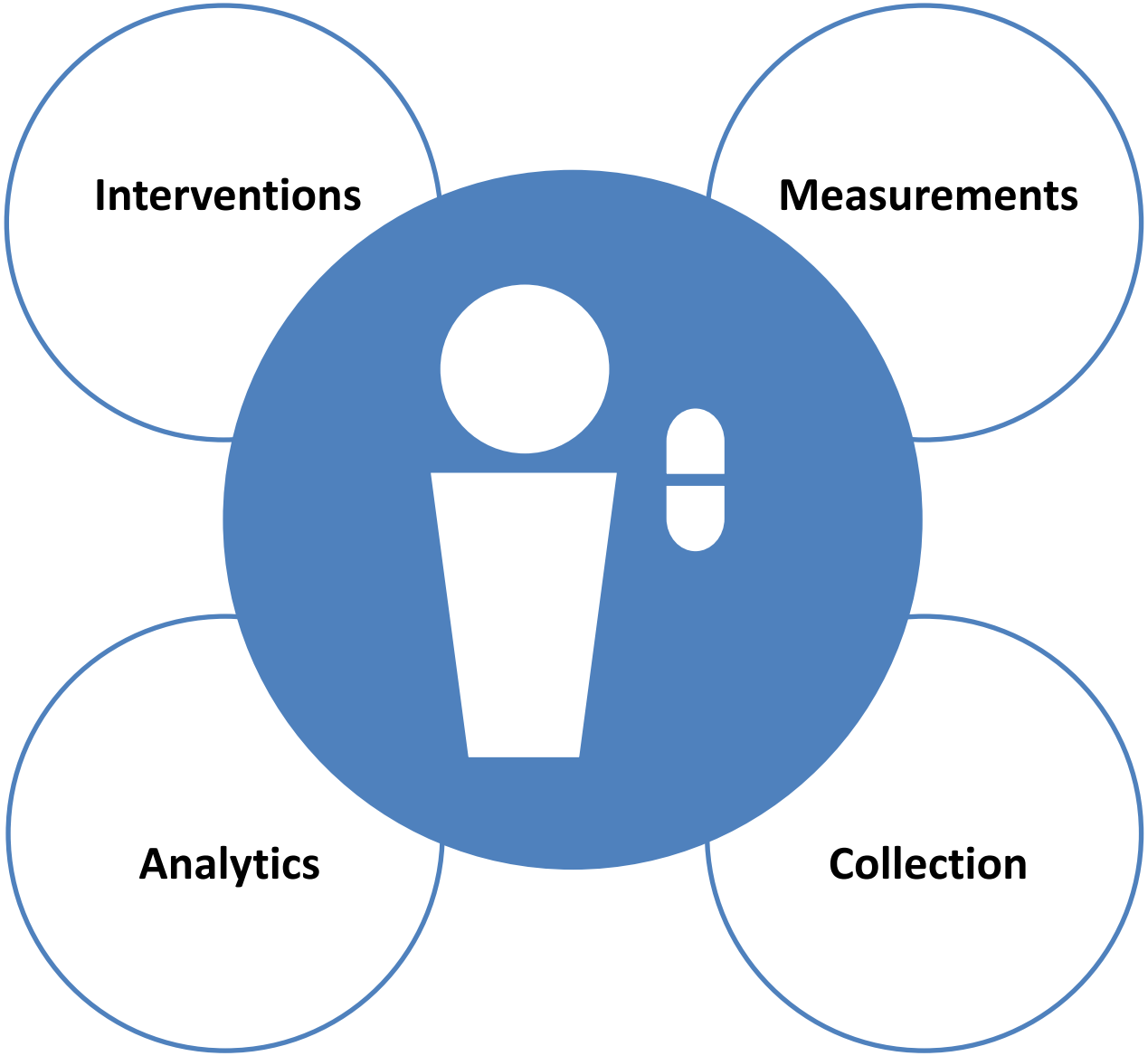
Nicolini, et al. Blood (2022) 140 (Supplement 1): 9656–9658.

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

Barriers	Lack of standardization and interoperability
	Data privacy and security
	Limited data availability and quality
	Resistance to change
	Lack of regulatory guidance
Solutions	Data integration and standardization
	Improved algorithms and models
	Collaboration and partnerships
	Clinical validation and implementation
	Investment in AI research

* According to ChatGPT

OpenAI. "ChatGPT". *Welcome to ChatGPT*, chat.openai.com/.



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

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

Artificial intelligence/ machine learning
Modeling and simulation
Pharmacoepidemiology methods
Bioinformatics

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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