Innovation in Drug Discovery and Development for Prevalent Chronic Diseases

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National Academies Forum on Drug Discovery, Development, and Translation

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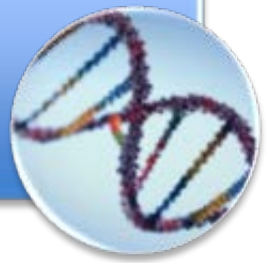
Disclosure

- Conflict of Interest: I have no competing interests for this work
- The views expressed are those of the author and do not reflect official policy of the FDA

Innovations in Drug Discovery and Development

- targeted therapies
- novel biologics (e.g., antibody-drug conjugates, and bispecific antibodies)
- cell/gene therapies
- microbiome/virus

New Therapeutic Modalities



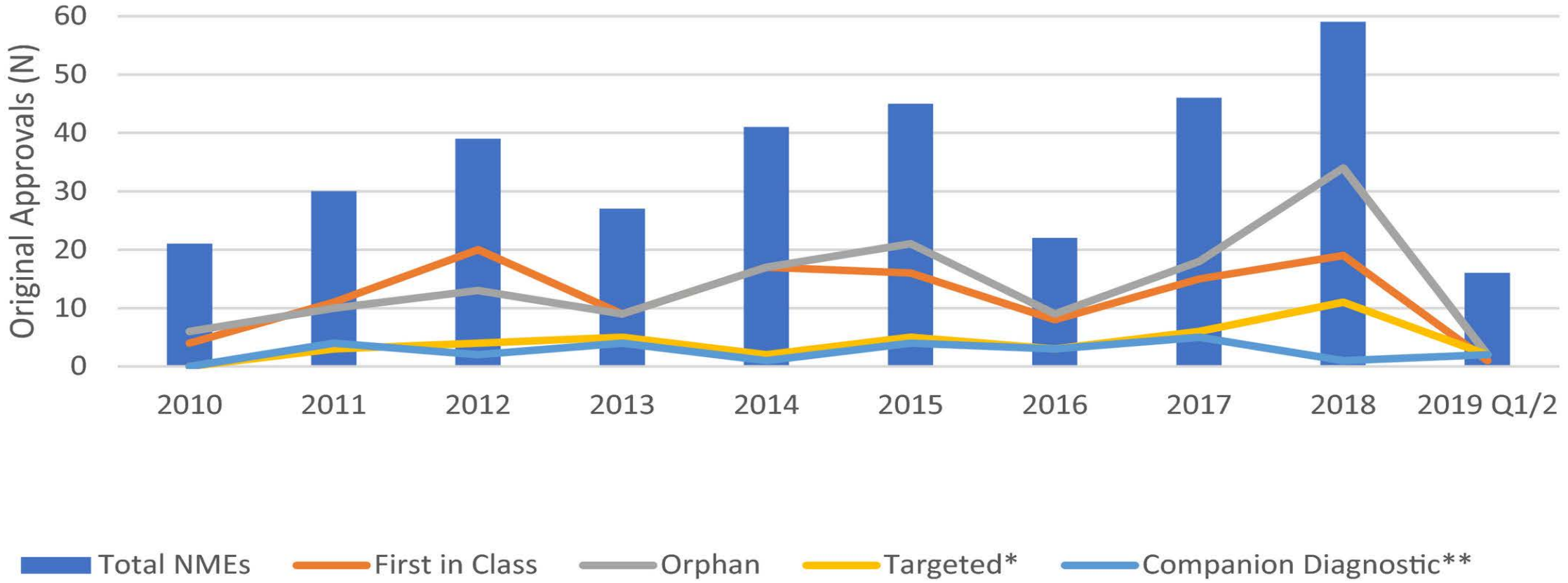
- multi-omics data
- real-world data (e.g., electronic health records and claims, and patient generated data)
- data from novel experiment systems (e.g., microphysiological systems)

New Types of Data

- modeling/simulation
- AI/Machine learning
- informatics/data mining tools/automation

New Analytical Tools

New Therapeutic Modalities: Targeted Therapies



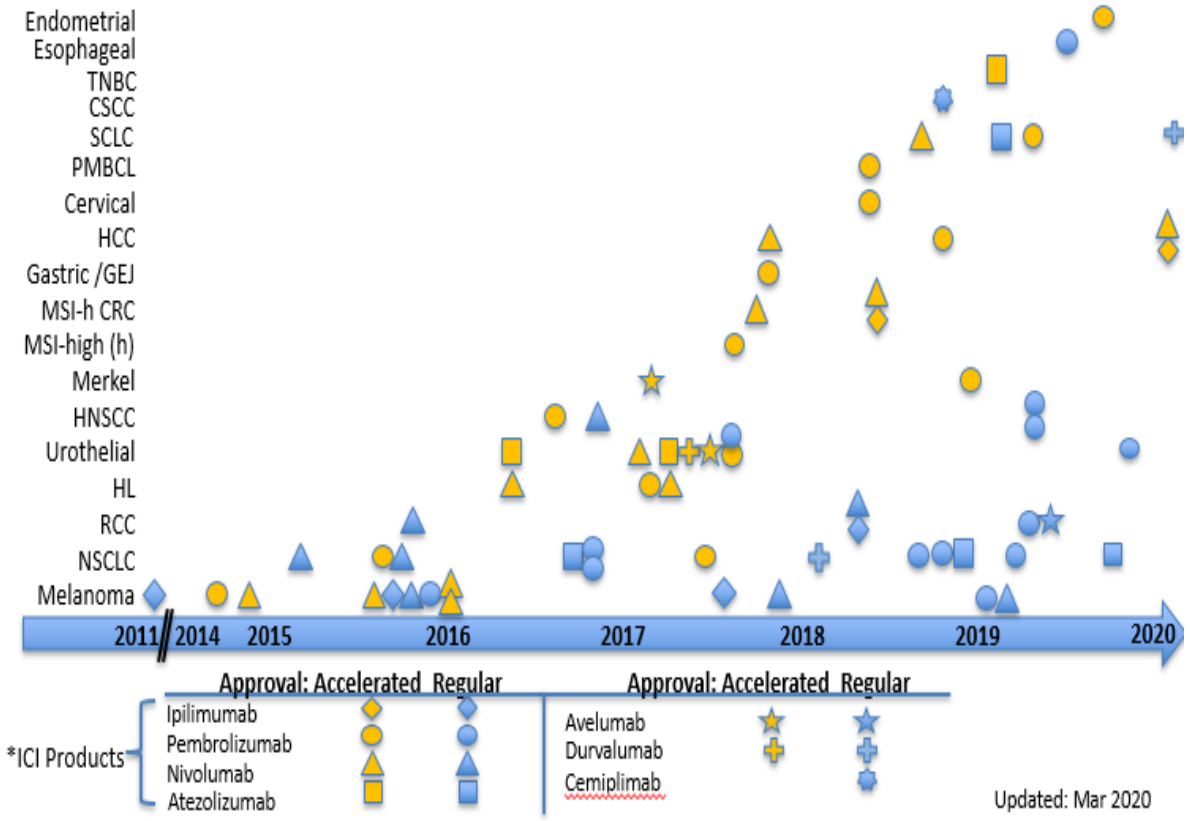
*Targeted drugs for the purpose of this figure are new molecular entities (NMEs) for which the initially approved indication is restricted to a subset of patients who are identified through molecular testing.
**Companion diagnostics reflect original premarket approvals or 510(k) authorizations.

(PMID: 31782136)

New Therapeutic Modalities: Monoclonal Antibodies (Some Oncology Examples)

Timeline of Immune Checkpoint Inhibitors Approvals

Slide courtesy of Dr. Marc Theoret

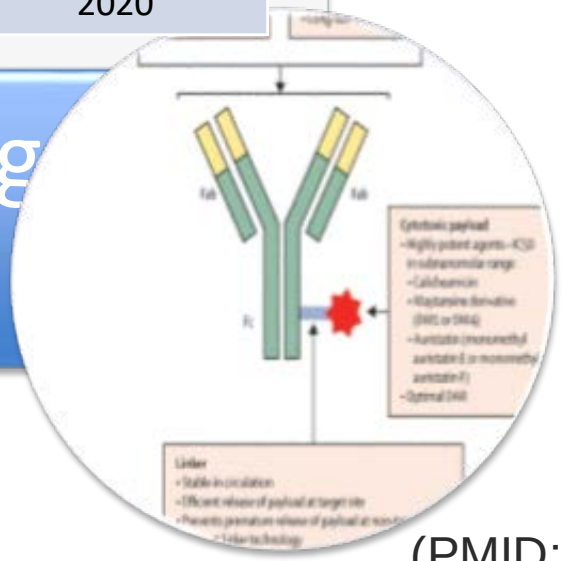


James Allison and Tasuku Honjo share the 2018 Nobel Prize in Physiology or Medicine. Left: Richard Drew/AP/Shutterstock. Right: MEXT/CC BY 4.0

New Therapeutic Modalities: Antibody-drug Conjugates and Bispecific Antibodies (Oncology Examples)

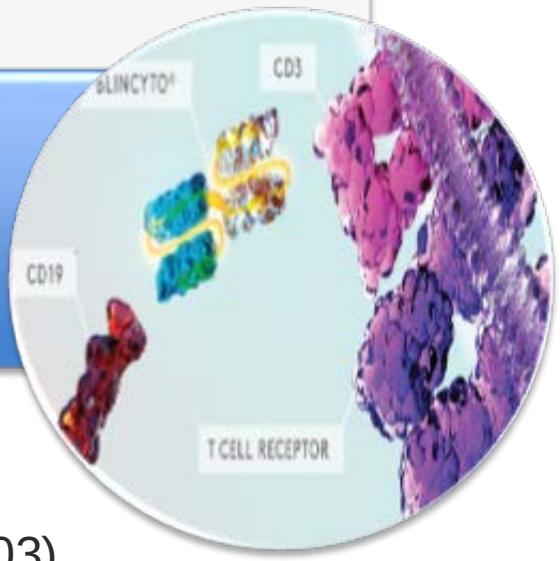
ADC	Year of Approval
gemtuzumab ozogamicin	2000
brentuximab vedotin	2011
trastuzumab emtansine	2013
inotuzumab ozogamicin	2017
polatuzumab vedotin	2019
enfortumab vedotin	2019
trastuzumab deruxtecan	2019
sacituzumab govitecan	2020
belantamab mafodotin	2020

antibody-drug conjugates



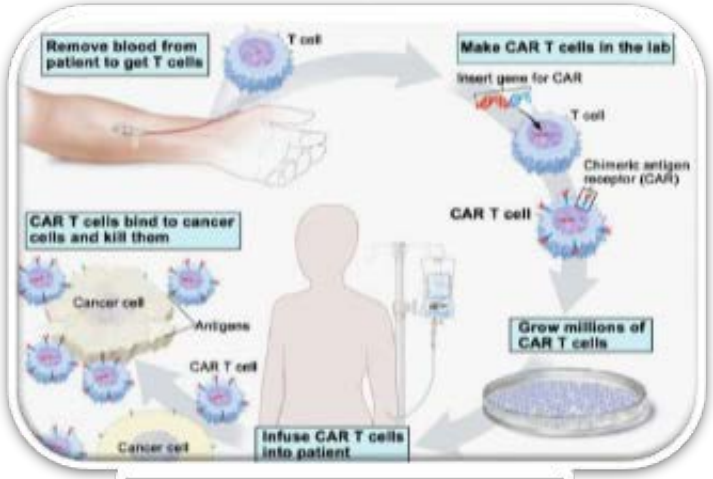
- Blinatumomab approved in 2014
- Many other bispecific antibodies under clinical development

bispecific antibodies

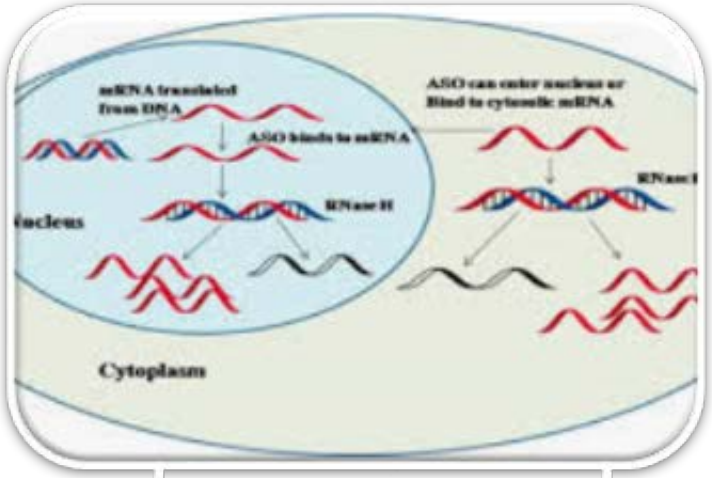


(PMID: 32937862; PMID: 31478503)

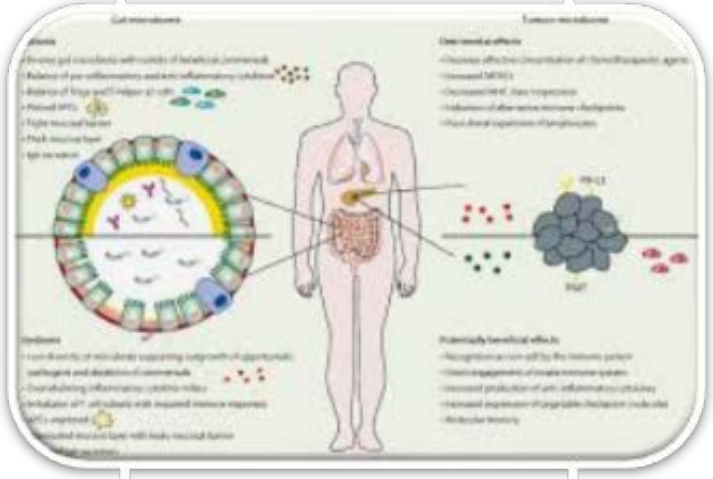
New Therapeutic Modalities: Others (Oncology Examples)



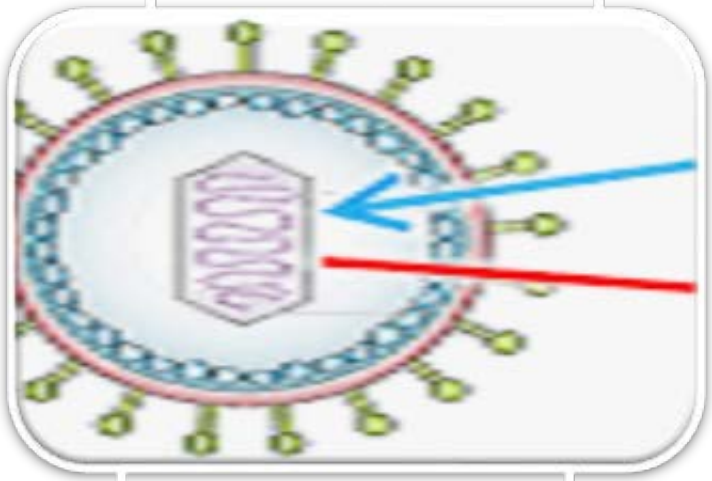
cell based therapy*



oligonucleotide based therapy



microbiome based therapy



viral therapy**

* FDA approval for cancer treatment:
sipuleucel-T,
tisagenlecleucel,
axicabtagene ciloleucel,
brexucabtagene autoleucel

** FDA approval for cancer treatment:
talimogene laherparepvec

Today's Breakthroughs in Oncology Are the Results of Decades of Investment in Cancer Research and Drug Development

- Scientific and technical breakthroughs have led to the novel therapies for cancer.

- Federal investment
  - National Cancer Act of 1971: "war on cancer"
  - Cancer Moonshot

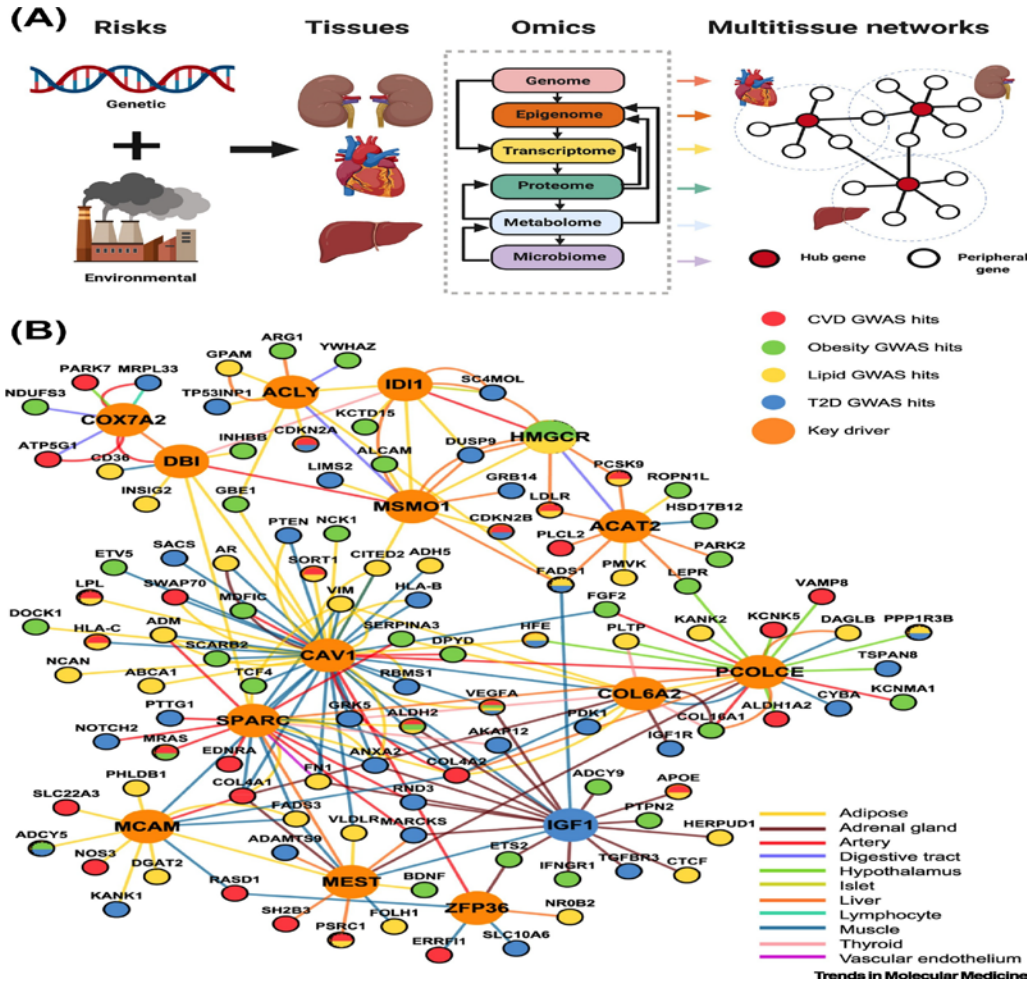
President Richard Nixon signing the National Cancer Act of 1971.
Credit: National Cancer Institute

- Industry investment
  - Vast investment in oncology
  - Why:
    - Basic research has lead to promising targets/drug candidates?
    - Financial incentive?
    - Flexibility and innovation in the FDA's regulatory approval strategies for cancer drugs?
      - Examples: breakthrough designation, accelerated approval, real-time oncology review, project Orbis

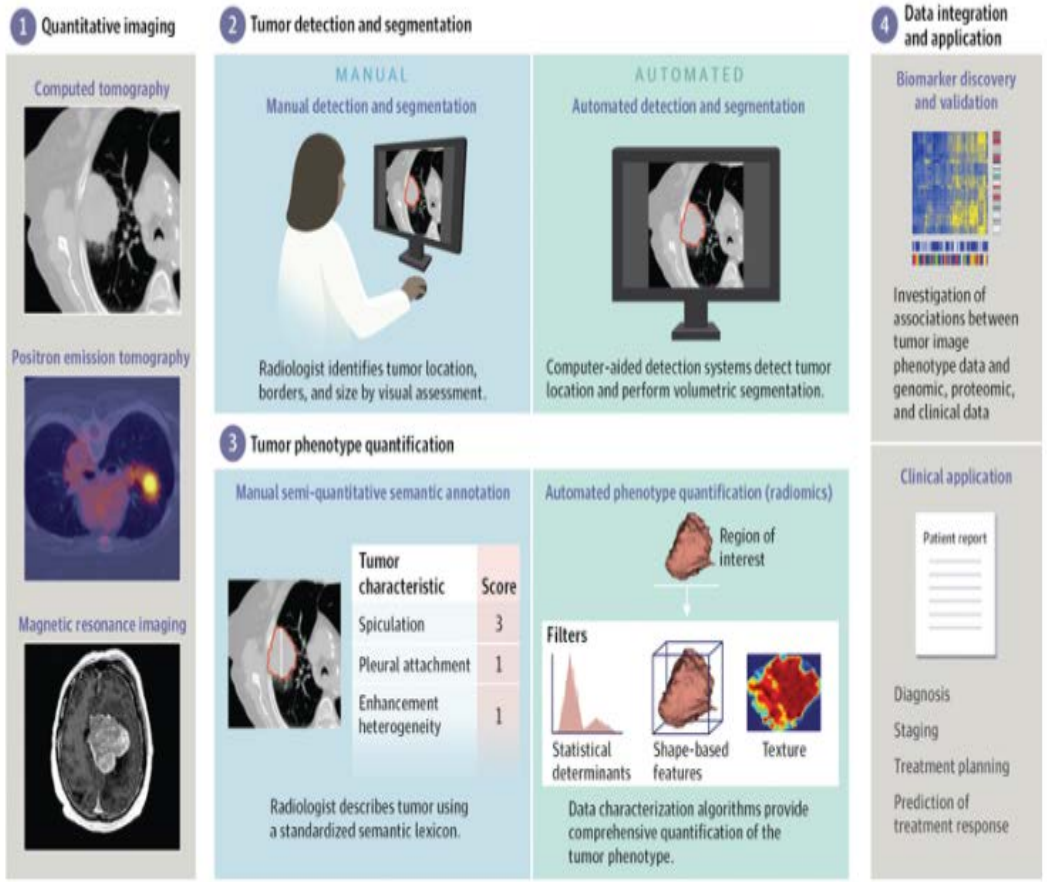
What can we learn from oncology, and apply to other prevalent chronic diseases?

New Types of Data: Multi-Omics Data

Multitissue Multiomics Systems Biology to Dissect Complex Diseases



The Potential of Radiomic-Based Phenotyping in Precision Medicine



(PMID: 32439301; 26278466)

New Types of Data: Real-World Data

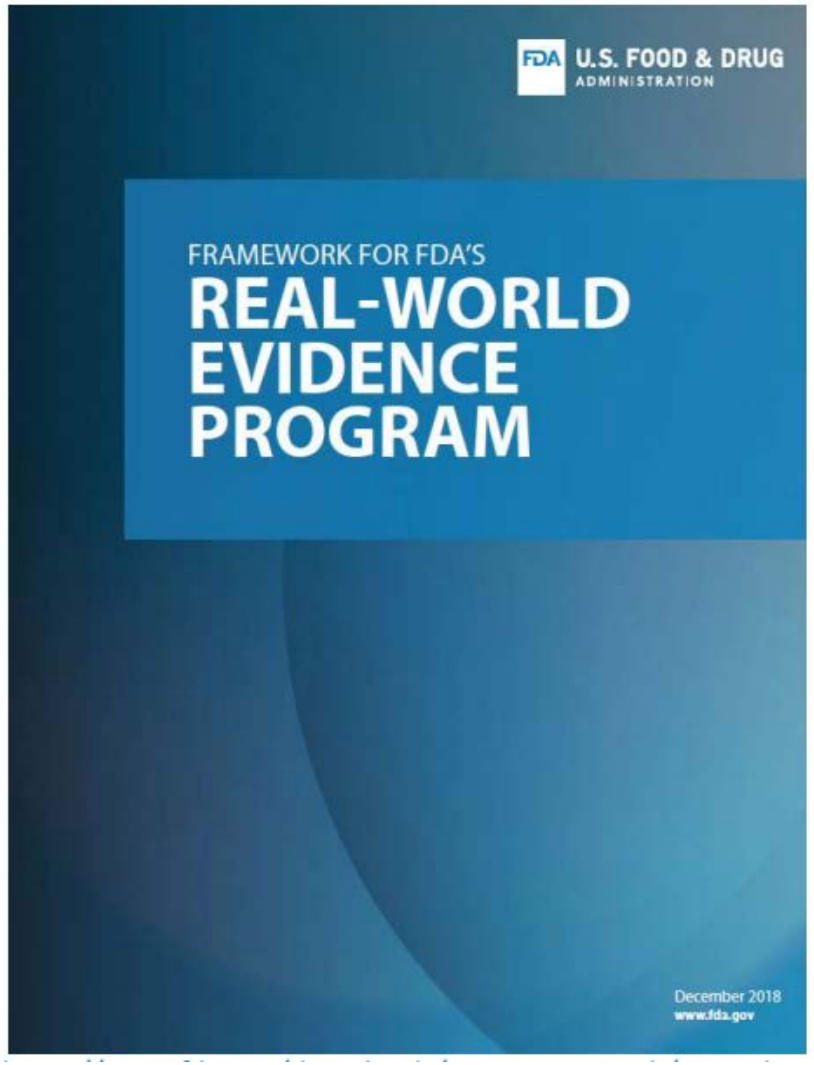
RWD is the data relating to patient health status and/or the delivery of health care routinely collected from a variety of sources, such as:

Electronic health records

Claims and billing activities

Product and disease registries

Patient-generated data including in home-use settings



https://www.fda.gov/science-research/science-and-research-special-topics/real-world-evidence

New Types of Data: Data from Novel Experiment Systems

FDA/CDER Microphysiological Systems Laboratory

Review | Open Access

Liver Microphysiological Systems for Predicting and Evaluating Drug Effects

Alexandre J. S. Ribeiro, Xinning Yang, Vikram Patel, Rajnikanth Madabushi, David G. Strauss

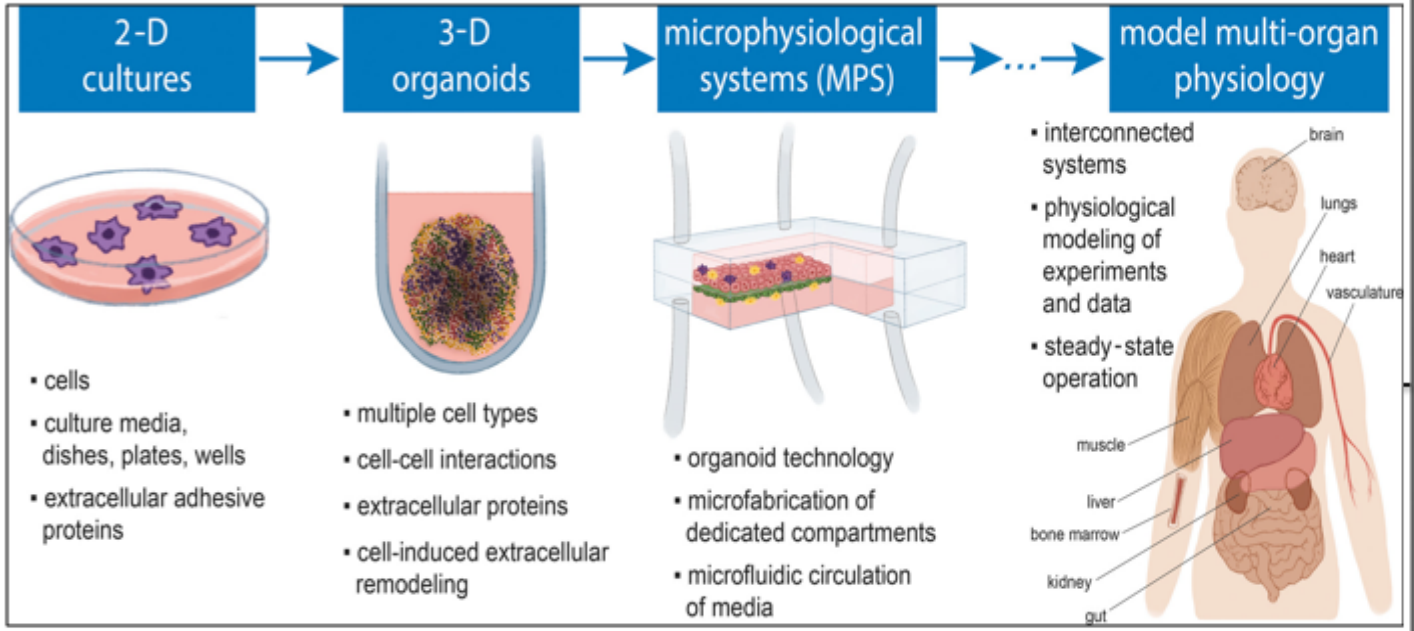
Clinical Pharmacology & Therapeutics 2019;106:139-47.

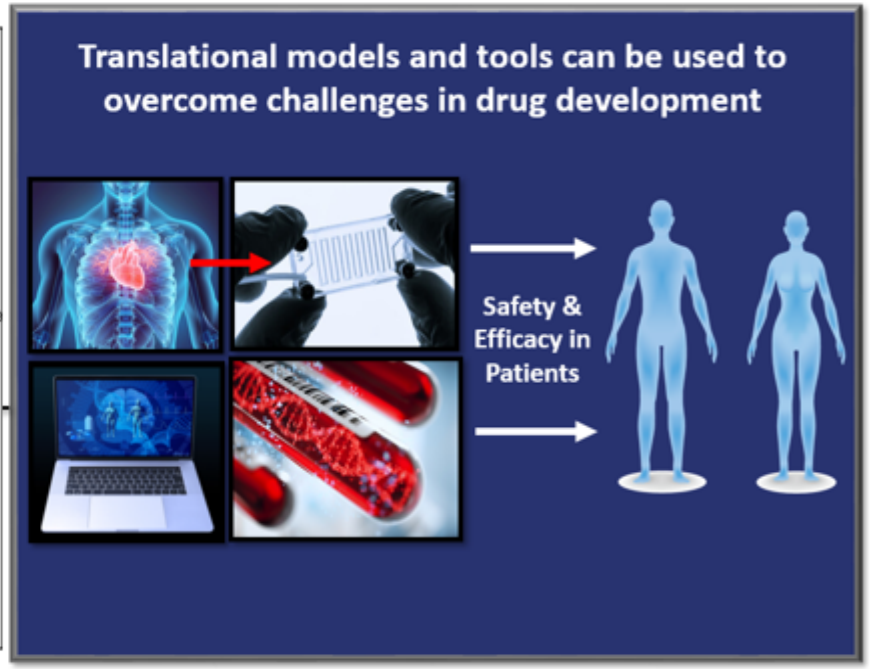
ARTICLE | Open Access

Characterizing the Reproducibility in Using a Liver Microphysiological System for Assaying Drug Toxicity, Metabolism and Accumulation

Andres Rubiano, Amruta Indapurkar, Ryosuke Yokosawa, Alina Miedzik, Barry Rosenzweig, Ayesha Arefin, Chloe M. Moulin, Keri Dame, Neil Hartman, Donna A. Volpe, Murali K. Matta, David J. Hughes, David G. Strauss, Tomasz Kostrzewski, Alexandre J.S. Ribeiro

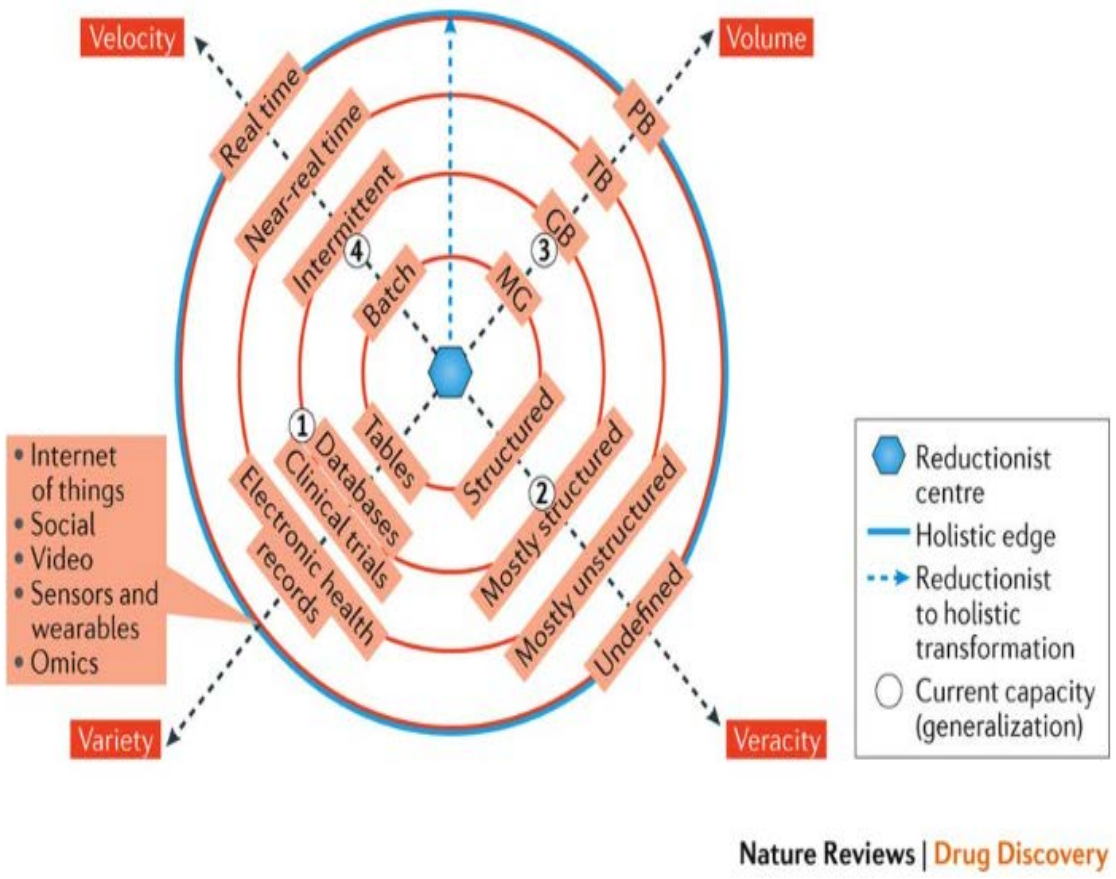
Clinical & Translational Science 2020 [epub].

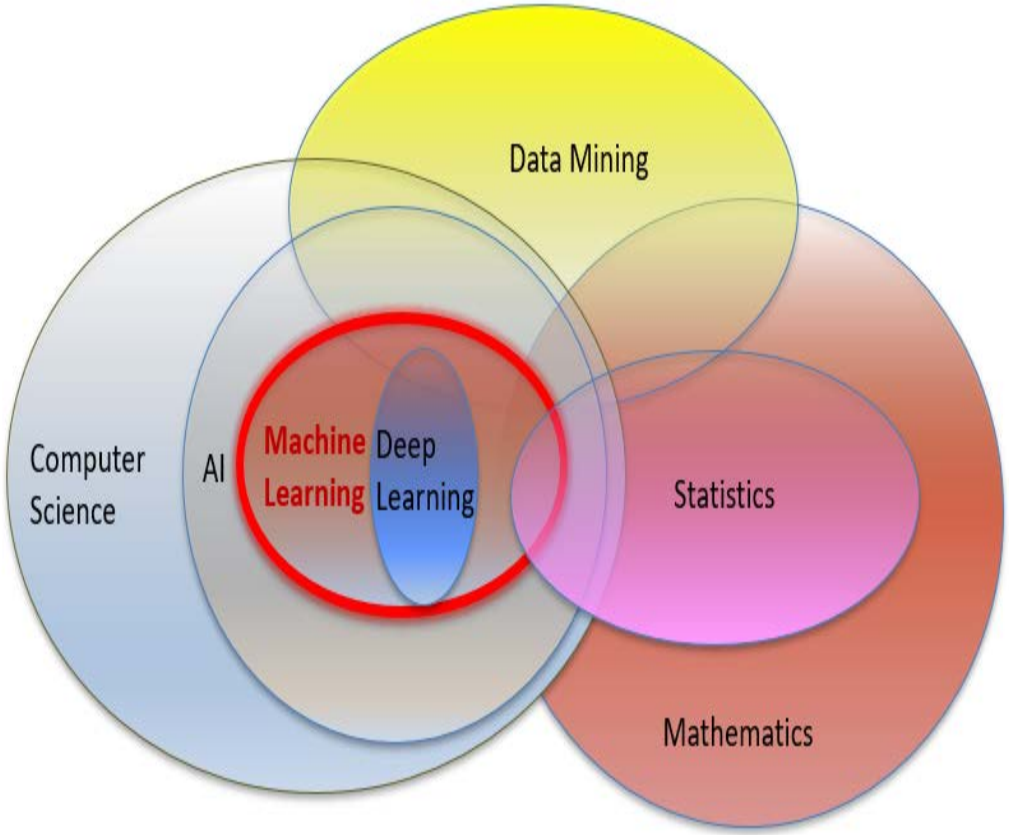




Slide courtesy of Dr. David Strauss

New Analytical Tools: Needed to Transform Big Data to Smart Decisions

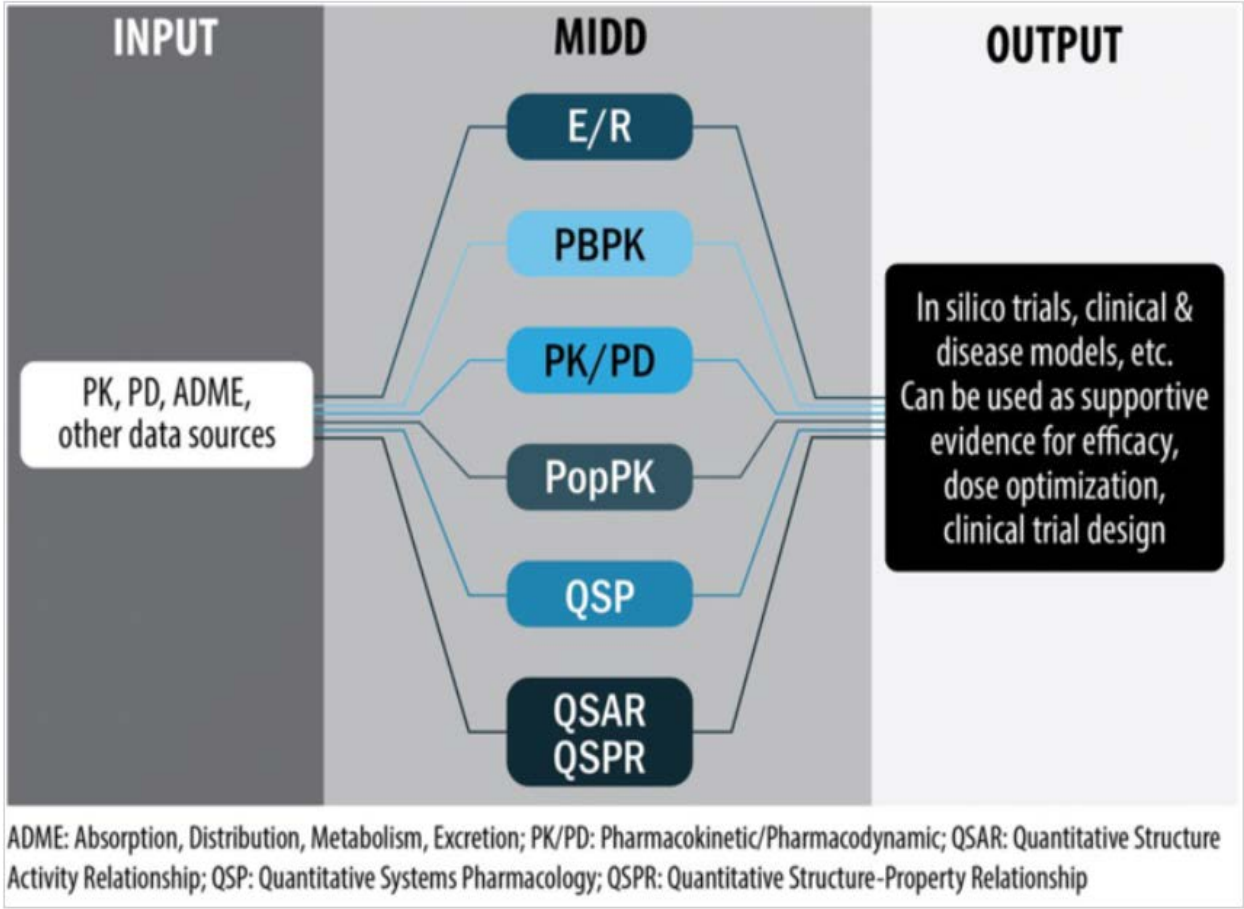




https://www.nature.com/articles/nrd.2017.26

New Analytical Tools: Model-Informed Drug Development (MIDD)

The application of exposure-based, biological, and/or statistical models, derived from preclinical and clinical data sources, to address drug development and/or regulatory issues.



https://www.federalregister.gov/documents/2018/04/17/2018-08010/pilot-meetings-program-for-model-informed-drug-development-approaches

"Clinical Pharmacology Regulatory Sciences in Drug Development and Precision Medicine: Current Status and Emerging Trends". AAPS Journal (accepted)

An Example of Application of MIDD for Drug Repurposing

Connecting Hydroxychloroquine In Vitro Antiviral Activity to In Vivo Concentration for Prediction of Antiviral Effect: A Critical Step in Treating Patients With Coronavirus Disease 2019

Jianghong Fan, Xinyuan Zhang, Jiang Liu, Yuching Yang, Nan Zheng, Qi Liu, Kimberly Bergman, Kellie Reynolds, Shiew-Mei Huang, Hao Zhu, Yaning Wang

Clinical Infectious Diseases, Volume 71, Issue 12, 15 December 2020, Pages 3232–3236, https://doi.org/10.1093/cid/ciaa623

Published: 21 May 2020 **Article history**

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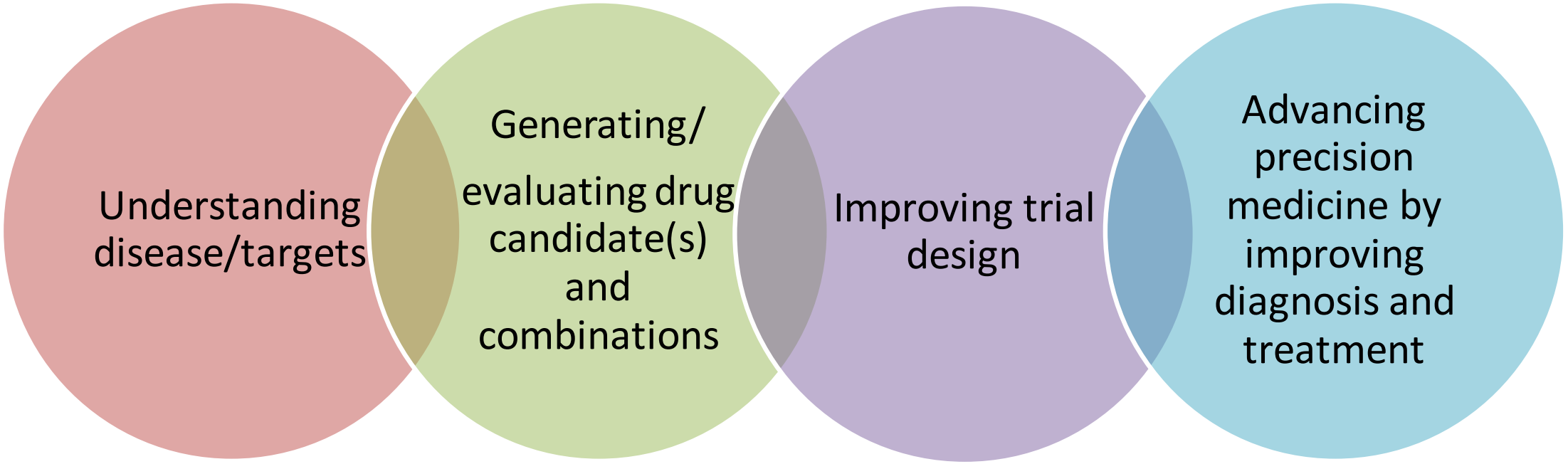
Abstract

Translation of in vitro antiviral activity to the in vivo setting is crucial to identify potentially effective dosing regimens of hydroxychloroquine. In vitro 50%/90% maximal effective concentration values for hydroxychloroquine should be compared to the in vivo free extracellular tissue concentration, which is similar to the free plasma hydroxychloroquine concentration.

Conclusion:
Under the assumption that in vivo cellular accumulation is similar to that from the in vitro studies, the calculated free lung concentrations that would result from proposed dosing regimens are well below the in vitro EC50/EC90 values, making the antiviral effect against SARS-CoV-2 not likely achievable with a safe oral dosing regimen.

New Analytical Tools: AI/Machine learning (ML)

Aggregating data, synthesizing information, seeking patterns and optimizing decisions



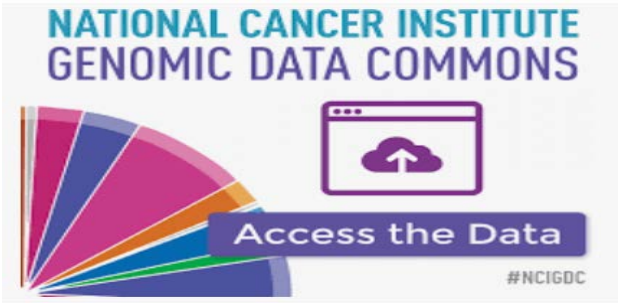
(PMID: 31925955)

Examples of AI/ML Submissions to the FDA

- Medical devices (e.g., diagnostic tools)
- Disease models as a drug development tool (randomization aid, patient enrichment, virtual control)
- Prediction of drug response based on baseline factors (e.g., genomic/ proteomic data) or imaging
- Identification of predictive biomarkers
- Application to claims and electronic medical records to identify drug abuse related problems in post marketing setting

To Make the Best Use of the Novel Analytical Tools, We Need Data Sharing and Precompetitive Collaboration

- It wasn't who has the best algorithm that wins, it was who has the most data for the application. - Andrew Ng
- Data Sharing Examples:



FNIH Biomarkers Consortium - Vol-PACT

Summary

- We expect to see upcoming innovations in drug discovery/development in 3 major categories: new therapeutic modalities, new types of data and new analytical tools.

- Investments from government and industry are needed for scientific breakthroughs.

- Data sharing and precompetitive collaboration can potentially benefit everyone, especially the patients.

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