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FDA / ISoP - Best Practices for Modeling and Simulation for Oncology

February 1, 2018
8:00am - 5:20pm

FDA U.S. FOOD & DRUG ADMINISTRATION
ONCOLOGY CENTER OF EXCELLENCE

Five inspiring examples…

but also one oncologist

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Clinical Perspective:
Bringing the Community Care Setting Into the Learning Versus Confirming Paradigm

Michael Maitland, MD, PhD
Director of Therapeutics, Inova Center for Personalized Health
Professor of Internal Medicine, Virginia Commonwealth University
Assoc. Director for Cancer Therapeutics, Inova Schar Cancer Institute

A nearby health system…

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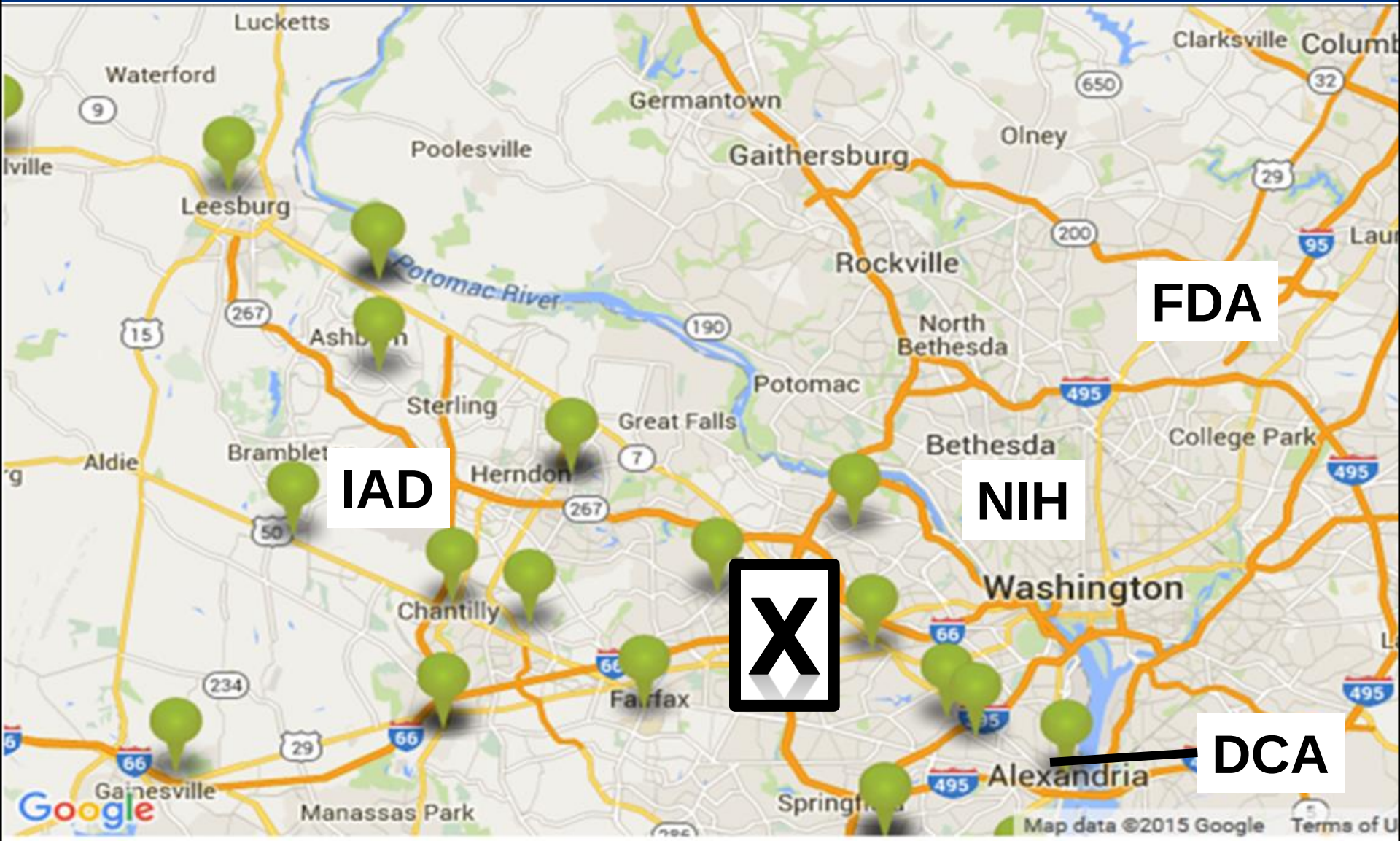

A HOSPITAL/HEALTH SYSTEM NEWLY COMMITTED TO SCIENCE/INNOVATION

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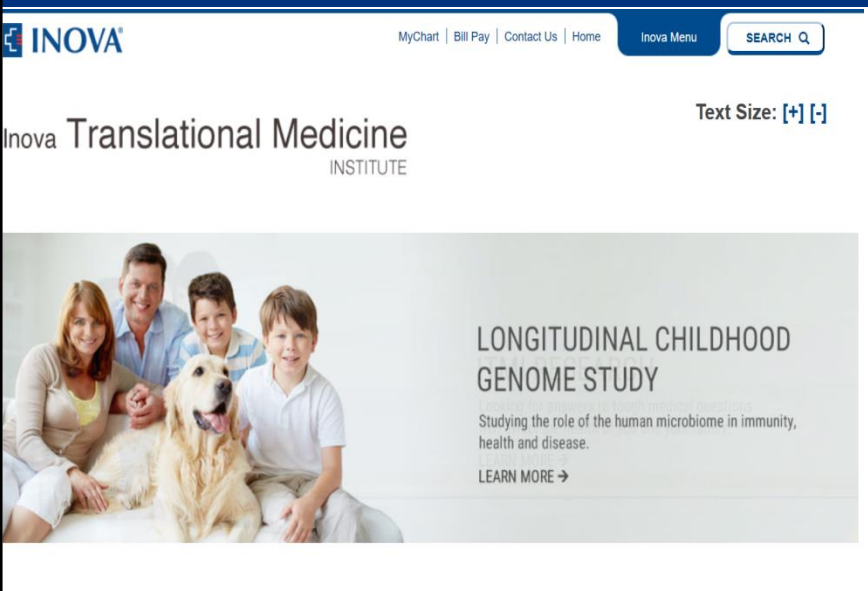

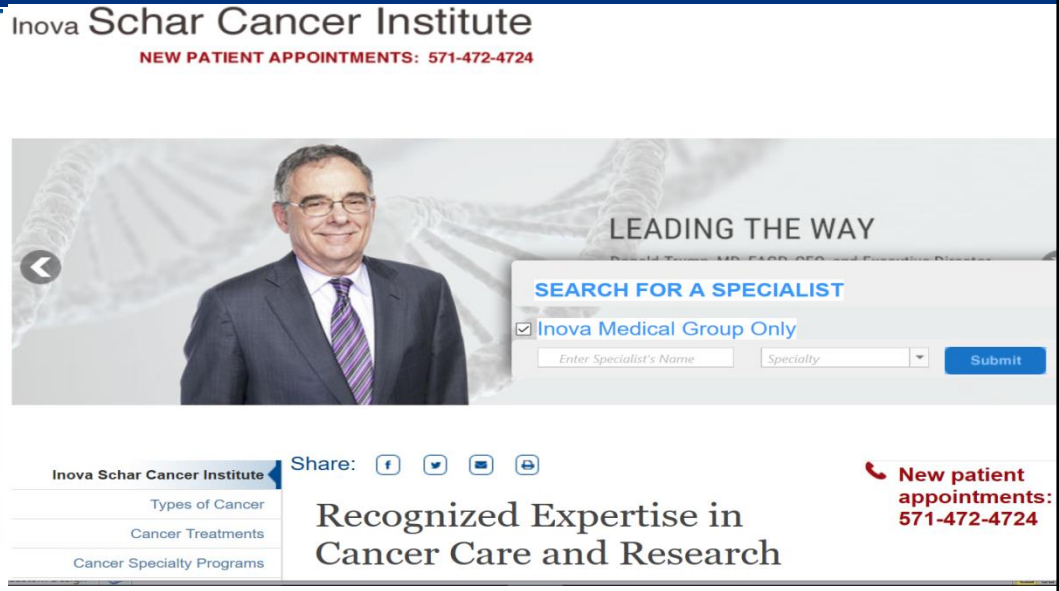

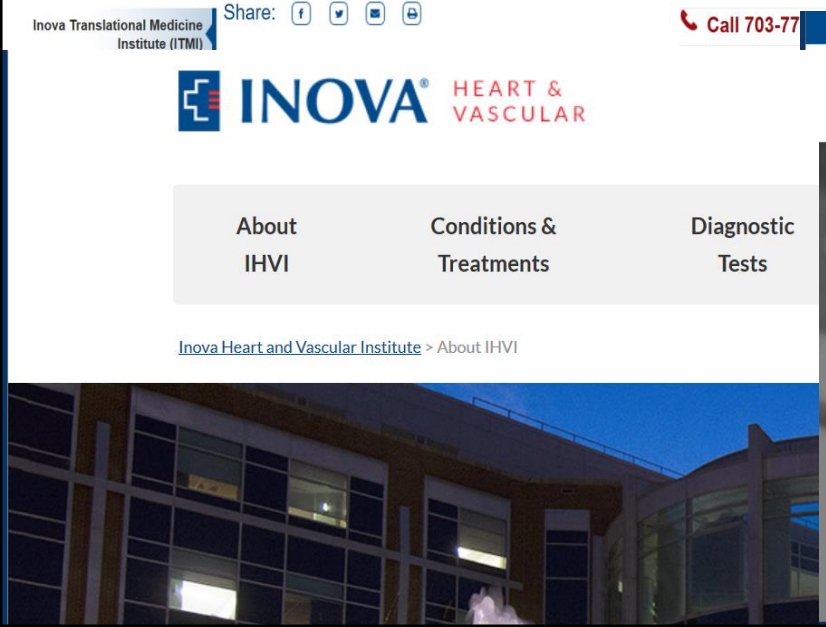

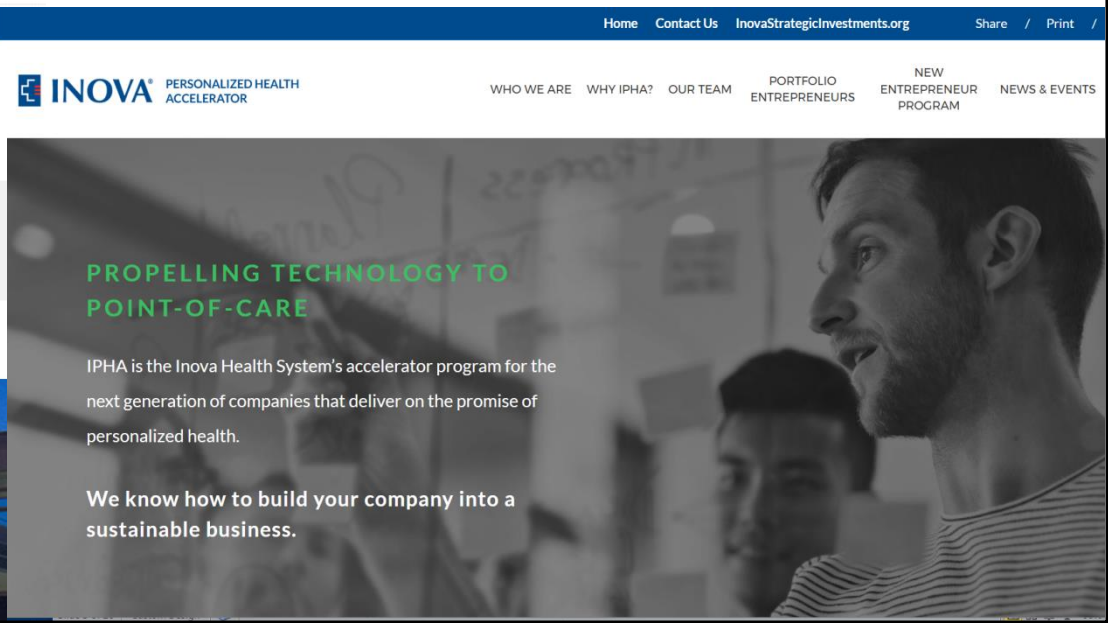

CENTER FOR PERSONALIZED HEALTH (ICPH)- 2019

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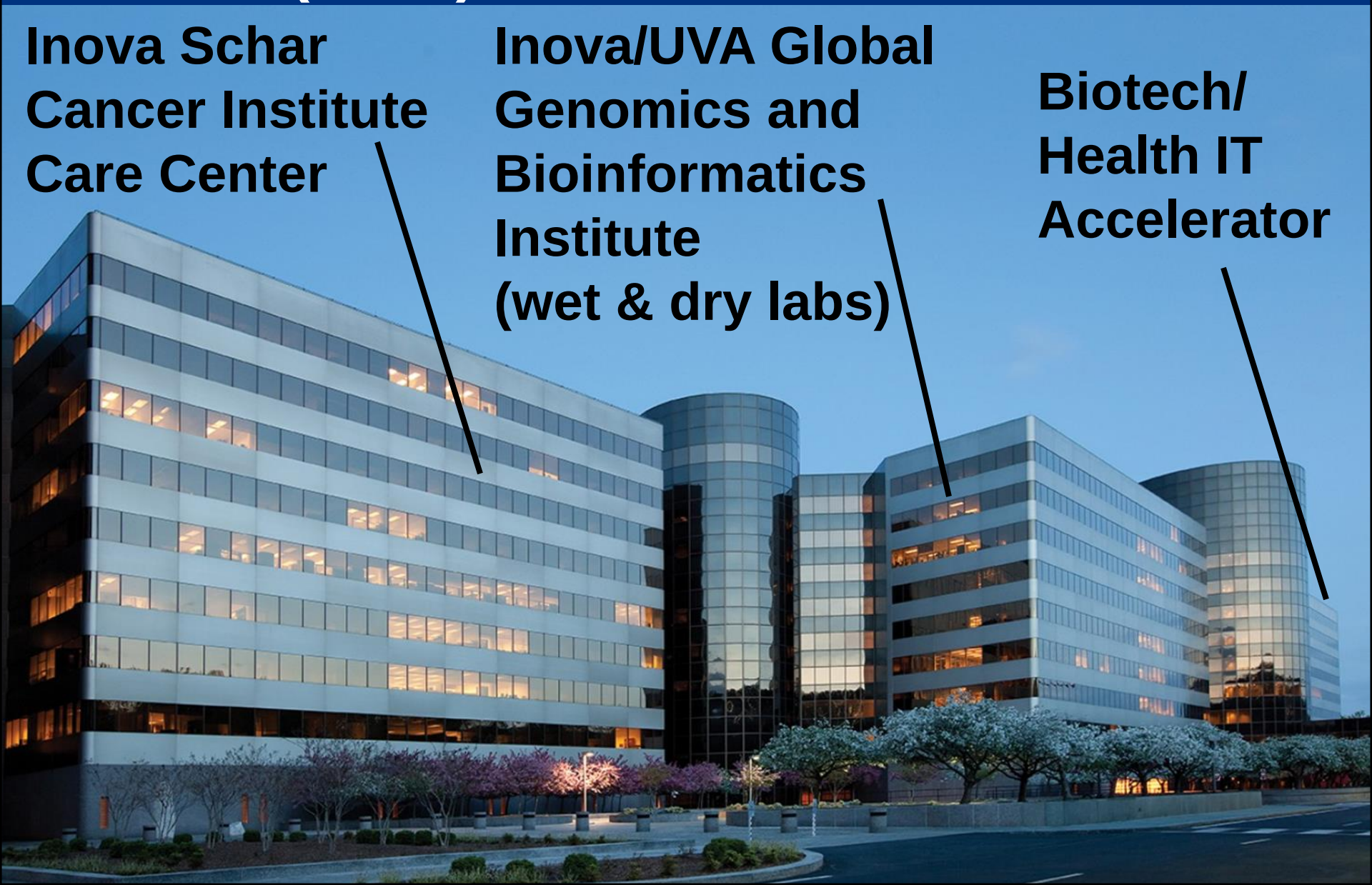

Research in community medical practice

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Molecular pathology as destiny

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Pt 1

- 30's yo presented w/ prolonged menses, endometrial bx 09/14 with endometrioid adenocarcinoma T2N2M0= IIIC2
- Adj. cddp/doxo->RT/prog.
- 03/16 cbcda/pac
- 11/16 procedure

Pt 2

- 30's yo presented abnl screening cytology, then developed sx, d&c 01/14 with endometrioid adenocarcinoma T3bN1M0= IIIC1
- Adj. cbcda/pac-> RT
- 10/15 cbcda/lipo-dox
- 12/15 doce/gem
- 09/16 bevacizumab

Molecular pathology as destiny

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Pt 1

- 08/17 nodal recurrence

***MLH1* M587fs*6**

TP53 R175H

"Additional findings"

High tumor mutation burden
21 Muts/Mb

Pt 2

- 09/17 progressive disease on bevacizumab

***PIK3CA* R88Q**

CTNNB1 S37C

PTEN N323fs

PTEN C.1026+1G>C

MSI testing not performed

Overall mutation burden intermediate

Professional Society (ASCO)-sponsored trial

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TAPUR
Targeted Agent and Profiling Utilization Registry Study
American Society of Clinical Oncology

ASCO's **Targeted Agent and Profiling Utilization Registry (TAPUR)** Study is a clinical trial to understand the efficacy and safety of FDA-approved, targeted anticancer drugs for patients whose advanced cancer has a genomic variant targeted by a TAPUR study drug.

OUR STUDY AIMS

- Collect data on clinical outcomes to help learn about new uses of approved drugs.
- Learn from real world prescribing practices.
- Educate oncologists about how to use genomically targeted drugs.
- Catalogue oncologists' choice of genomic profiling tests.
- Learn about the use of registry data to generate hypotheses for additional clinical trials.

ELIGIBILITY

- Advanced cancer (including solid tumors, multiple myeloma, and B cell non-Hodgkin lymphoma) with a genomic variant that can be targeted with a study drug
- No longer benefiting from standard treatment, or no standard treatment available
- Healthy enough to participate

WHO BENEFITS

- **Participants:** Access to targeted study drugs matched to the genomic profiles of their cancers
- **Physicians:** Assistance interpreting genomic results and identifying potential treatment options
- **Cancer Community:** New uses of targeted anticancer drugs for patients who have exhausted standard options
- **Drug Manufacturers:** Insights on new uses of existing drugs
- **Regulatory Authorities:** Learn about side effects and treatment outcomes from use of approved drugs in other cancers

HOW IT WORKS

1. Treating physician reviews patient's genomic profile and determines that patient is eligible for TAPUR study. Patient makes informed decision to participate
2. Physician matches participant to an available study drug
   OR
   Physician refers case to study Molecular Tumor Board in cases of:
   - No protocol-defined matches and potential clinical benefit (review required)
   - Multiple drug matches (review optional)
   - Desire for guidance (review optional)
3. Physician and participant confirm choice of TAPUR study drug (consistent with Molecular Tumor Board report, if applicable)
4. A central TAPUR study pharmacy provides the approved study drug at no cost to the participant
5. Patient data on standard toxicity and efficacy outcomes are collected for analysis

Molecular pathology as destiny

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Pt 1

- 05/23/17 Keytruda/pembrolizumab indication for advanced MSI-H/dMMR solid tumors that have progressed following prior treatment and who have no satisfactory alternative treatment options
- 08/17 begins pembrolizumab

Pt 2

- No FDA-approved PI3Ki
- NRG GY008 A Phase II Evaluation of Copanlisib (BAY 80-6946), a Selective Inhibitor of PI3KCA, in Patients With Persistent or Recurrent Endometrial Carcinoma Harboring PIK3CA Hotspot Mutations
- 09/17 begins paclitaxel

Molecular pathology as destiny

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Pt 1

- 10/17 CT imaging reveals decreased retroperitoneal adenopathy
- Had elevation of liver enzymes associated with fatigue now resolved
- Had changes in TSH, but no symptoms
- Works full time

Pt 2

- 10/17 vaginal bleeding controlled, pain persists
- Develops progressive, manageable peripheral neuropathy
- Pain/fatigue continue
- 11/17 NRG copanlisib study still on hold, team pursues single pt IND

The Oncologist®

Editorial

Approval After Phase I: Ceritinib Runs the Three-Minute Mile

BRUCE A. CHABNER
Massachusetts General Hospital Cancer Center, Boston, Massachusetts, USA

Disclosures of potential conflicts of interest may be found at the end of this article.

Bruce A. Chabner

Thirteen years ago, I wrote an editorial applauding discovery, development, and marketing approval of imatinib for chronic myelogenous leukemia (CML), a signal event in the history of targeted therapy, and the oncology equivalent of the four-minute mile [1]. It took 3 years from the start of trials and required the confirmatory evidence of two phase II studies to receive the U.S. Food and Drug Administration's (FDA) stamp of conditional approval. A decade later, these pages called attention to the rapid 3-year development of crizotinib for ALK-translocated non-small cell lung cancer (NSCLC), again based explained by its greater potency and its particular ability to inhibit ALK with gatekeeper mutations that confer resistance to crizotinib. In this trial, mechanisms of resistance were characterized in a subset of 19 crizotinib-resistant tumors prior to ceritinib treatment, and responses to the new drug were observed in settings where gatekeeper mutations were present, where ALK was amplified, or where no obvious mechanism was identified. While activation of alternative pathways is suspected of contributing to resistance, particularly when tumors fail to show amplification or mutation

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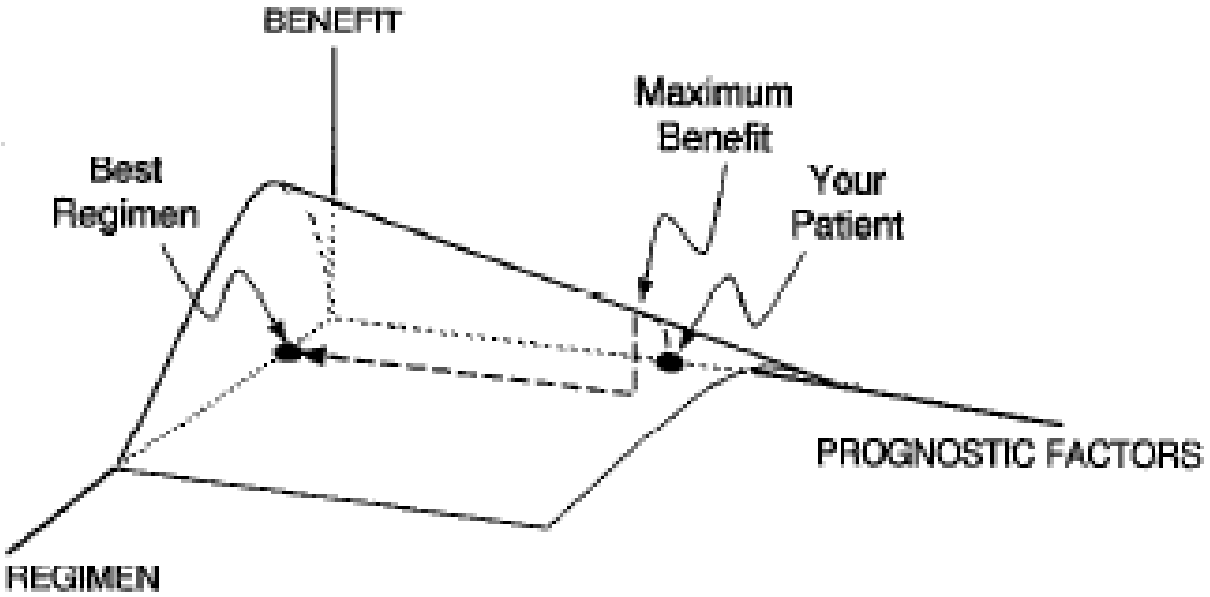
Learning versus confirming in clinical drug development

CLINICAL PHARMACOLOGY & THERAPEUTICS
MARCH 1997

Lewis B. Sheiner, MD *San Francisco, Calif.*



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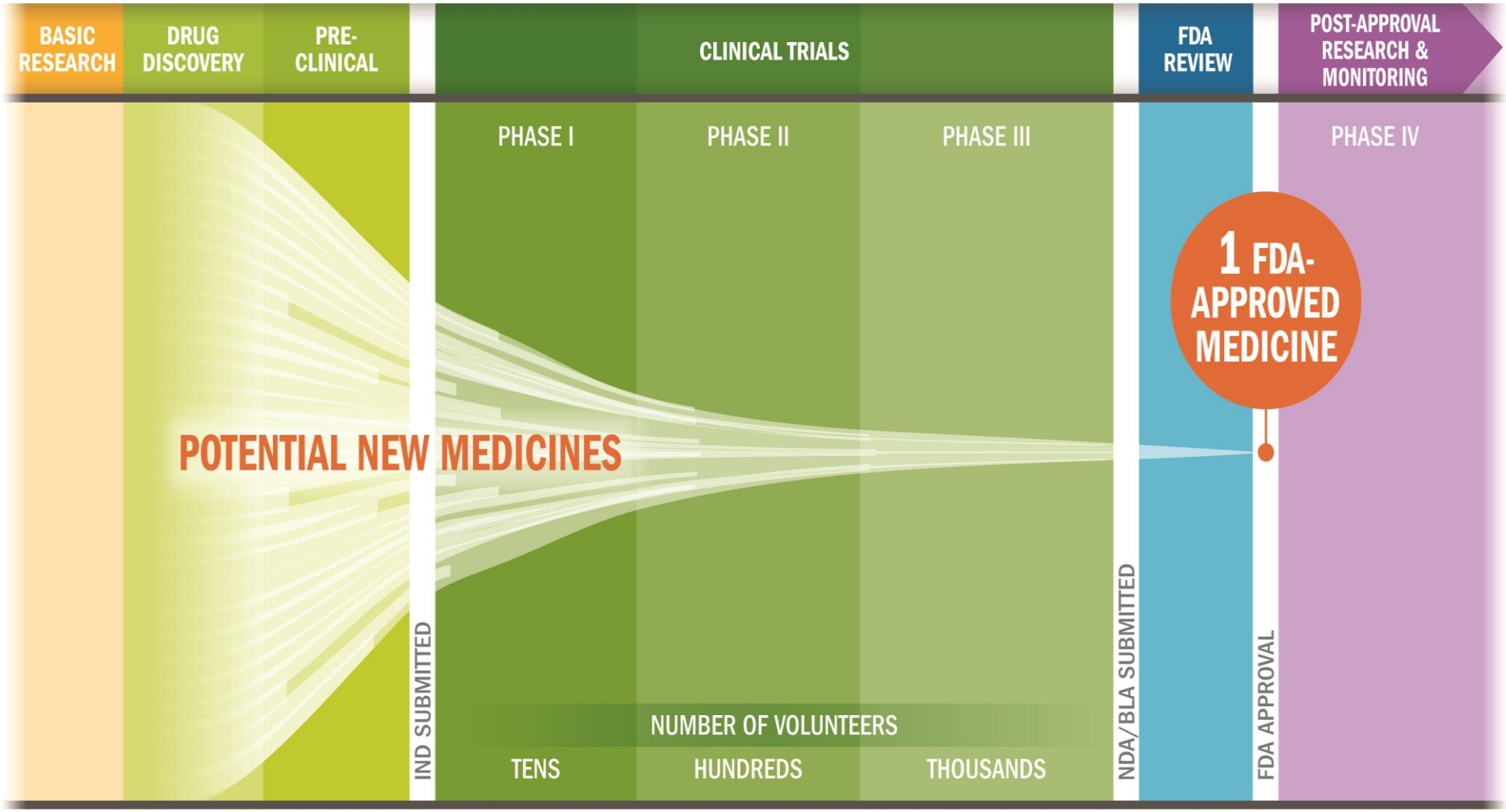
THE BIOPHARMACEUTICAL RESEARCH AND DEVELOPMENT PROCESS



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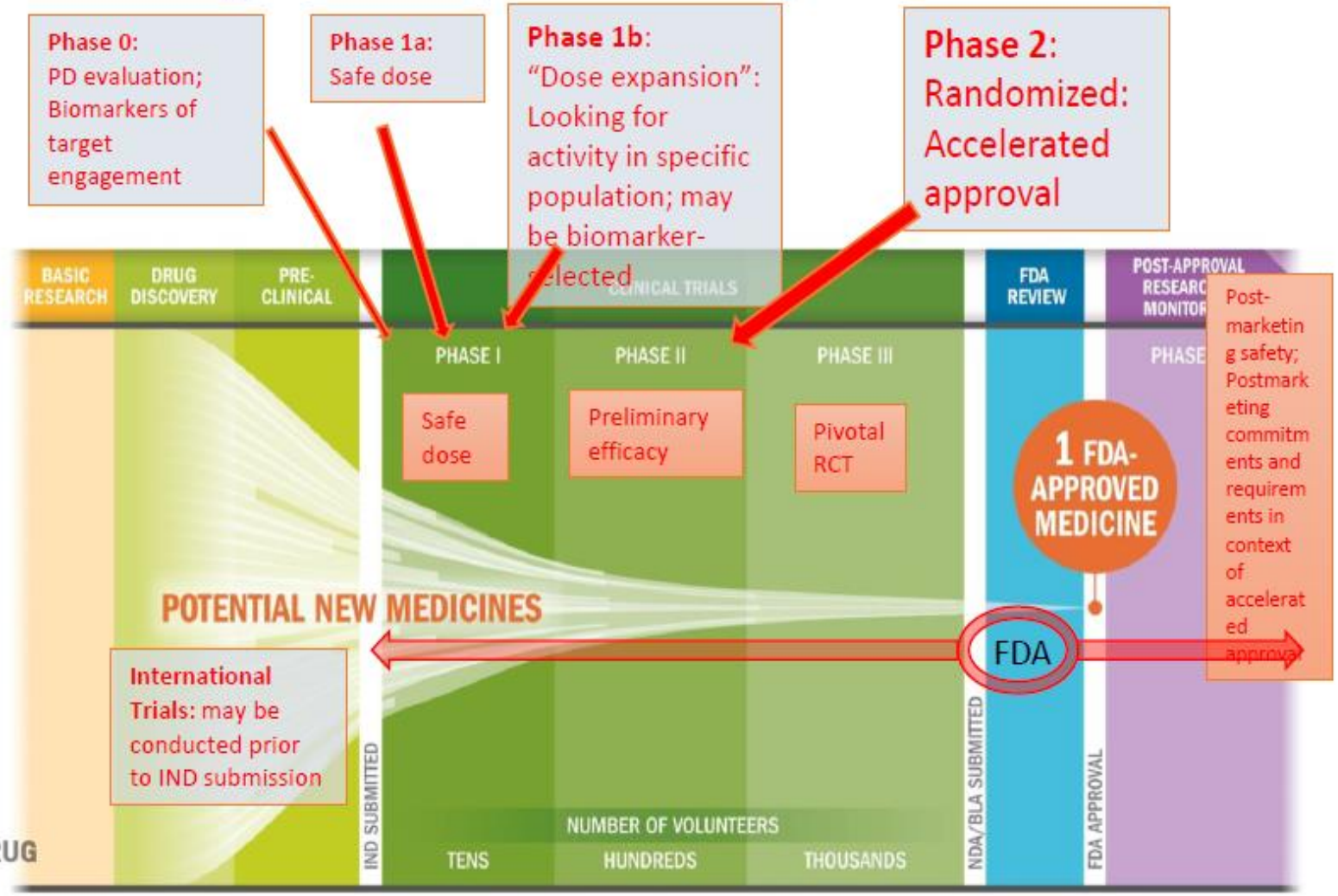
Clinical Regulatory Pathway: Now



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Our near future…

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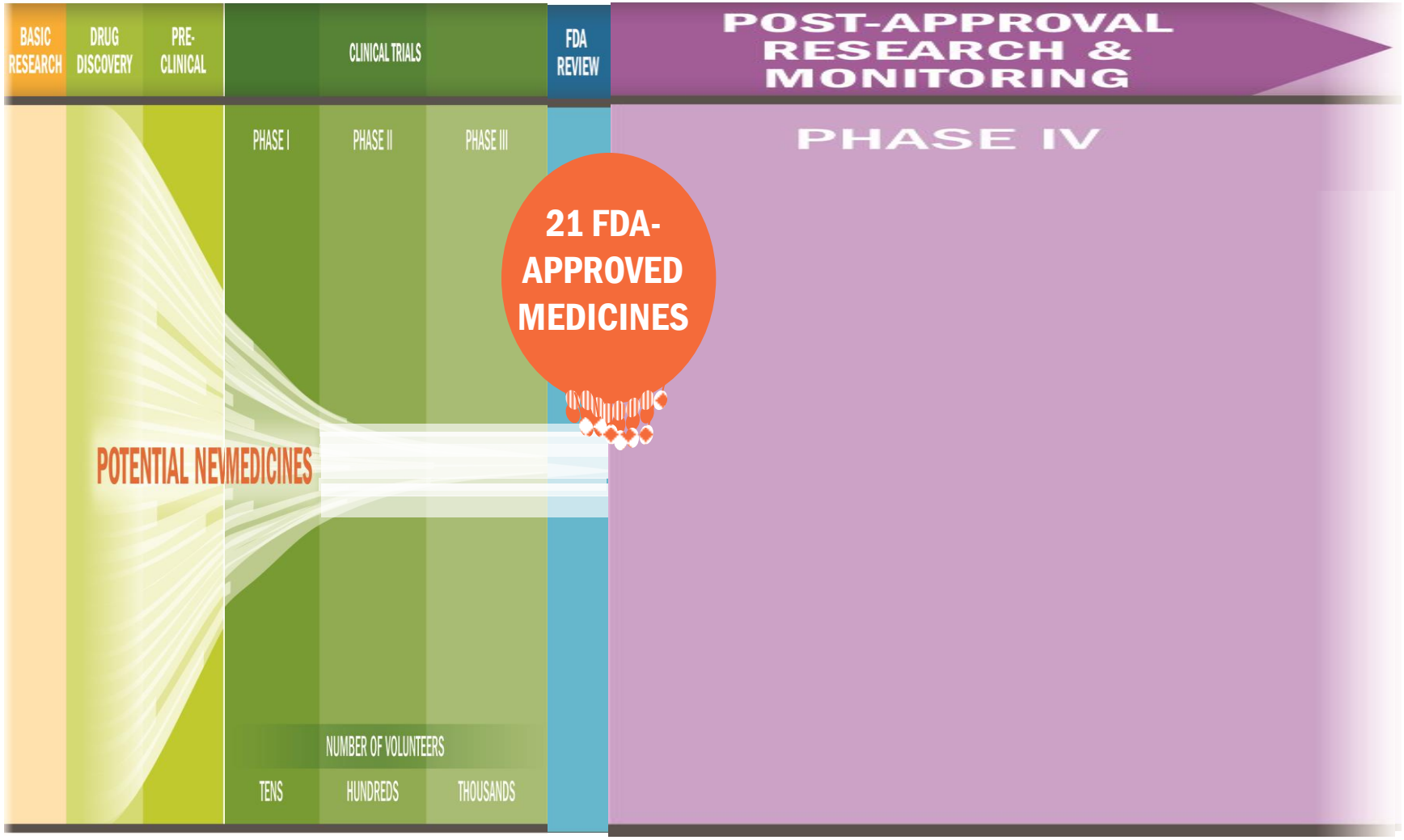

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With 20 agents, 803 Trials, and 166,736 Patient Slots, Is Pharma Investing Too Heavily in PD-1 Drug Development?

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Better data in the context of routine care?

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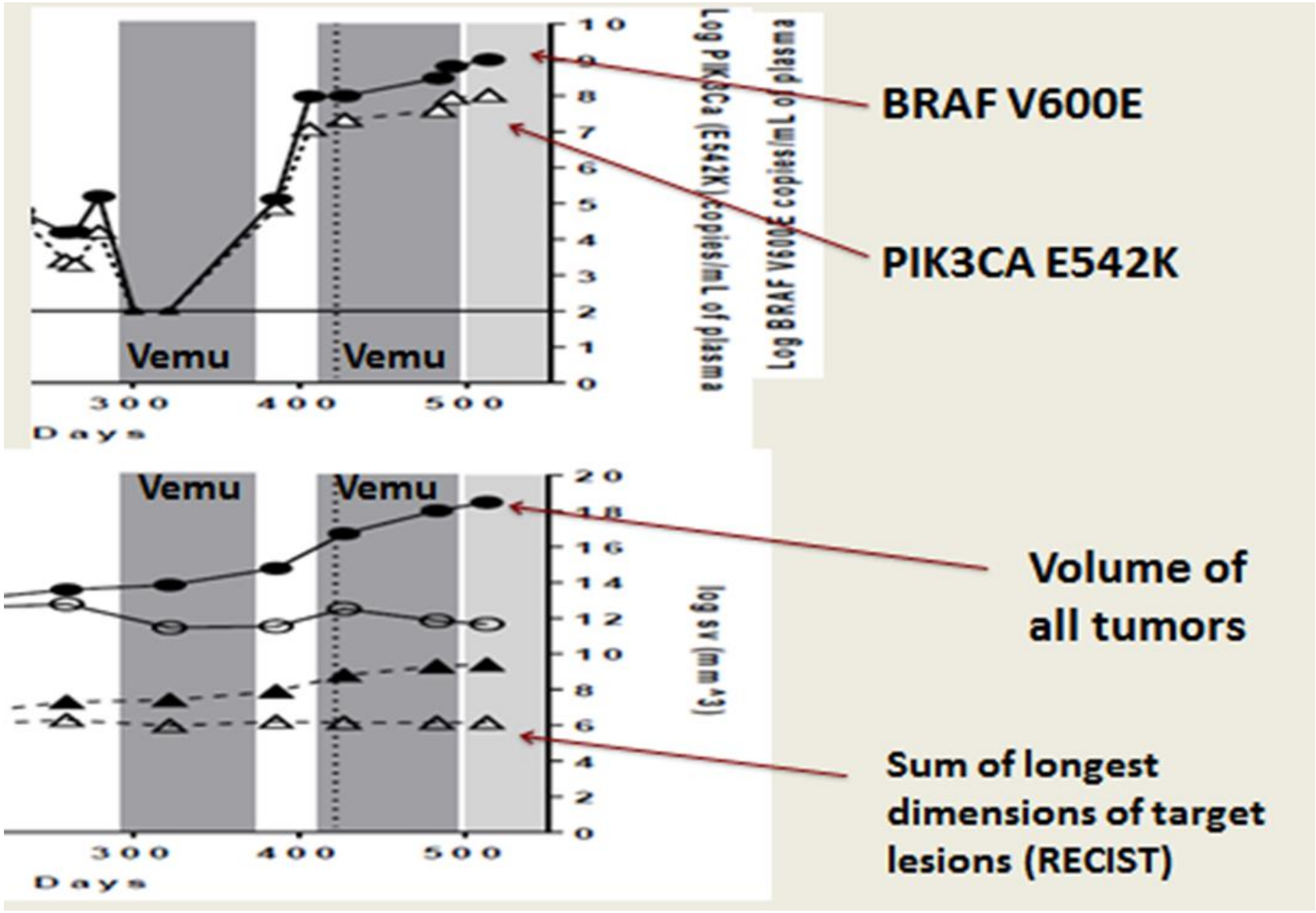

Better quality of pilot study assessments?

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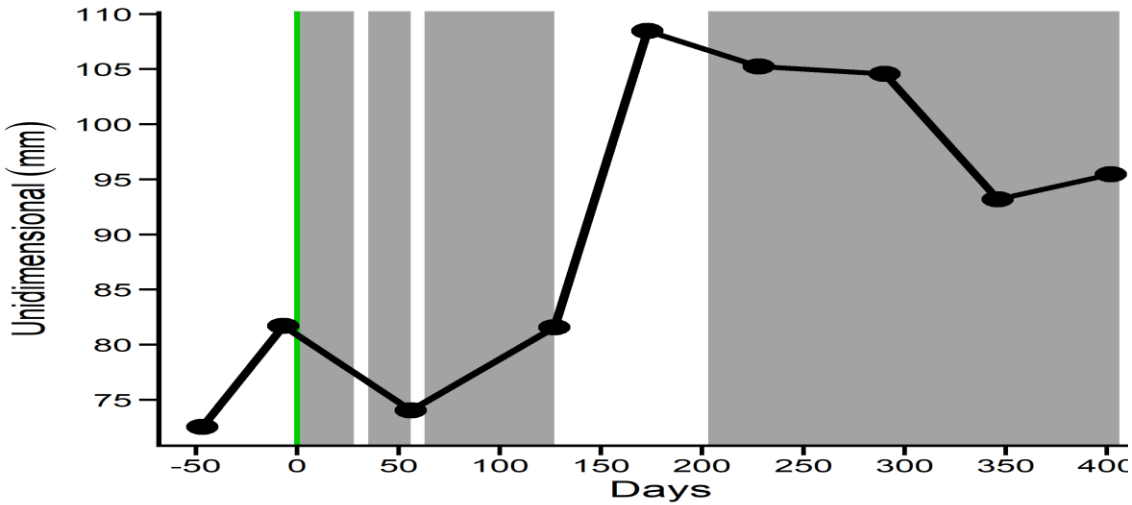

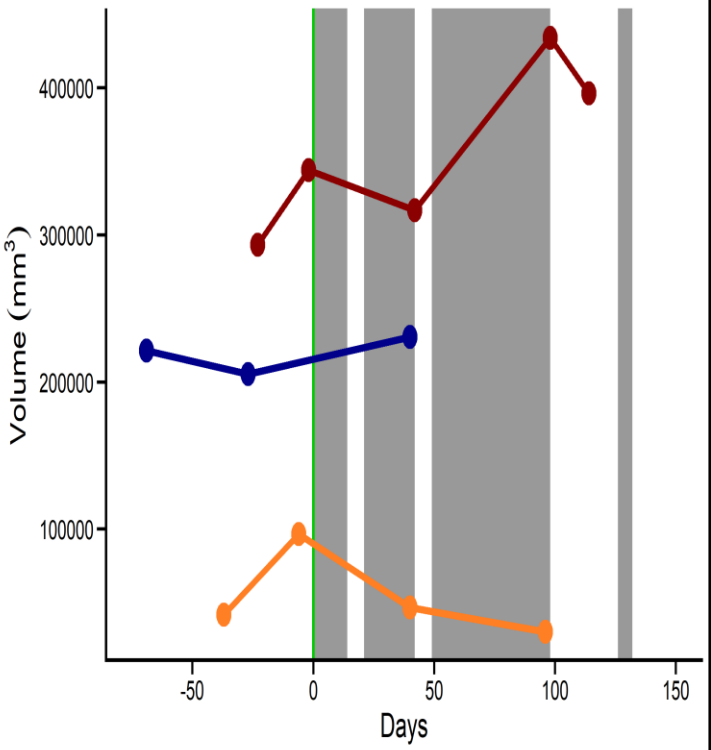

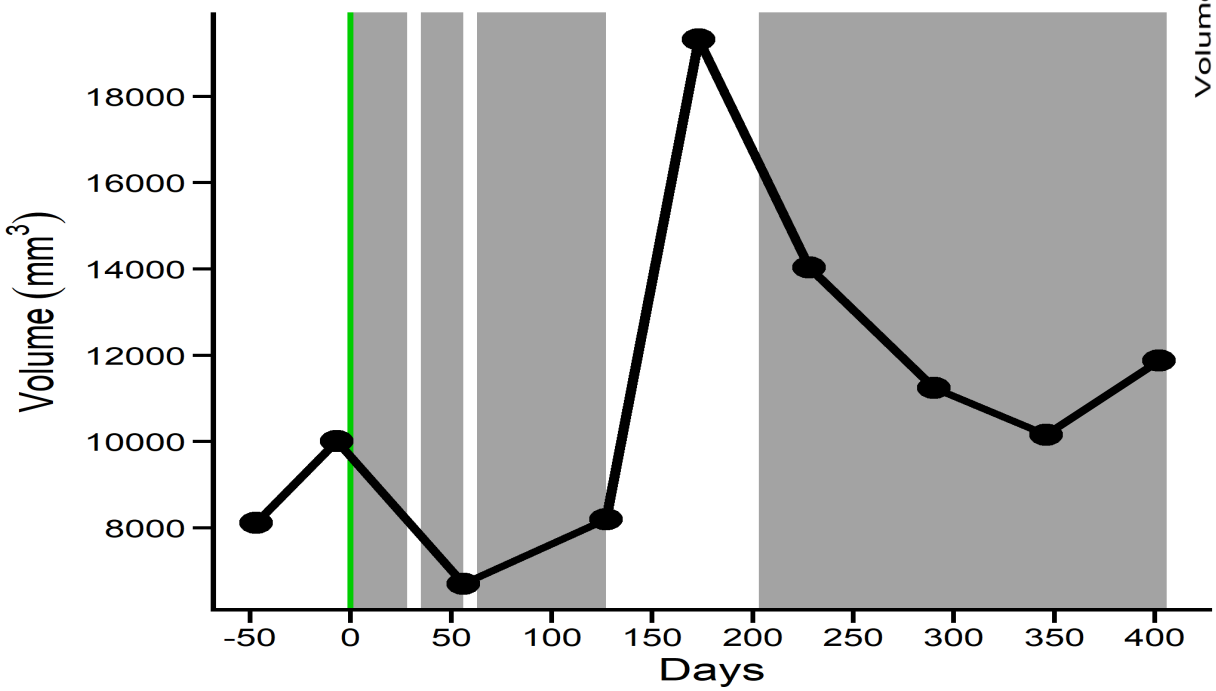

More learning and innovative confirming…

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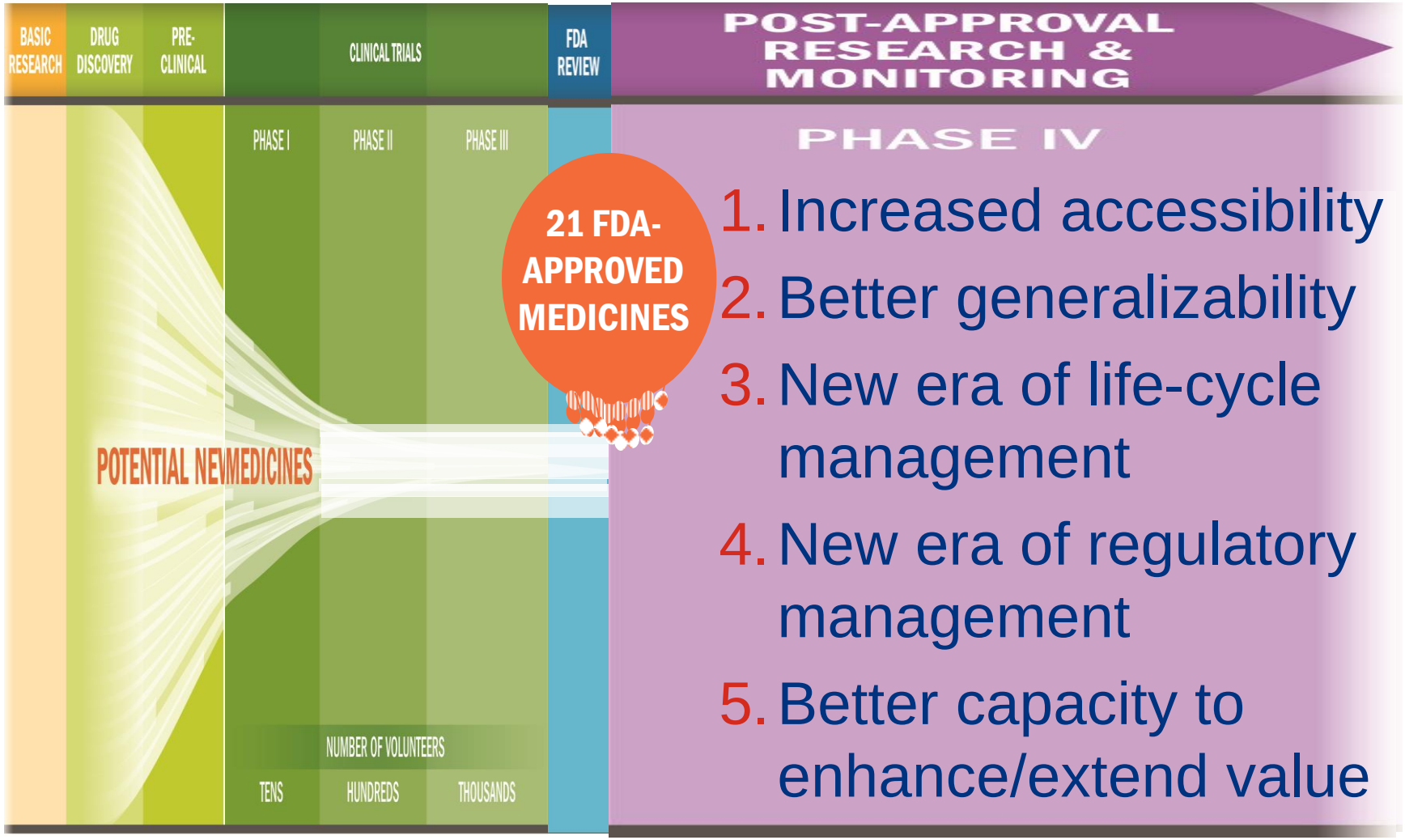

Sheiner- “What does the physician need to know?”

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- What is an appropriate initial dose for my particular patient?
- How soon will intended effect start?
- How long will it last?
- Will tolerance develop?
- What happens if my patient misses some doses?
- What are the chances that the initial dose will have to be altered?
- What do I follow to see if it needs to be altered?
- How do I alter it? Do I wait 1 week, 2 weeks, 3? Do I then suggest a big increment or a small one?

“It’s all immunotherapy these days…”

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- **PEMBROLIZUMAB**- Case Example I: Characterization of Post-progression Outcomes as a Function of Time on Treatment – **David Turner, Ph.D.**
- **DURVALUMAB**- Case Example II: Durvalumab in NSCLC and mUC – **Yanan Zheng, Ph.D.**
- **IPILIMUMAB**- Case Example III: Tumor Growth Dynamic-Overall Survival Modeling with Ipilimumab in Melanoma – **Amit Roy, Ph.D.**
- **ATEZOLIZUMAB**- Case Example IV: Applications of Tumor Growth Inhibition-Overall Survival Models to Support Atezolizumab Combination Studies – **René Bruno, Ph.D.**
- **AVELUMAB**- Case Example V: Using Modeling Approach to Inform the Decision at Early Drug Development Stage – **Jenny Zheng, Ph.D.**