

Transformation of Our Ability to Generate, Analyze, Integrate and Share Information Across Regulatory Science Applications

RUSS B ALTMAN, MD, PHD
STANFORD UNIVERSITY

October 20, 2015

<https://pharm.ucsf.edu/cersi>



Mission of UCSF-Stanford CERSI: Vision/Goal/Overall Charge

- To create a self-sustaining Center of Excellence in Regulatory Science and Innovation (CERSI) on the West Coast.
- To promote research and education in innovative regulatory sciences at UCSF and Stanford.
- To facilitate multi-sector interactions in regulatory sciences between scientists at the FDA and those in academic and industry.



The UCSF-Stanford CERSI Team



Kathy Giacomini, PhD
Co-Director



Russ Altman, MD, PhD
Co-Director



Terry Blaschke, MD
Educational Program Advisor



Natalia Khuri, PhD
Educational Program Director



Maria Friciello
Program Director



Lawrence Lin, PhD
Director, External Relations & Outreach



CERSI Education and Training



- Home
- My Channel
- Subscriptions
- History
- Watch Later 2

SUBSCRIPTIONS

Add channels

- Popular on YouTube
- Music
- Sports
- Gaming

- Browse channels
- Manage subscriptions

Stanford Videos **Playlists** Channels Discussion

UCSF-Stanford CERSI Lecture Series

by Stanford • 8 videos • 322 views • Last updated on Jul 2, 2015

Lectures from the UCSF-Stanford Center of Excellence in Regulatory Science and Innovation, a joint undertaking among UCSF, Stanford and the FDA

[▶ Play all](#) [◀ Share](#) [+ Save](#)

- Measurement Science in Stem Cell Research and Applications in Regenerative Medicine**
by Stanford
- Regulatory Challenges for Stem Cell-based Products**
by Stanford
- Introduction to Regulatory Science at the FDA**
by Stanford
- Evaluating a Biomarker for Pluripotency with Time Lapse Imaging**
by Stanford
- What Science Got to Do at the Regulatory Agency**
by Stanford
- Examples of Regulatory Science Research Projects**
by Stanford
- Unmet needs in regulatory science for generic drugs**
by Stanford



CERSI Scientific Research Projects:

Involving teams of FDA, UCSF and Stanford scientists focused on areas of research critical to the FDA

CERSI received 22 proposals from the FDA in areas of unmet needs



13 Total Collaborative Research Projects Funded:

- Improving Efficiency and Rigor of Pharmacovigilance at FDA (CDER & CBER)
- Improving the Diagnostic Accuracy of ADR Signal Detection (CDER)
- Renal Impairment in New Drug Development (CDER)
- Spinal Orthopedic Device Mechanics (CDRH)
- eSource Pathology Checklist (CDER)
- Safer Labeling of Pediatric Medications (Office of Minority Health)
- Regenerative Medicine/Product Characterization (CBER)
- Patient Reported Outcomes for Minimally Invasive Glaucoma (CDER)
- Two Supplements:
 - › Shoichet and Giacomini: Office of Generic Drugs: Are Excipients Inert?
 - › Altman (4): PrecisionFDA, FDA Knowledge Management, OpenFDA, FAERS Triage

CERSI Scientific Research Projects:

Involving teams of FDA, UCSF and Stanford scientists focused on areas of research critical to the FDA

CERSI received 22 proposals from the FDA in areas of unmet needs



13 Total Collaborative Research Projects Funded:

- Improving Efficiency and Rigor of Pharmacovigilance at FDA (CDER & CBER)
- Improving the Diagnostic Accuracy of ADR Signal Detection (CDER)
- Renal Impairment in New Drug Development (CDER)
- Spinal Orthopedic Device Mechanics (CDRH)
- eSource Pathology Checklist (CDER)
- Safer Labeling of Pediatric Medications (Office of Minority Health)
- Regenerative Medicine/Product Characterization (CBER)
- Patient Reported Outcomes for Minimally Invasive Glaucoma (CDER)
- Two Supplements:
 - › Shoichet and Giacomini: Office of Generic Drugs: Are Excipients Inert?
 - › Altman (4): PrecisionFDA, FDA Knowledge Management, OpenFDA, FAERS Triage

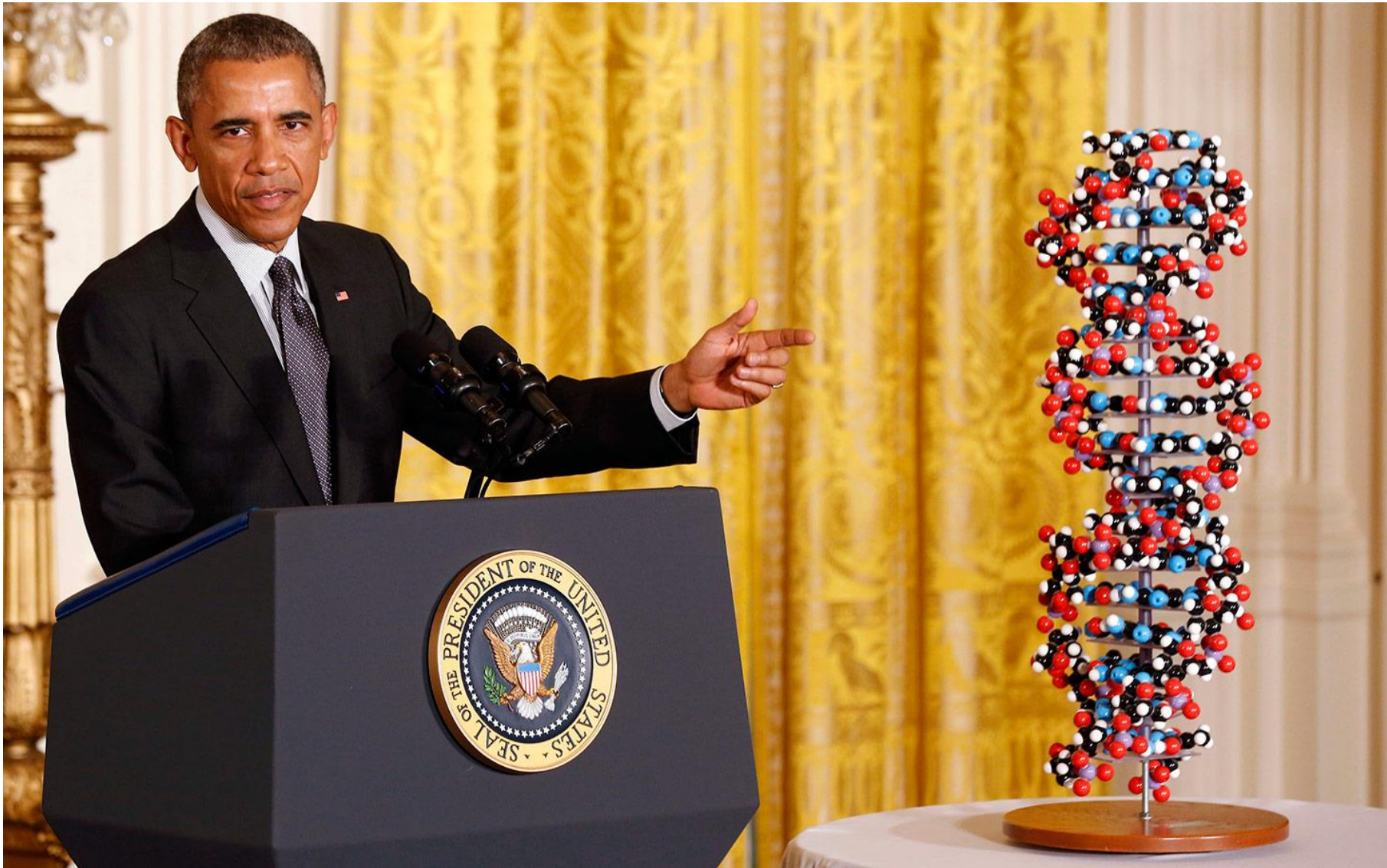
10 Key data science themes for regulatory science.

1. Bringing structure to unstructured (textual) data for computational analysis of the enterprise-wide effort (**knowledge management**)
2. Integrating information across Phase I, II, III and post-marketing surveillance sensitively to **detect efficacy and safety signals**.
3. Automated **triage and prioritization** of post-marketing adverse event reports
4. **Integration** of spontaneous report data with electronic medical record infrastructure (for hypothesis testing and/or validation)
5. Computational infrastructure and statistical **models for approval of “next generation” biomarkers**

10 Key data science themes for regulatory science.

6. Standards for **mobile health software quality** control
7. Validated **electronic infrastructure for clinical trials** and post-marketing data collection
8. Using **social media** to assess population trends in food/drug/diagnostic uses
9. **Systems pharmacology** & modeling for deep understanding of mechanism and efficacy/toxicity
10. Electronic infrastructure for **patient-recorded outcomes** and elicitation of patient preferences

Precision Medicine Initiative -> PrecisionFDA



A message about RFA-HG-12-016:

If you are submitting a proposal to RFA-HG-12-016 "[Clinically relevant genetic variants resource: a unified approach for identifying genetic variants for clinical use \(U01\)](#)" and looking for a letter of support from PharmGKB, please contact us at feedback@pharmgkb.org with the request and a short description of the institutions/people involved in the proposal. Thank you.





Search PharmGKB: **What is the PharmGKB?***Find out how we go from extraction of*[Clinical Annotations Update](#)[Zidovudine Pathway Publication](#)

http://www.pharmgkb.org/

[Primary Pharmacogenomic Literature](#)[CPIC: PGx Drug Dosing Guidelines](#)**Clinically-Relevant PGx**

- [Well-known PGx associations](#)
- [Clinically relevant PGx summaries](#)
- [PGx drug dosing guidelines](#)
- [Drug labels with PGx info](#)
- [Genetic tests for PGx](#)
- [Star \(*\) allele translations](#)

hint: enter a gene, drug, rsid, disease**PGx-Based Drug Dosing Guidelines**

- [SLCO1B1/simvastatin:](#)
[article](#)  and [supplement](#) 
- [HLA-B/abacavir:](#)
[article](#)  and [supplement](#) 
- [more guidelines...](#)

[CPIC Gene-Drug Pairs](#)[TPP Gene Tables](#)**CPIC: Implementing PGx**
a [PharmGKB](#) & PGRN collaboration**PGx Research**

- [VIP: Very Important PGx gene summaries](#)
- [PharmGKB pathways](#)
- [Annotated SNPs by gene](#)
- [Drugs with genetic information](#)

hint: enter a gene, rsid, drug, disease

Follow us on:





































Get your PGx fix:

Download
PharmGKB Data

PharmGKB is a partner of the

Pharmacogenomics
Research Network[Feedback](#)[Citing PharmGKB](#)[Acknowledgements](#)

Table S9. Variants associated with adverse drug response

Key: Father, Mother, Brother, Sister = 		Family members' genotypes as compared to other possible genotypes; not a population-based statistic				
Gene Symbol	SNP Location	Drug(s)	Drug(s) More Likely to Cause Side Effect	Drug(s) Less Likely to Cause Side Effect	No PGx Action/ Phenotype Unknown	Confidence Level
TPMT	rs1800460	purine analogues	.		.	High
HTR3B	rs1800497	antipsychotics		.	.	Medium
HTR2C	rs1414334	antipsychotics, clozapine, <u>risperidone</u>			.	Medium
ARVCF, COMT	rs9332377	<u>cisplatin</u>	.		.	Medium
FAM119A, CREB1	rs7569963	citalopram				Medium
ABCC2	rs17222723	doxorubicin			.	Medium
ABCB1	rs1045642	<u>efavirenz</u> , <u>nelfinavir</u>			.	Medium
CYP1A2	rs762551	<u>leflunomide</u>	.		.	Medium
PICK1, ENTHD1	rs2076369	methamphetamine	.			Medium
ADORA2A	rs2298383	methotrexate			.	Medium
ABCC1	rs246240	methotrexate		.	.	Medium
REN, ETNK2	rs2368564	<u>muraglitazar</u>			.	Medium
CHRNA4	rs2236196	nicotine			.	Medium
MTHFR	rs1801131	nitrous oxide	.		.	Medium
HTR2C	rs518147	olanzapine				Medium
EPHX1	rs1051740	phenytoin		.		Medium
EPHX1	rs1051740	phenytoin		.		Medium
EPHX1	rs2234922	phenytoin	.			Medium
<u>intergenic</u>	rs1695	platinum compounds		.	.	Medium

9/25/15 Next Generation Sequencing Forum



PrecisionFDA (Dr. Taha Kass-Hout, FDA CHIO)

- Collaboration of FDA, vendors, contractors, grantees
- Build a open-source cloud infrastructure for NGS regulatory science
- Focus on software to evaluate/characterize NGS
- Share genomes
- Share pipeline software for NGS annotation
- Share software for evaluation of pipelines
- “Beta” release 12/15/2015

NGS as example of “next gen” biomarkers

- Make many measurements for cost-effectiveness
- May discover uncharacterized variation in an individual
- “Full” validation difficult to imagine (3×10^9 measurements)
- Not always a specific “intended use” but more of a “screen”
- Each platform has different profile of strengths/errors
- Complex computational pipeline is a mandatory component of read out
- Human inspection is still required in current clinical applications

Proposed Roadmap for PrecisionFDA Informatics

1. Understand how to securely store/share human genomes for regulatory science.
2. Understand how to securely store/share computer software for NGS
3. Understand issues of creating gold standards: synthetic genomes or “injected” genomes
4. Understand how to represent error models for different NGS platforms—where do they succeed/fail? Can they be combined?
5. Understand how to evaluate a pipeline output against gold standard genome annotation—total performance vs. focused performance.
6. Understand how to use ethnically diverse and admixed genomes to validate dynamic range of annotation tools.
7. Understand tradeoffs of accuracy in context of intended use (cost-benefit)
8. Work with clinical genetics repositories to understand where to focus initial efforts and how to evolve focus over time.

Conclusion

- Exciting set of regulatory science challenges with data science and informatics components
- Enthusiasm for FDA collaboration with external partners (e.g. CERSI program) to tackle these challenges
- Need to provide basic regulatory science curriculum to data scientists

Thanks!

`russ.altman@stanford.edu`

<https://pharm.ucsf.edu/cersi>