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

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https://pharm.ucsf.edu/cersi

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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.

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The UCSF-Stanford CERSI Team

Kathy Giacomini, PhD
Co-Director

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Educational Program Director

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Program Director

Lawrence Lin, PhD
Director, External Relations & Outreach

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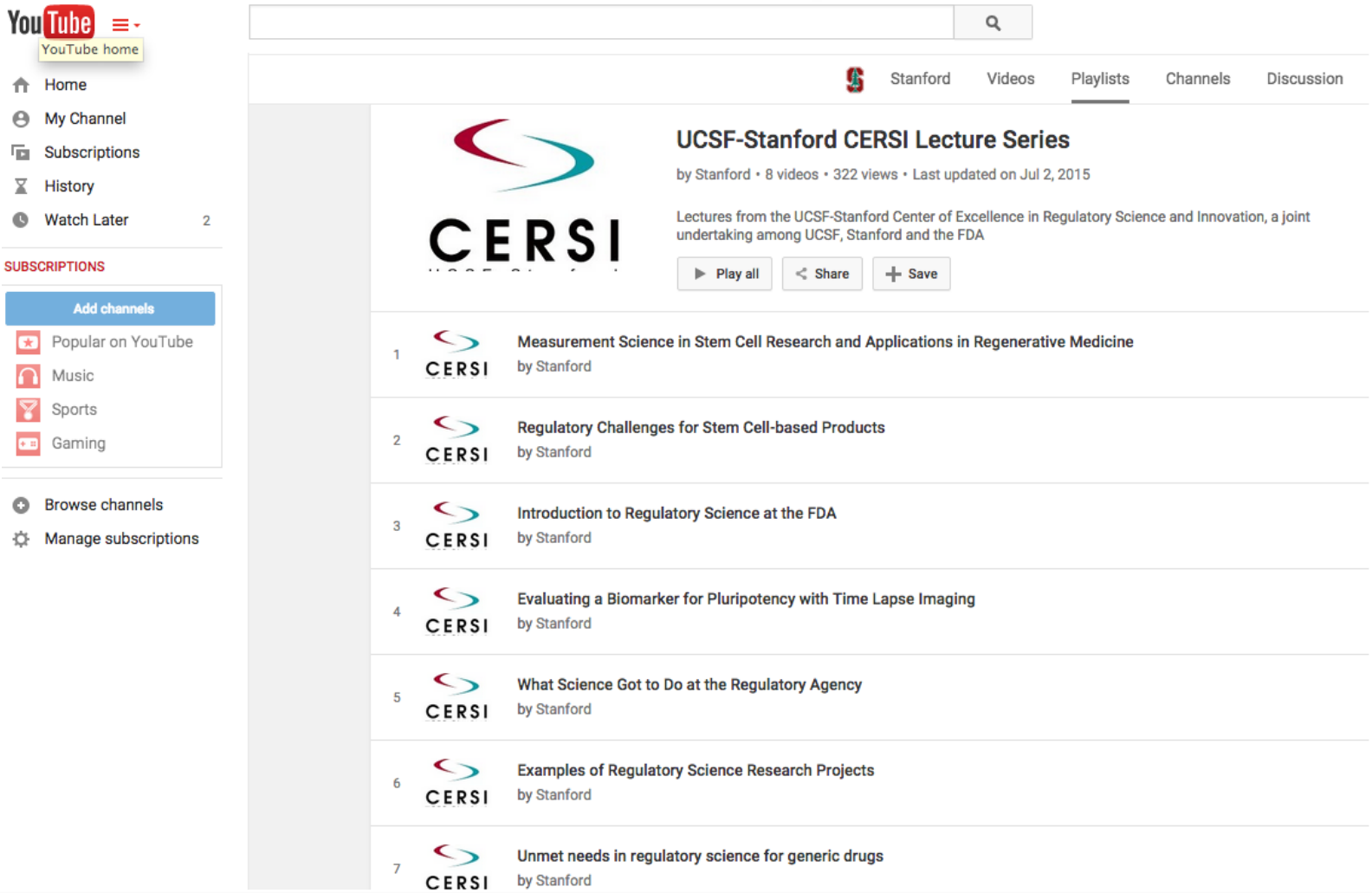
CERSI Education and Training



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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

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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 eletronic medical record infrastructure (for hypothesis testing and/or validation)
5. Computational infrastructure and statistical models for approval of “next generation” biomarkers

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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

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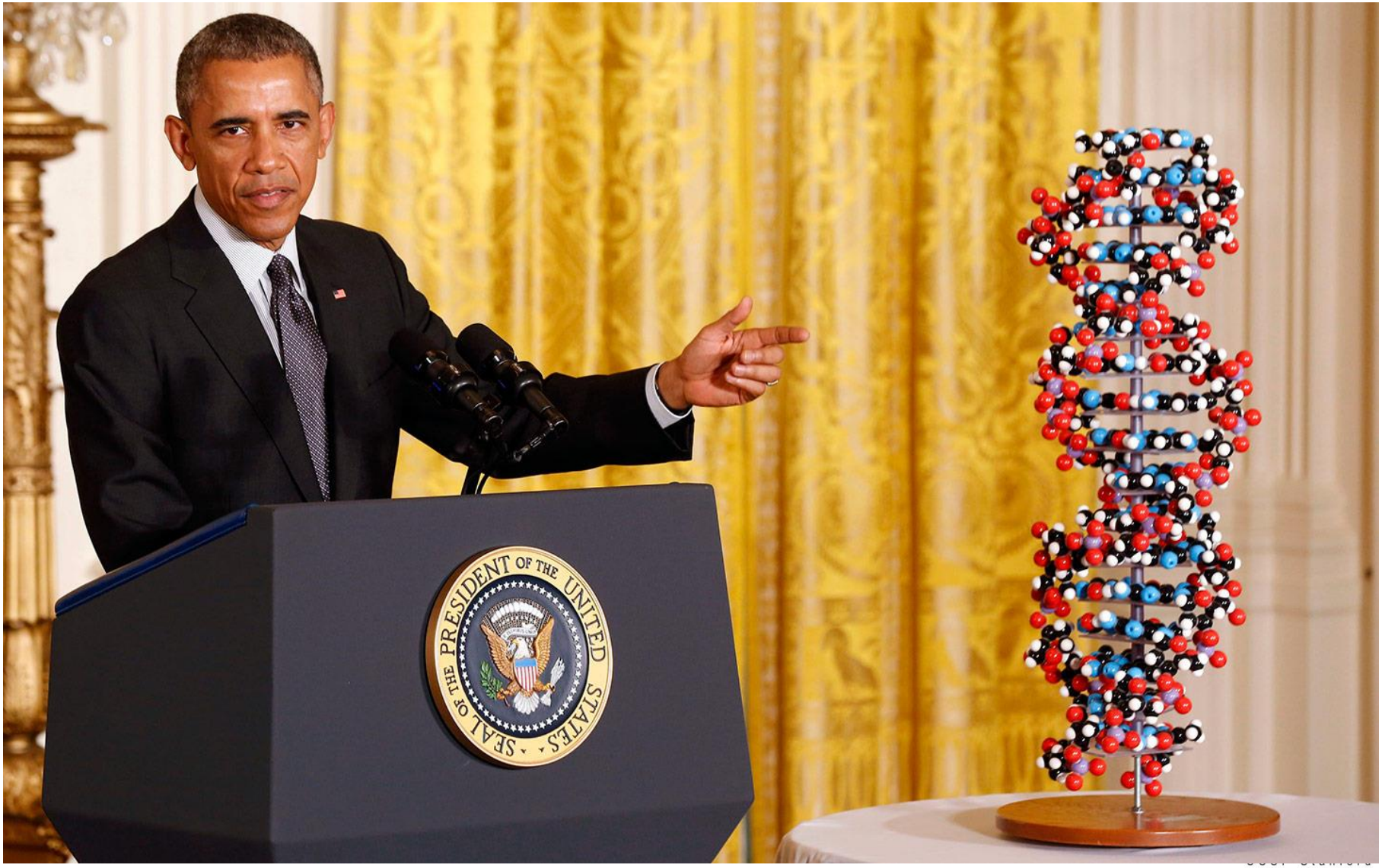
Precision Medicine Iniative -> PrecisionFDA



http://www.pharmgkb.org/

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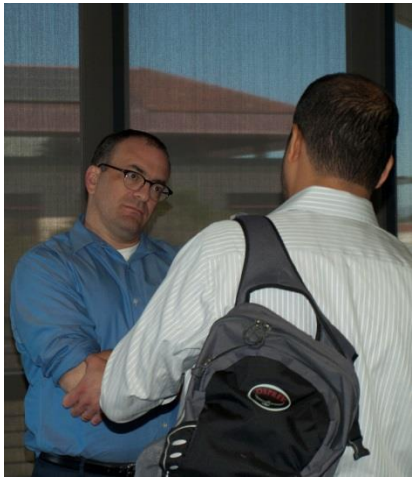
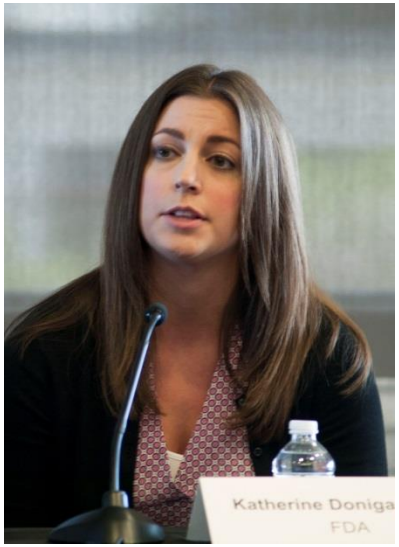
Table S9. Variants associated with adverse drug response

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, risperidone	■○	○■	·	Medium
ARVCF, COMT	rs9332377	cisplatin	·	■○■○	·	Medium
FAM119A, CREB1	rs7569963	citalopram	■	■	○○	Medium
ABCC2	rs17222723	doxorubicin	■■	○○	·	Medium
ABCB1	rs1045642	efavirenz, nelfinavir	■	■○○	·	Medium
CYP1A2	rs762551	leflunomide	·	■○■○	·	Medium
PICK1, ENTHD1	rs2076369	methamphetamine	·	○	■■○	Medium
ADORA2A	rs2298383	methotrexate	■○■	○	·	Medium
ABCC1	rs246240	methotrexate	■○■○	·	·	Medium
REN, ETNK2	rs2368564	muraglitazar	■	■○○	·	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
intergenic	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

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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 x 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

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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 the 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.

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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

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Thanks!

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