Disrupting Clinical Research: Transforming a System

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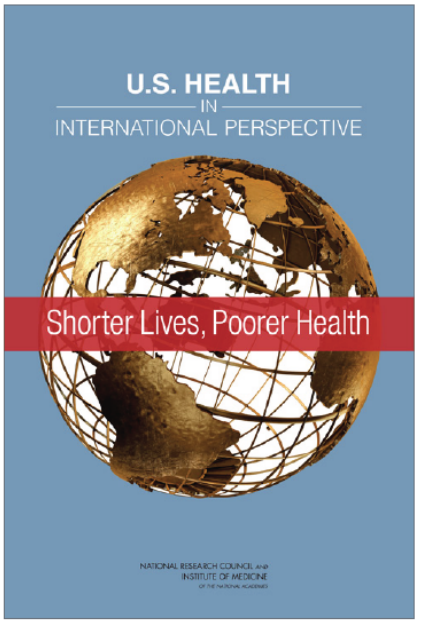
Conflicts

- All of my “industry relationships” can be found at www.dcri.org/about-us/conflict-of-interest/Califf-COI_2013
- I work as an official in an academic health and science system that depends on a margin from the current reimbursement system that rewards behaviors that may not be good for your health!

The Best of Times, the Worst of Times

Fundamental science unprecedentedly advanced, but:

- Poor transition of basic or clinical observations into interventions that tangibly improve human health
- Drug/device/diagnostic development system in crisis
- Clinical trials system in crisis
- Poor adoption of demonstrably useful interventions



People unhealthier and funders of biomedical research enterprise (public and private) impatient

PHARMACEUTICAL INDUSTRY

RECENT TRENDS AND CHALLENGES

+ $1.1 TRILLION BY 2014. WORLDWIDE PHARMACEUTICAL SALES ARE EXPECTED TO INCREASE AT A COMPOUND ANNUAL GROWTH RATE OF 5–8%. FUELING THESE GAINS ARE PROJECTED DOUBLE-DIGIT GROWTH RATES IN EMERGING ECONOMIES.

THE CHALLENGES

EXPIRING PATENTS

2011

↓ $142 billion

2015

AS PRODUCTS COME OFF PATENT PROTECTION, MANY LARGE FIRMS ARE AT RISK OF REVENUE REDUCTION OF UP TO 30–40%.

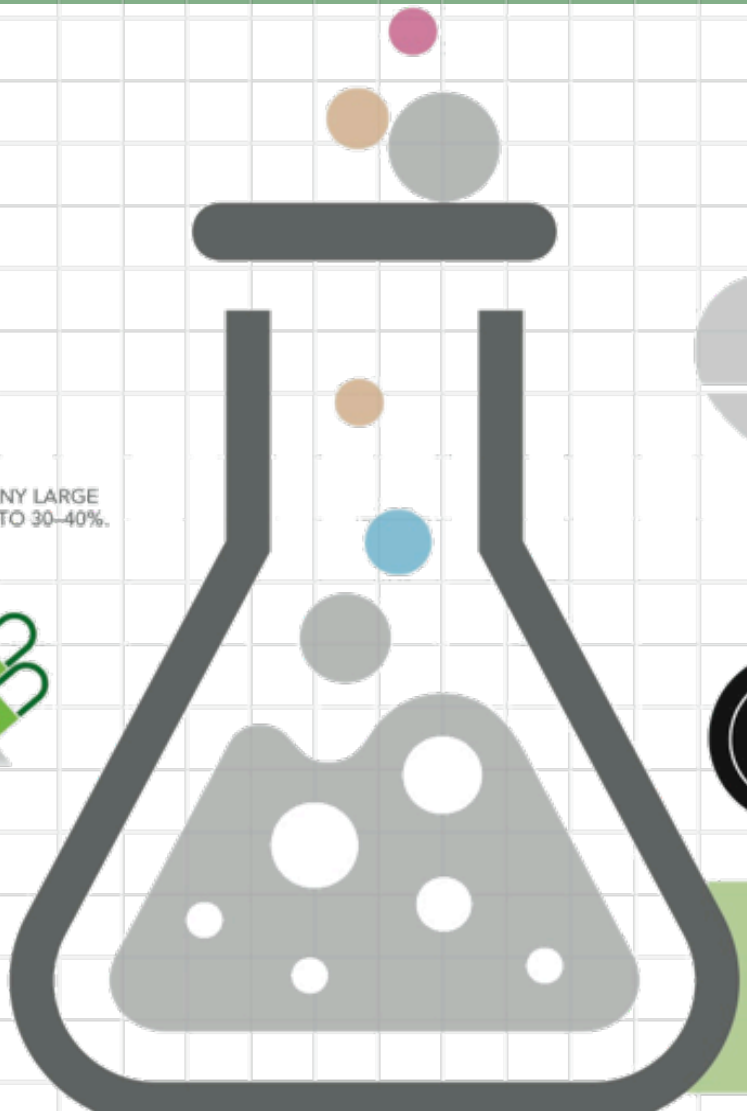
GROWTH OF GENERICS

THE US GENERICS MARKET IS ANTICIPATED TO GROW 10% ANNUALLY DURING 2010–2013, FUELED BY THE PRESSURE TO REDUCE COSTS IN HEALTHCARE, THE EXPIRATION OF PATENTS AND THE ESTABLISHMENT OF AN APPROVAL PATHWAY FOR BIOSIMILARS.

DRUG RECALLS

↑ 309% IN 2009

CONCERNS OVER SAFETY AND SUPPLY CHAIN QUALITY HAVE SURGED.



THE OPPORTUNITIES

HEALTHCARE REFORM

32 MILLION +

ADDITIONAL PEOPLE WILL HAVE HEALTH INSURANCE AND ACCESS TO PRESCRIPTION DRUGS UNDER THE NEW HEALTH PLAN.

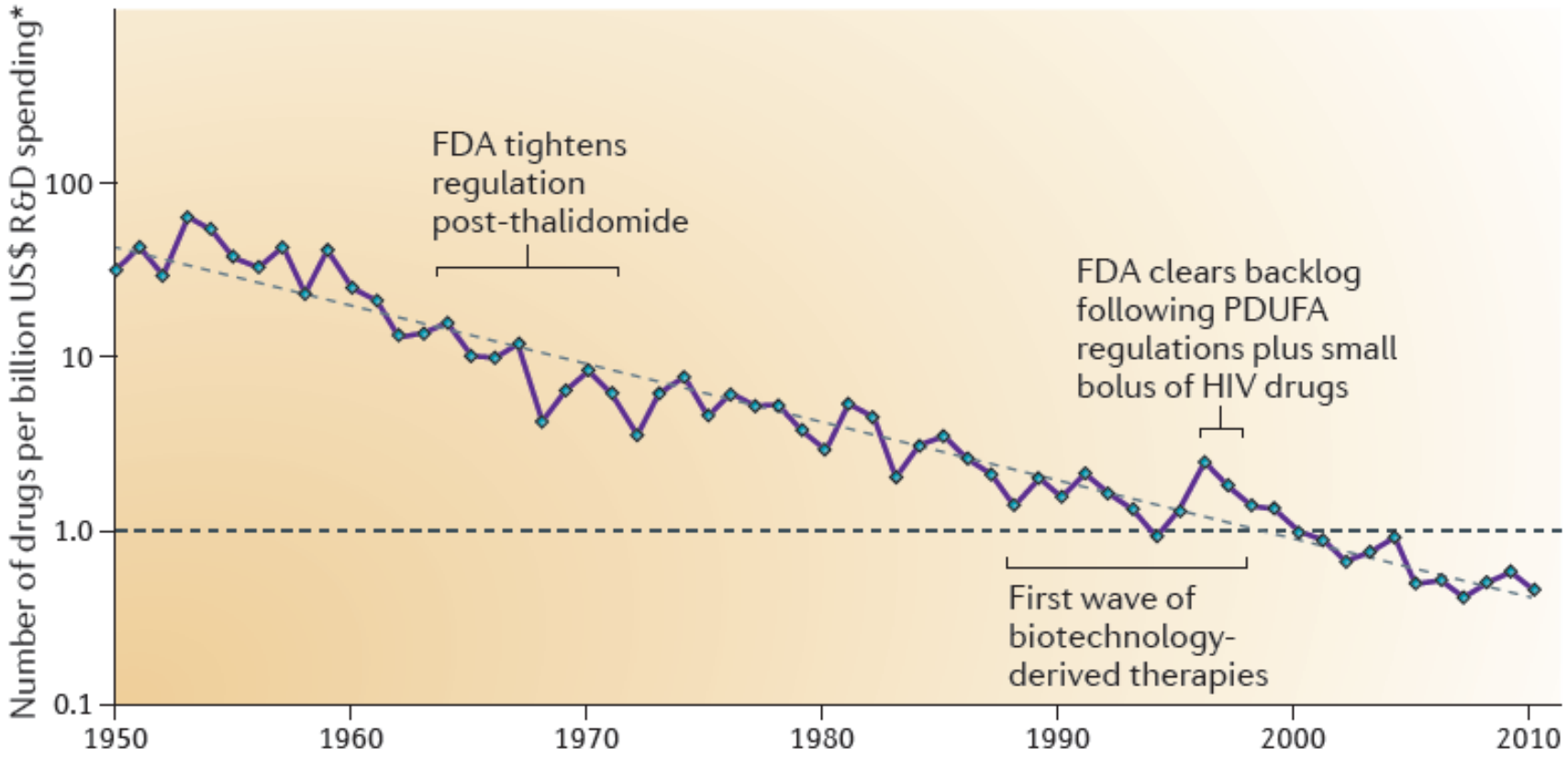
OUTSOURCING, COLLABORATIVE PARTNERSHIPS AND STRATEGIC ALLIANCES WITHIN THE INDUSTRY ARE FORGING NEW BUSINESS MODELS.

2x

THE 65+ SEGMENT OF THE POPULATION WILL NEARLY DOUBLE BETWEEN 2010 AND 2030. ON AVERAGE, THOSE OVER 65 YEARS OLD TAKE BETWEEN 5 TO 6 PRESCRIPTION MEDICINES.

Progressive pharmaceutical companies are realizing that in order to respond to these pressures and command a competitive position in the marketplace, they must take a new approach to their overall workforce strategy, finding new strategies for accessing and deploying critical talent where and when they need it.

Eroom's Law



The number of new drugs approved by the FDA per billion US dollars (inflation-adjusted) spent on research and development (R&D) has halved roughly every 9 years since 1950.

NIH National Center for Advancing Translational Sciences

Scannell et al., *Nature Reviews Drug Discovery* 11:191, 2012

Our national clinical research system is well-intentioned but flawed

- High percentage of decisions not supported by evidence*
- Health outcomes and disparities are not improving
- Current system is great **except**:
  - Too slow
  - Too expensive
  - Unreliable
  - Doesn't answer questions that matter most to patients
  - Unattractive to clinicians & administrators

We are not generating the evidence we need to support the healthcare decisions that patients and their doctors have to make every day.

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**Tricoci P et al. JAMA 2009;301:831-41.*

The Clinical Trials Transformation Initiative

- Public private partnership co-founded by Duke and FDA in late 2007
- All stakeholders involved
- Through a MOU with FDA, Duke convenes the initiative

Mission

To identify and promote practices that will increase the quality and efficiency of clinical trials

Vision

A high quality clinical trial system that is patient-centered and efficient, enabling reliable and timely access to evidence-based prevention and treatment options

CTTI Member Organizations

17 Academia
17 Patient Reps
12 Pharmaceutical
10 Government US
5 Biotech
4 Clinical Research Organization
4 Device/Diagnostics
4 Institutional Review Boards
4 Professional Societies
4 Other
3 Clinical Investigators
2 Professional Services

How does CTTI seek to effect change?

- Identify and eliminate activities in the conduct of trials that do not add value
- Understand incentives to maintain non-value-added activities
- Develop solutions that are mindful of the needs of patients and all sectors in the clinical research enterprise
- Maintain an open and respectful dialogue across sectors
- Involve all sectors in selection, conduct, and interpretation of projects

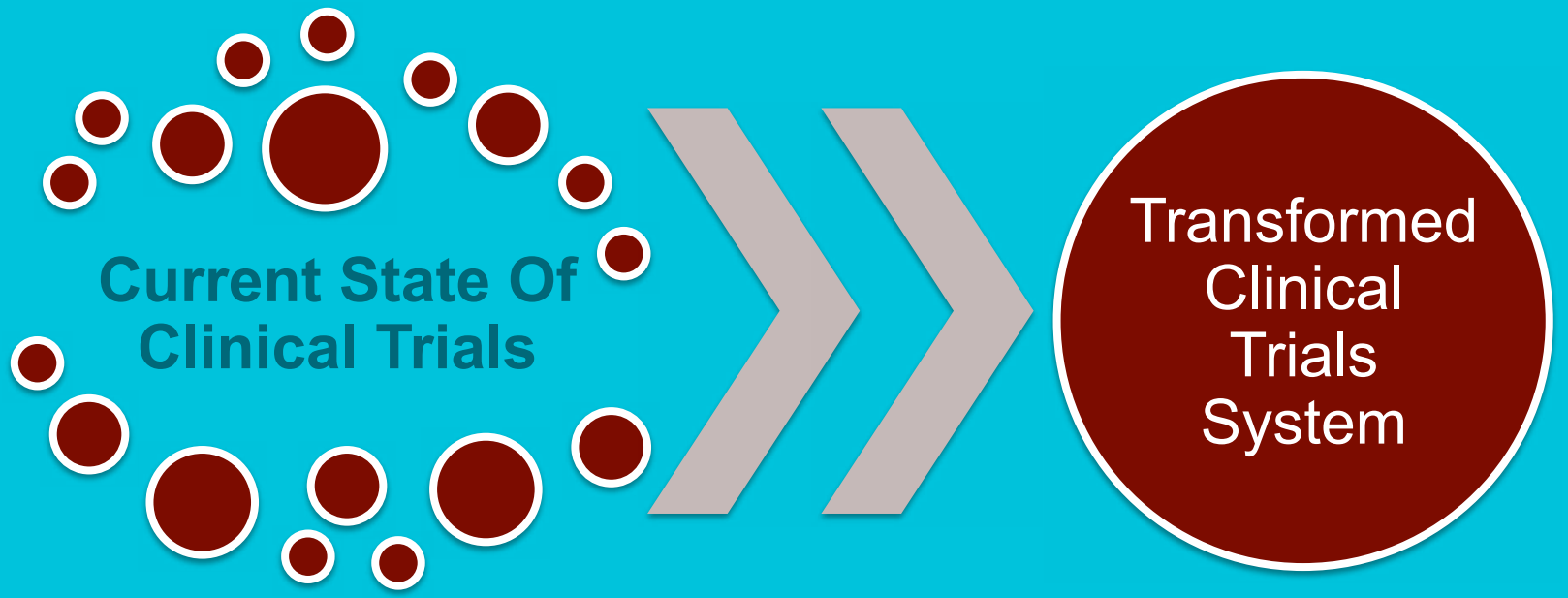
CTTI Strategy

1. Identify and shape potential **TRANSFORMATIONAL** changes to the system
2. Seek **INCREMENTAL** improvements to current system
3. Consider **PORTFOLIO** improvements of clinical trials being done relative to public health needs

Portfolio of CTTI Projects

	Investigational Plan	Study Start-Up	Study Conduct	Analysis & Dissemination
Completed	Long-Term Opioid Data Uses of Electronic Data	**Central IRB** Site Metrics	Adverse Event Reporting **IND Safety** Monitoring	
Ongoing	Antibacterial Drug Development Large Simple Trials Patient Groups & Clinical Trials Pregnancy Testing **QbD & QRM**	Central IRB Advancement GCP Training Informed Consent Recruitment & Retention	Safety Case Studies	State of Clinical Trials
2014	Trials based on registries		Site Quality and Performance	DMCs

CTTI Projects



A high quality clinical trial system that is patient-centered and efficient, enabling reliable and timely access to evidence-based prevention and treatment options

Every day, patients and doctors face questions for which evidence is lacking to guide answers

- "Does ibuprofen cause heart attacks or strokes? If so, how much does it increase my risk?"
- "For 'short cervix,' does bed rest prevent early labor?"
- "Should my daily blood pressure medicine be taken in the morning or at night?"
- "What should I do about the new guidelines for prescribing statins for people with high cholesterol, but no symptoms?"
- "How can I help my 87-year-old patient with multiple myeloma decide which chemotherapy option is best?"
- "My child has been diagnosed with ADHD. What are the benefits and risks of giving him medication?"

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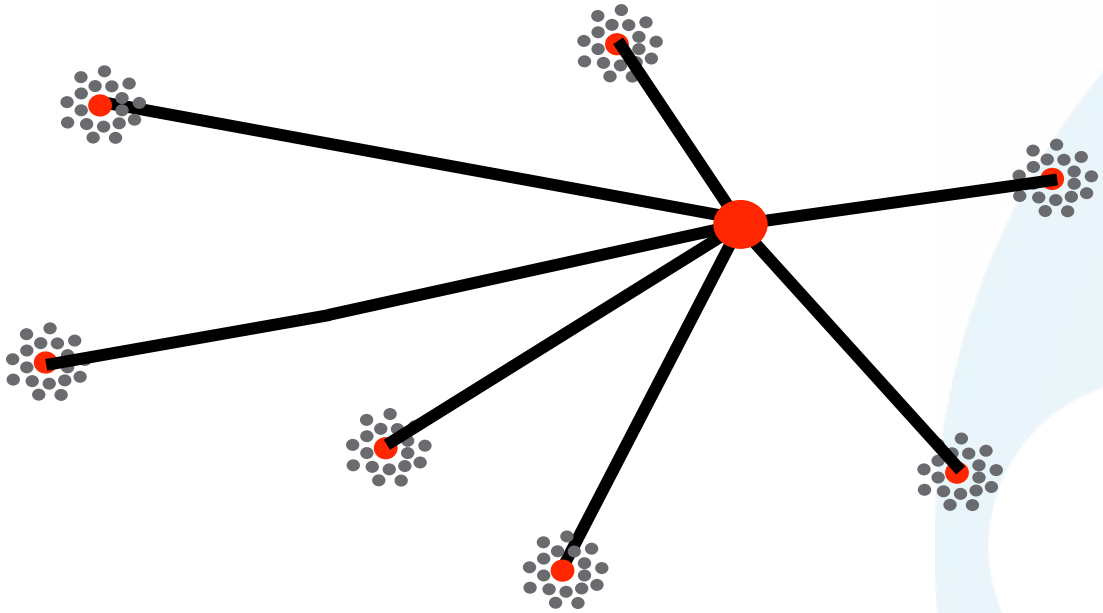
Historical model of clinical research: Many recruitment sites and a coordinating center



- Hub & spoke model
- Top-down decision-making
- Sites operate independently

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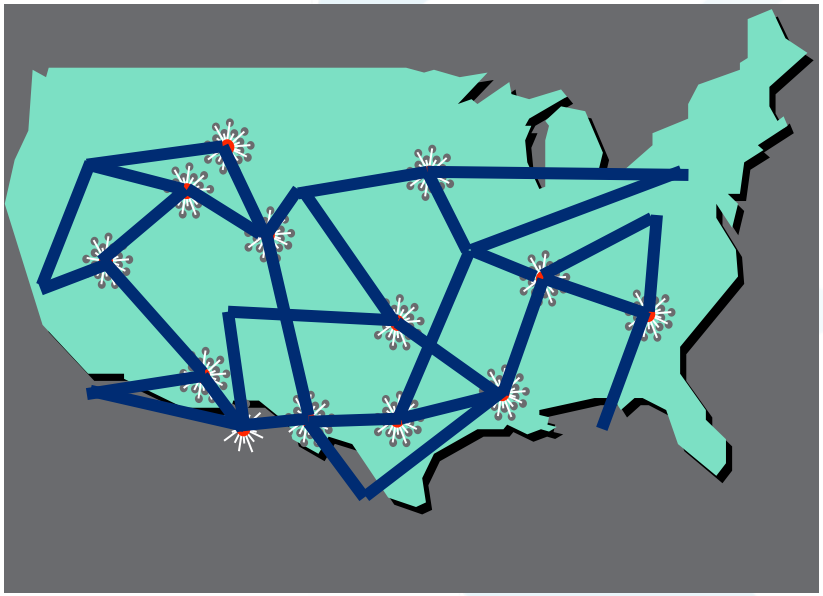
Both researchers and funders now recognize the value in integrating clinical research networks

- Linking existing networks means clinical research can be conducted more effectively
- Ensures that patients, providers, and scientists form true “communities of research”
- Creates “interoperability” – networks can share sites and data



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The missing link: An agile and efficient infrastructure to support rapid, reliable studies

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Health Care Systems Research Collaboratory

A Virtual Home for Knowledge about Pragmatic Clinical Trials using Health Systems: www.theresearchcollaboratory.org

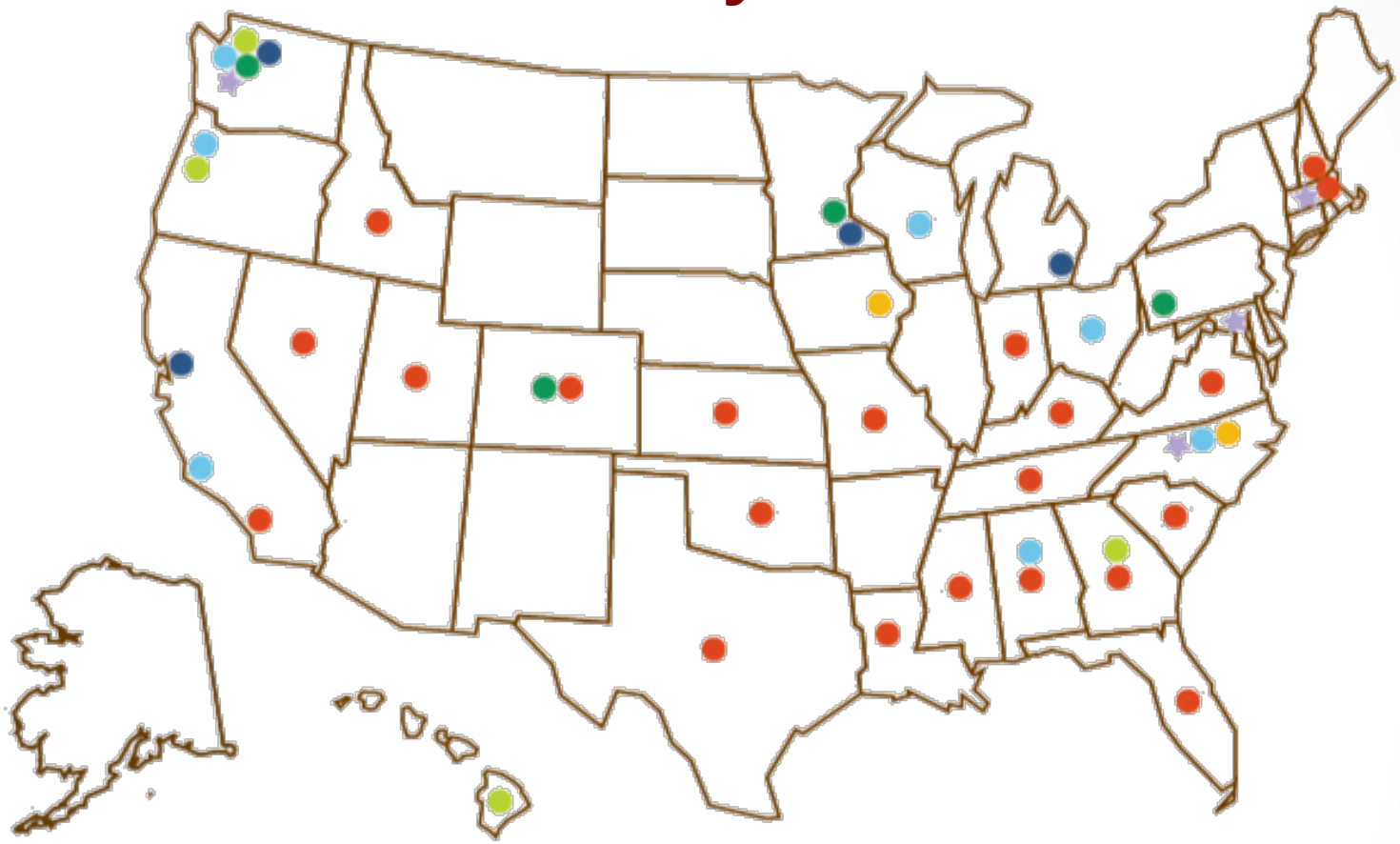
The Collaboratory

Health Care Systems Research Collaboratory

1. Pragmatic trial design
2. Electronic health record as core data collection instrument
3. At least 2 integrated health systems collaborating to answer the question

* Over 80 applications—7 funded to go forward with planning phase

NIH Health Care System Collaboratory



- Collaboratory Coordinating Center
- Nighttime Dose of Anti-Hypertensive Medications
- Prevent Suicide Attempt
- Reduce Mortality in End Stage Renal Disease (sites to be selected from units across all 50 states)
- Stop Colon Cancer in Priority Populations
- Chronic Pain in Primary Care
- Reduce Infections and Readmissions
- Lumbar Image Reporting and Epidemiology

Additional sites to be determined

The Collaboratory

PRAGMATIC TRIALS IN HEMODIALYSIS

Demonstration Project:
The Time to Reduce Mortality in Endstage Renal Disease (TiME) Trial

Principal Investigator:

Laura M. Dember, MD

University of Pennsylvania

NIH HCS Collaboratory

Penn

NIDDK

TiME Trial Design

- ***Hypothesis:***
  - extending dialysis sessions improves health outcomes
- ***Interventions:***
  - extended dialysis sessions vs usual care
- ***Cluster Randomization:***
  - by dialysis facility
- ***Eligibility:***
  - all patients starting chronic hemodialysis
- ***Outcomes:***
  - mortality, hospitalizations, HRQoL

TiME

Introducing PCORnet:
The National Patient-Centered Clinical Research Network

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The National Patient-Centered Clinical Research Network

PCORnet's goal

PCORnet seeks to improve the nation's capacity to conduct clinical research by creating a large, highly representative, national patient-centered network that supports more efficient clinical trials and observational studies.

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PCORnet's vision

PCORnet will support widespread capability for the US healthcare system to learn from research, meaning that large-scale research can be conducted with greater speed and accuracy within real-world care delivery systems.

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Overall objectives of PCORnet: achieving a single functional research network

- **Create** a secure national research resource that will enable teams of health researchers, patients, and their partners to work together on researching questions of shared interest
- **Utilize** multiple rich data sources to support research, such as electronic health records, insurance claims data, and data reported directly by patients
- **Engage** patients, clinicians & health system leaders throughout the research cycle from idea generation to implementation
- **Support** observational and interventional research studies that compare how well different treatment options work for different people
- **Enable** external partners to collaborate with PCORI-funded networks
- **Sustain** PCORnet resources for a range of research activities supported by PCORI and other sponsors

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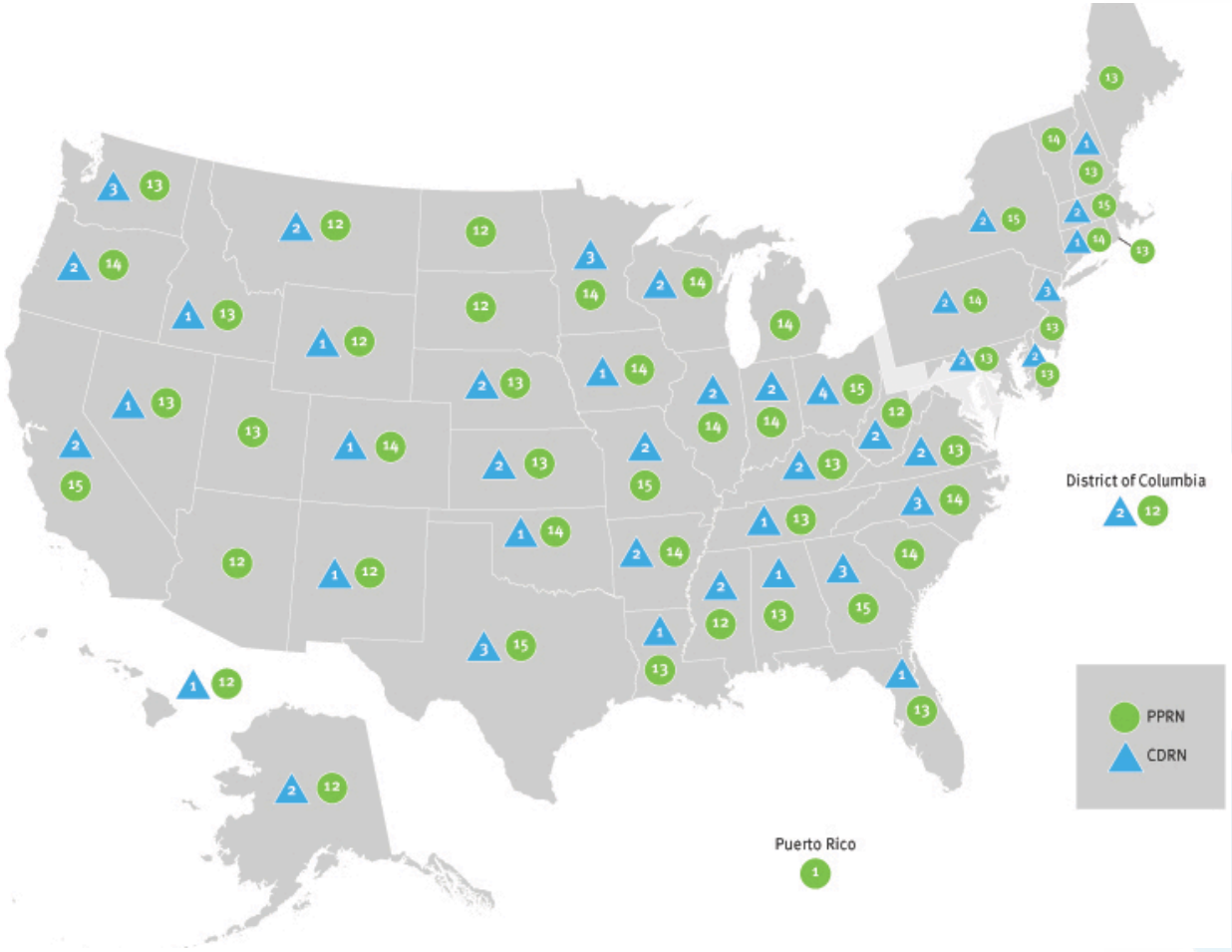
29 CDRN and PPRN awards were approved on December 17th by PCORI's Board of Governors



This map depicts the number of PCORI-funded Patient-Powered or Clinical Data Research Networks that have coverage in each state.

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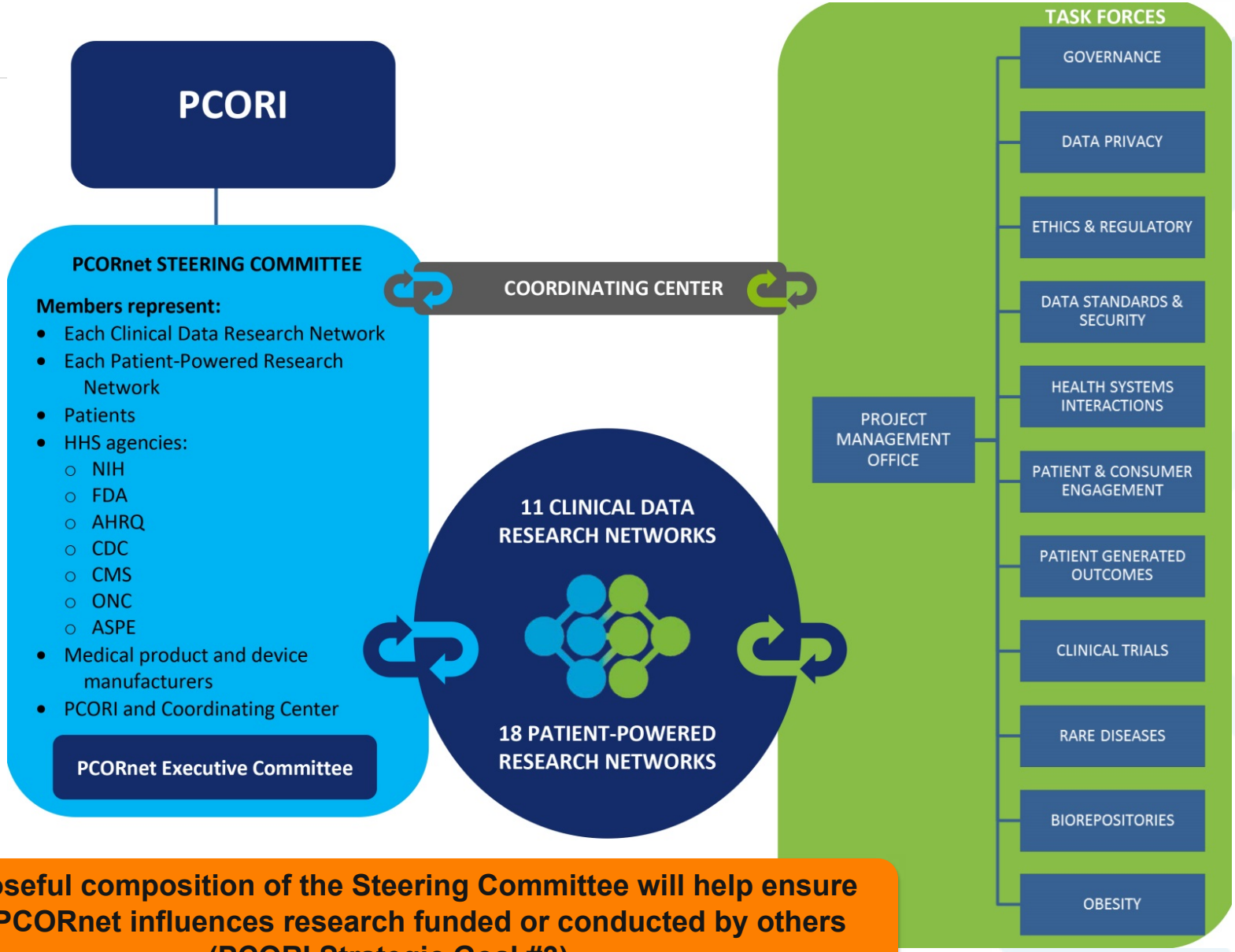
PCORnet organizational structure



Purposeful composition of the Steering Committee will help ensure that PCORnet influences research funded or conducted by others (PCORI Strategic Goal #3)

Goals for each Clinical Data Research Network (CDRN)

- Create a research-ready dataset of at least 1 million patients that is:
  - **Secure** and does not identify individual patients
  - **Comprehensive,** using data from EHRs to describe patients' care experience over time and in different care settings
- Involve patients, clinicians, and health system leaders in all aspects of creating and running the network
- Develop the ability to run a clinical trial in the participating systems that fits seamlessly into healthcare operations
- Identify at least 3 cohorts of patients who have a condition in common, and who can be characterized and surveyed

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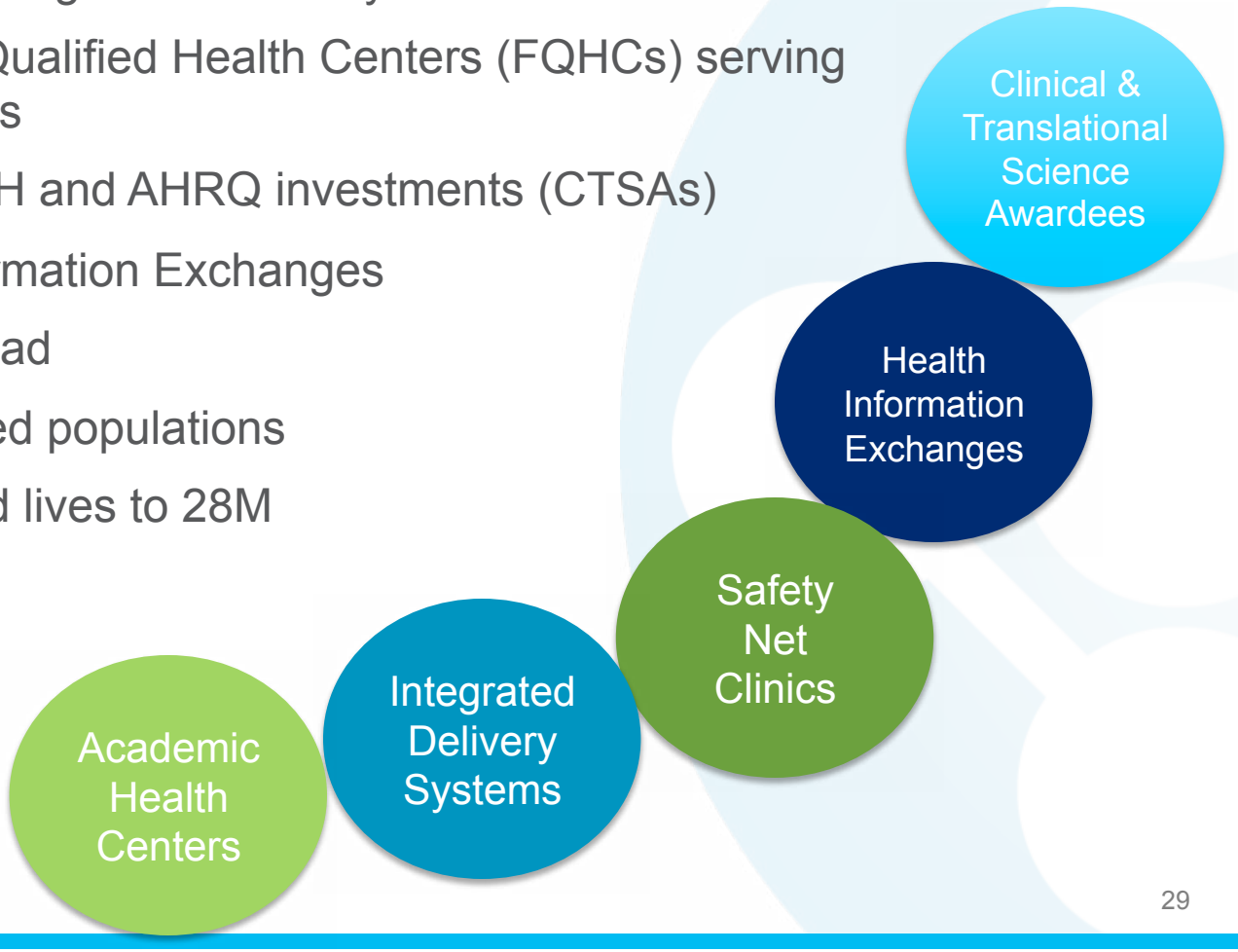
CDRN highlights

- Networks of academic health centers, hospitals & clinical practices
- Networks of non-profit integrated health systems
- Networks of Federally Qualified Health Centers (FQHCs) serving low-income communities
- Networks leveraging NIH and AHRQ investments (CTSAs)
- Inclusion of Health Information Exchanges
- Wide geographical spread
- Inclusion of under-served populations
- Range from 1M covered lives to 28M



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CDRNs organizations and leadership

CDRN Name	Lead Organization	Principal Investigator
ADVANCE	Oregon Community Health Information Network	Jennifer DeVoe
CAPriCORN	The Chicago Community Trust	Terry Mazany
Greater Plains Collaborative	University of Kansas Medical Center	Russ Waitman
Louisiana Clinical Data Research Network	Louisiana Public Health Institute	Thomas Carton
Mid-South CDRN	Vanderbilt University	Russell Rothman
NYC-CDRN	Weill Medical College of Cornell University	Rainu Kaushal
PEDSNet	The Children's Hospital of Philadelphia	Christopher Forrest
PORTAL	Kaiser Foundation Research Institute	Elizabeth McGlynn
pSCANNER	University of California, San Diego	Lucila Ohno-Machado
PaTH	University of Pittsburgh	Rachel Hess
SCIHLS	Harvard University	Kenneth Mandl

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CDRNs: disease cohorts

Organization	Common Cohort	Rare Cohort
ADVANCE	Diabetes	HIV & hepatitis C virus co-infection
CAPriCORN	Anemia; asthma	Sickle cell disease; recurrent *C. difficile* colitis
Great Plains Collaborative	Breast cancer	Amyotrophic lateral sclerosis
Louisiana Clinical Data Research Network	Diabetes	Sickle cell disease; rare cancers
NYC-CDRN	Diabetes	Cystic fibrosis
Mid-South CDRN	Coronary heart disease	Sickle cell disease
PEDSNet	Inflammatory bowel disease	Hypoplastic left heart syndrome
PORTAL	Colorectal cancer	Severe congenital heart disease
pSCANNER	Congestive heart failure	Kawasaki disease
P2ATH	Atrial fibrillation	Idiopathic pulmonary fibrosis
SCIHLS	Osteoarthritis	Pulmonary arterial hypertension

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Goals for each Patient-Powered Research Network (PPRN)

- Establish an activated patient population with a condition of interest (Size >50 patients for rare diseases; >50,000 for common conditions)
- Collect patient-reported data for ≥80% of patients in the network
- Involve patients in network governance
- Create standardized database suitable for sharing with other network members that can be used to respond to “queries” (ideas for possible research studies)

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PPRN highlights

- Participating organizations and leadership teams include patients, advocacy groups, clinicians, academic centers, practice-based research networks
- Strong understanding of patient engagement
- Significant range of conditions and diseases
- Variety in populations represented (including pediatrics; under-served populations)
- 50% are focused on rare diseases
- Varying capabilities with respect to developing research data
- Several PPRNs have capacity to work with biospecimens

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PPRNs represent a number of conditions…

Organization	Principal Investigator	Condition	Population Size
Accelerated Cure Project for Multiple Sclerosis	Robert McBurney	Multiple sclerosis	20,000
American Sleep Apnea Association	Susan Redline	Sleep apnea	50,000
Cincinnati Children's Hospital Medical Center	Peter Margolis	Pediatric Crohn's disease and ulcerative colitis	15,000
COPD Foundation	Richard Mularski	Chronic obstructive pulmonary disease	50,000
Crohn's and Colitis Foundation of America	R. Balfour Sartor	Inflammatory bowel disease (Crohn's disease and ulcerative colitis)	30,000
Global Healthy Living Foundation	Seth Ginsberg	Arthritis (rheumatoid arthritis; spondyloarthritis), musculoskeletal disorders (osteoporosis), and inflammatory conditions (psoriasis)	50,000
Massachusetts General Hospital	Andrew Nierenberg	Major depressive disorder and bipolar disorder	50,000
University of California, San Francisco	Mark Pletcher	Cardiovascular health	100,000
University of South Florida	Rebecca Sutphen	Hereditary breast & ovarian cancer	17,000

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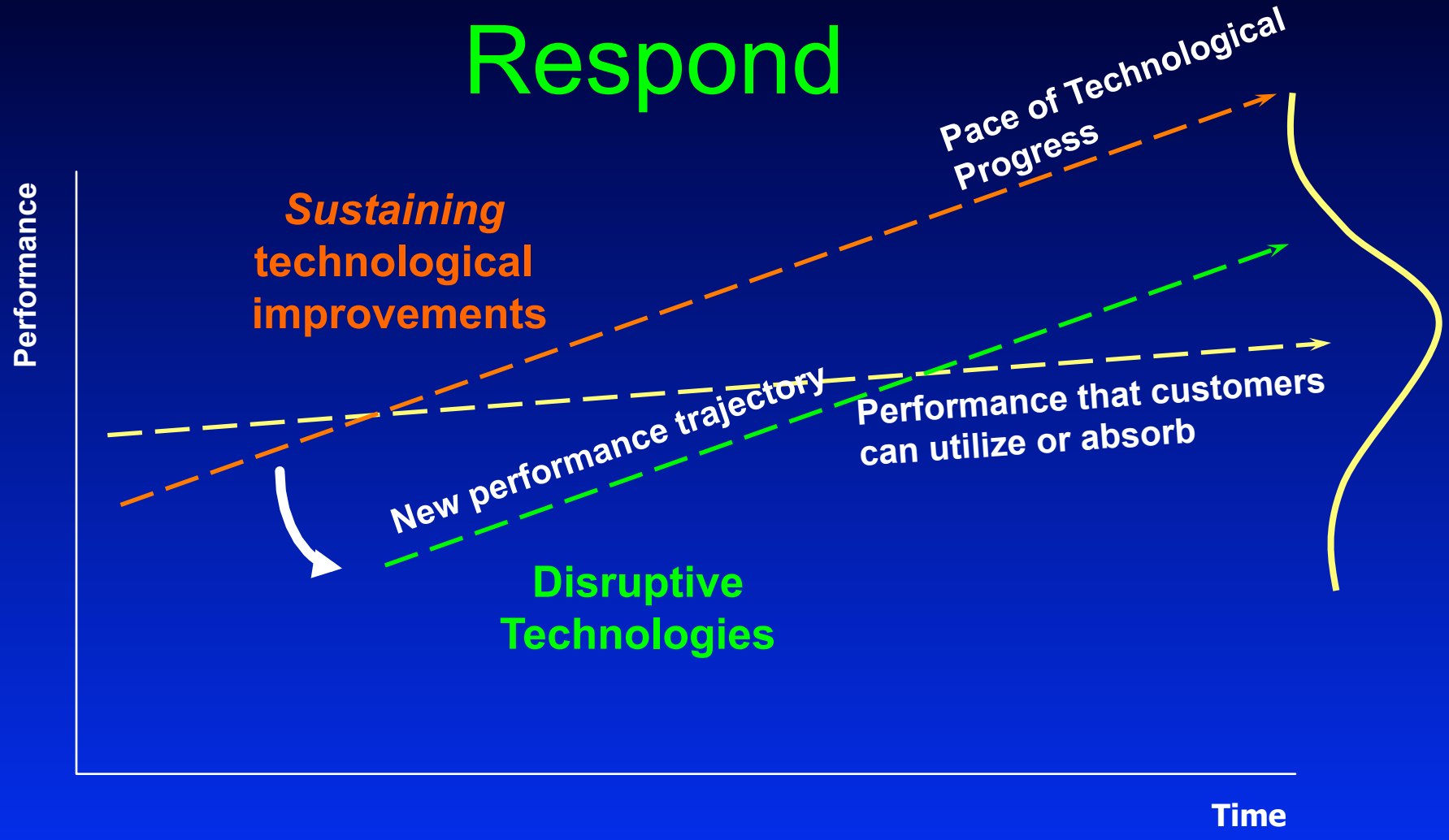
….including rare diseases

Organization	Principal Investgator	Condition	Population Size
ALD Connect, Inc	Florian Eichler	Adrenoleukodystrophy	3,000
Arbor Research Collaborative for Health	Bruce Robinson	Primary nephrotic syndrome; focal segmental glomerulosclerosis; minimal change disease; and membranous nephropathy multiple sclerosis	1,250
Duke University	Laura Schanberg	Juvenile rheumatic disease	9,000
Epilepsy Foundation	Janice Beulow	Aicardi syndrome; Lennox-Gastaut syndrome; Phelan-McDermid syndrome; hypothalamic hamartoma; Dravet syndrome, tuberous sclerosis	1,500
Genetic Alliance, Inc	Sharon Terry	Alström syndrome; dyskeratosis congenital; Gaucher disease; hepatitis; inflammatory breast cancer; Joubert syndrome; Klinefelter syndrome & associated conditions; psoriasis; metachromatic leukodystrophy; pseudoxanthoma elasticum	50- 50,000
Immune Deficiency Foundation	Kathleen Sullivan	Primary immunodeficiency diseases	1,250
Parent Project Muscular Dystrophy	Holly Peay	Duchenne and Becker muscular dystrophy	4,000
Phelan-McDermid Syndrome Foundation	Megan O'Boyle	Phelan-McDermid syndrome	737
University of Pennsylvania	Peter Merkel	Vasculitis	500

Innovation: How Markets Respond



Adapted from: The Innovator's Dilemma, Clayton M. Christensen, 2000.

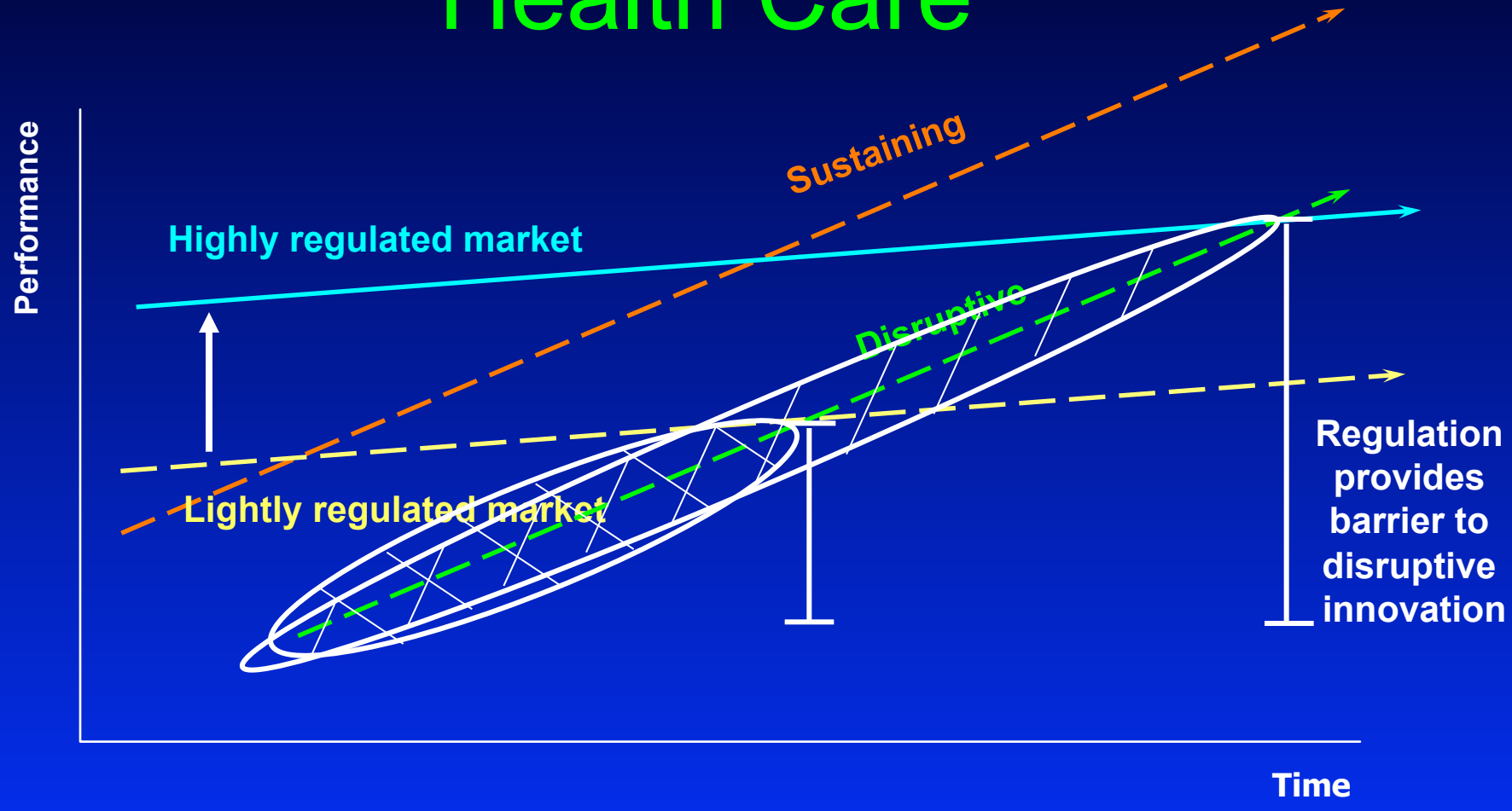
Innovation: How Markets Respond

"…as a rule the new does not grow out of the old but appears alongside of it and eliminates it competitively..."

-Joseph A. Schumpter, *The Theory of Economic Development* (1911)

- In most markets, technology & organizational innovation drive cost and quality improvement

Disruptive Innovation in Health Care



Source: Curtis LH and Schulman KA. Law and Contemporary Problems. Autumn 2006

Re-engineering the Clinical Research Enterprise

Increasing Level of Difficulty

Plan and start a few demonstration networks Simplify complex regulatory systems – demonstration projects Plan for networks in place for all institutes	Funding mechanism to sustain national system through consensus of all constituents ("1% solution") Simplified regulatory system in place for networks	**National Clinical Research System** creates effectiveness data that moves rapidly into the community AND data on outcomes and quality of care; sustained efficient infrastructure to rapidly initiate large clinical trials; scientific information for patients, families, advocacy groups
Establish repositories of biological specimens and standards for collection Standardize nomenclature, data standards, core data, forms for most major diseases Start a library of these elements shared between institutes and NLM Develop efficient network administration infrastructure at NIH Develop standards for capturing images for research	Data standards shared across NIH institutes Funding mechanisms evaluated to determine which are most efficient	ONE medical nomenclature with national data standards (agreed to by NIH, CMS, FDA, DOD, CDC) Data standards updated 'in real time' through networks National repository of images and samples Critical national "problem list" Most efficient network funding mechanisms in place across NIH
Create NIH standards to provide "safe haven" for clinical research Inventory and evaluate existing public-private partnerships, networks, CR institutions, and regulatory systems Establish FORUM(S) of <u>all</u> stakeholders Establish standards for and pilot creation of a National Clinical Research Corps Demonstration/planning grants to enhance/evaluate/develop model networks	NIH standards for safe haven in place Regulations and ethics harmonized with FDA, CMS Public private partnership mechanisms in place 100,000 members of certified "Clinical Research Corps" Standards shared across NIH	Participation in research is a professional standard (taught in all health professions schools) Study, evaluation and training regarding clinical research a part of every medical school, nursing school, pharmacy school Clinical research practices documented and updated regularly to maintain safe haven Networks provide detailed training about network specific issues

1-3 years 4-7 years 8-10 years

Time