

# Summary of the Big Think

## Strategic Planning for the Common Fund

Division of Program Coordination, Planning, and Strategic Initiatives/Office of Strategic Coordination

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A distinguished panel of experts gathered at the NIH to provide input about the most pressing issues facing health research today, and to provide ideas about how the NIH might use the Common Fund to address these issues. The conversation was structured around three of the NIH Director's five priorities for the NIH (High Throughput Technologies, Translation, and Science of Health Care Reform), since the other two priority areas (Global Health and Invigorating the Research Enterprise), have been the subjects of other expert panel meetings. This synopsis provides summaries of Breakout Sessions addressing each of the three priority areas as well as the Closing Session in which each topic, as well as overarching needs, were discussed.

A general theme formed around the need to define and refine disease phenotypes. This will require extracting the widest array of information possible from patient samples, to include genomic data from many people (including rare disease variants), epigenomic, metabolomic (including lipidomic), and imaging data, and developing technologies to manage/mine these complex datasets and make them interoperable. Another cross-cutting theme was single cell analyses.

Other cross-cutting themes that emerged included the need to develop methods for single cell analyses, the need for resource development, new therapeutic approaches, new research models, new models of career development, and global health issues. The ideas for these topics are summarized below.

### **DEFINING AND REFINING DISEASE PHENOTYPES**

#### **Broadening access to whole genome sequence data:**

- Genomic sequence data should be collected from a large set of individuals that have agreed to share their electronic medical records along with permission to re-contact for follow-up studies on patients with genotypes of interest.
- Making the most use of each sample by collecting additional types of data e.g. lipidomic, proteomic, expression analyses, etc. was discussed as was the challenge of different assays potentially requiring different sample collection methodologies.
- Other impediments included knowledge management of complex datasets to integrate different types of data, the non-interoperability of databases, and the need for technology development, which outside of incremental advances, was considered to not fare well in peer review.

#### **Apply HTP technologies to biosignature discovery and validation:**

- Develop a comprehensive way of measuring and validating quantitative biosignatures that reflect disease states and that can be used to develop diagnostics that are likely to be nano-tech based point-of-care systems.
- Genomic and proteomic data would be collected from bodily fluids, but other data such as imaging, was also discussed.

#### **Metabolomics for clinical medicine:**

- Discussed the impact that the identification and quantification of multiple metabolic biomarkers could have on health with a focus on the thousands of lipid species that change with disease.

Right now, cholesterol, LDL and HDL are included as standard readouts in a blood test but this provides limited information on health status.

- Plasma samples from thousands of individuals would be collected along with appropriate clinical information and the lipid profiles would be correlated with disease types.
- Lipid analyses need to be consolidated in to 1 mass spectrometry run instead of utilizing several extraction systems for different species of lipids. Technology development is needed for this and data needs to be integrated with genomic and proteomic data.

#### **Metabolic profiling of a broad array of tissues in a variety of disease states:**

- Intermediate metabolites modify proteins and their role in biological processes e.g. epigenetic chromatin remodeling and disease should be explored.
- Multiple metabolites need to be profiled simultaneously using rigorous standards for different disease states.
- Mass spectrometric analyses will need to be refined and standards developed.

#### **RESOURCE DEVELOPMENT**

##### **Renewable antibody reagents for entire human proteome:**

- The idea was to use *E.coli* to generate renewable, well-validated affinity reagents that cover the entire human proteome.
- Envisioned to occur in a “factory” that would make affinity reagents to order perhaps through a public-private partnership.
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- Intellectual property was raised as a critical issue that would need to be resolved should a company do this, such that common goods (reagents) could be produced while retaining the ability to make commercial-izable derivatives.

##### **Functionalizing genetic variation:**

- It’s much easier to identify genetic variation at a given gene locus than it is to functionally characterize the effects of the variation on disease.
- Accelerate the discovery of genetic variation-disease associations by constructing a comprehensive allelic series for selected human ORFs followed by functional characterization of each protein was proposed. Construction of this series entails overcoming technological hurdles.

- Discussion centered on the challenge of developing generic assays for characterizing the function of different proteins or regulatory variants. How to do this in a high throughput manner? What's the readout? The only types of generic assays are those for measuring post-translational modifications or metabolites, but this does not get at actual protein function as a function of genetic variation. Was some discussion about a library of human cells with every gene knocked-out.

#### **Adaptive informatics for rich biological data:**

- Create a flexible information processing system that would gather lots of different types of "rich" biological data e.g. from multi-PI projects that can be characterized and grouped through machine learning processes and made available to investigators at large.
- Right now, genomics data is readily available for example, but other types of data such as imaging and biochemical data are not widely disseminated in a format that can be incorporated in to cumulative data sets.
- A lot of discussion centered on the difficulty of hardening any software created.

#### **NEW THERAPEUTIC APPROACHES**

Targeting treatment resistant cells within cancer as a separate population:

- Current success in cancer treatment is measured by how many tumor cells are killed by chemotherapy/radiation therapy but these therapies are toxic to normal, dividing cells.
- An argument was made that this was the wrong approach and that the 1% of cells that are resistant to treatment should be the target of new therapies.
- First these cells need to be defined genetically and metabolically and then they should be made to differentiate as a true stem cell within a tissue would, which would preserve normal cells.

#### **HTP functional screening:**

- Should develop a high throughput system that can rapidly assess changes in pre-synaptic neurotransmitter release as opposed to post-synaptic since many human disease and disorders involve changes in pre-synaptic function.
- This would allow for rapid screening of drugs; treatment of alcoholism was given as an example.

#### **Personalized disease prevention- an environmental health viewpoint:**

- There is an environmental component to most diseases. Genetic make-up cannot be changed but environment can be altered.

- Idea was to assess personalized responses to environmental exposures/drugs using cell types differentiated from induced pluripotent cells as surrogates. These cell types would have to behave as they do in vivo.
- Cells would be placed on a high throughput chip to create a human body on a chip.
- Some talk about not knowing how many different cell types there are in the body.
- Discussed starting with different strains of mice with different environmental sensitivities.

## **NEW RESEARCH MODELS**

### **Multidisciplinary centers for research translation:**

- Develop multi-disciplinary centers that house people with a wide-range of expertise in order to go all the way from basic research to clinical solutions.

## **PROFESSIONAL DEVELOPMENT**

### **Increasing time to intellectual independence:**

- Researchers lose the 10 best years of their professional life in terms of creativity.
- Expanding the Pioneer and New Innovator awards was proposed as well as providing an unmentored mechanism to achieve independence earlier.
- In addition, the length of the medical school curriculum needed to be shortened.
- Another point of discussion was a biotech-like spin-off satellite entity where smart people could be unleashed within a system that rewarded risk-taking (invoked Janelia Farm).

## **GLOBAL HEALTH**

- An argument was made that many so called “emerging” infectious diseases that lead to outbreaks such as Lassa Fever are in reality undiagnosed infections and that constant surveillance of infectious disease hotspots is needed to prevent the spread of pathogens.
- To do this, a few sentinel Centers of Excellence could be created that febrile patients can visit and the pathogens causing infection determined by high throughput sequencing.
- Part of this venture would include the development of affordable and deployable diagnostics.

## **IC IDEAS:**

### **NIMH**

#### **Tools for single cell biology:**

- NIMH made a pitch for single cell analyses and the need for technology development to improve detection of single cell responses/outputs.

### **NIDA**

#### **Linking genetic variation with brain morphology:**

- NIDA made a case for whole genome sequencing and brain imaging studies to get at brain structure as a function of genetic variability in different diseases and during drug addiction.
- Genetic abnormalities occur years before disease characteristics appear but imaging during a developmental window could identify changes that occur early on in the brain.
- The idea proposed using the National Children's Study infrastructure to fill a gap in the Study.

#### **Connecting pharmacogenomics, pharmacokinetics, and pharmacodynamics through deep sequencing:**

- Use pharmacogenomics to predict adverse drug responses.

### **NIEHS**

#### **The personal environmental exposure initiative:**

- Similar to one of the panel ideas. Involves the monitoring of exposures to drugs, stress, different nutrition, etc. taking in to account that exposure responses can be inherited via transgenerational epigenetic changes (starvation response was given as an example).
- Suggested building a consortium to explore what a person has been exposed to at any given time—would test accessible body fluids.
- There was some discussion on how to handle continually changing exposures and responses.

### **NCCAM**

#### **Genomics of the biosynthesis of natural products**

- There are only a few places where genomics is being brought to bear on the area of natural product chemistry to help in the synthesis of complex natural products.

### **NIBIB**

- Dr. Pettigrew mentioned that NIBIB develops HTP platforms such as microfluidic platforms and supports dataset development and tools.

## *Translation of Basic Science*

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The group split into two subgroups and identified several barriers to translational research and proposed solutions:

- Heavy regulatory burden of clinical research (IRB, FDA, etc.): Providing “safe havens” for clinical research would encourage investigators to continue doing translational research. Interagency cooperation was emphasized as a way streamline applications, reports, etc.
- Little credit for clinical research, study section service, etc.: Providing prizes, funding tied to milestones would focus trial design and provide career recognition.
- Misplaced incentives: Providing recognition for FDA-approvals, not high profile publications, would encourage clinical researchers
- Complex application procedures: Providing a common application for NIH funding and FDA (IND) approval would facilitate translational pipeline
- IP/COI issues: Developing new NIH policies, standards, or research networks to provide safe havens to do trials, could allow experts/inventors to continue to contribute, for example, to trial design, and facilitate involvement of pharma
- Insufficient access to compounds, toxicology/PK, patient populations: Providing access to failed drug candidates would expedite translation by leveraging safety data, etc.; expanding RAID would increase access to toxicology/PK; forming a national translation network to select the top drug candidates for trials would decrease number of trials and burden on patient populations
- Pharmacology is a dying science: NIH should reinvigorate the pharmacological sciences in medical schools. Also need more robust training for scientists who study biology of humans.
- Inadequate understanding of human biology:
  - Marrying informatics with “contrastive” biology (as opposed to comparative biology) would lead to information about distinctively human biology.
  - Provision of new phenotyping methodologies (emphasizing metabolomics) would allow more detailed knowledge of human biology.
  - More “granularity” to our understanding of disease (networks, circuits) will allow development of better hypotheses about new treatments.
- Inefficiency in collection and analysis of human samples limits ability of researchers to use them for research purposes: Need better methods and technologies to take micro quantities of blood, urine, saliva, etc and measure all cytokines, all metabolites. Standards are needed first; then the development of sensors.
- Social barriers to clinical science: Need patients with electronic records so questions can be answered without new recruits for every question. Data need to be comparable between studies.

The group discussed each of the proposals nominated by extramural scientists and selected two proposals to move forward:



1. **Mouse Models to Markers, Modifiers, and Medicines (5M)** intends to accelerate the identification of treatments for common, distal phenotypes of disease instead of proximal causes. The idea is that one effective treatment against, for example, fibrosis, could ameliorate several different disorders.
  - Focus on common distal events that culminate in clinical outcomes, not individual diseases.
  - Utilize an allelic series rather than strict reliance of knockouts, informed by heavy reliance on human studies for appropriate candidate genes and phenotypes.
  - Profile mice to obtain signatures of predisposition, progression, and (hopefully) response.
  - Carry out clinical trials with a carefully vetted panel of agents with broad therapeutic potential or desirable target repertoire (allow for serendipitous discovery).
  - Harmonize mouse trails with human trials (experimental design, endpoints).
  - Introduce 5M alleles on multiple inbred and outbred backgrounds to identify genetic modifiers and increase likelihood of translation of results to humans.
  - All data would be obtained using standardized protocols, and deposited in central databases with public access. 5M strains would be maintained centrally and widely distributed via a biorepository.
  - Complement with parallel mechanistic studies in people (iPS cells for some disorders, cell culture, tissues, advanced imaging)
2. **Probes in People, a National Indications Discovery Initiative**, is based on the two proposals: Comparative Target Validation Network and Competitive Access to Peptides, Antagonists, and Other Probes. It aims to accelerate the identification of novel treatments for known diseases by validating targets via “preclinical” assessments in people. This project has components that overlap with existing Common Fund (and other NIH) programs and continued to evolve during the discussion.
  - Construct a virtual medicine cabinet: would include small molecules and biologics with known mechanisms of action that have failed initial indication; compounds would be linked to an annotated database of their properties in vitro and in vivo.
  - Facilitate investigator-initiated shopping in this medicine cabinet through a portal; ‘inventions’ needed to encourage compound deposition (pharma, biotech, etc.) and investigator shopping from multiple institutions (pharma and academia).
  - Move to proof of clinical concept e.g., via CTSA network (?capacity); other entities.

- Encourage combinatorial approaches to therapy.
- Use compounds to probe human biology in a variety of contexts (genetic, cultural, nutritional, etc.); reinforce and enhance value of efforts to understand human genetic/physiologic variation.
- Focus on orphan diseases, global health.
- Carry out comparative analyses; biomarkers, biosensors, advance quantitative phenotyping.
- Provide data access (e.g. toxicology); new data mining tools (e.g. machine learning approaches).
- Integrate with Mol Libraries/TRND/RAID/CTSA/CAN.
- Manage COI constructively.
- Facilitate interactions with Pharma/Biotech and academia (by leveraging NIH and private sector investments = national co-investments).

In addition to “5M” and “Probes in People”, the group was interested in “**Bionic Joint Regeneration via Multi-Tissue Engineering**”, which proposed to encourage interdisciplinary teams to bioengineer joints. However, the group felt this project was not as appropriate for the Common Fund as for NIBIB and perhaps NIAMS.

One of the subgroups also spent considerable time building to the concept of a prospective cohort study of children, from pre-natal through 4-5 years. They saw this as a hypothesis generating study in which the methodologies for micro-scale analysis of molecular phenotype could be developed and used to correlate genotype and phenotype. IC Directors in the group informed the group about the National Children’s Study which seemed to address most of their interests. However, they felt that technology development in support of better phenotyping could significantly strengthen the NCS and other cohort studies.

Based on ideas submitted by panel members in advance, the session co-chairs framed the discussion around an overall concept and grouped proposals into five themes. The overall sense was that NIH has an unprecedented opportunity to affect health care in a practical and sustainable way by developing and applying research methods to real world clinical and health care practices to identify new models and best practices of care and prevention. To accomplish this, networks of health care systems could be formed to address systems-level questions about efficiencies and costs in health care and impacts on health outcomes. Specific studies could identify systems-level parameters that differentiate poor-performing centers from high-performing ones, and evaluate how social networking impacts care delivery, decision making, and patterns of disease. Networked systems of care could be assembled around specific chronic diseases to create “hubs” of education, training and care that would enable community-based research programs. Data-rich electronic health records (EHRs) and clinical registries could be tapped to study risk factors for disease, support patient-centric wellness programs, and identify “best practices” for health care delivery.

NIH can play an important role in health systems analysis, but this is a highly political arena. Research concepts would require a rational scientific basis; policy changes would not be the primary goal, although may be downstream effects. While research efforts are ongoing elsewhere, this bold new area of research for the NIH has the potential to transform health care practice and disease prevention on a national and global scale.

**Concept: Study the Performance of Health Care Delivery and Disease Prevention Across a Continuum of Care**

Goal and Rationale: Create an “applied systems research” portfolio

- Is possible because of NIH’s unique credentials in research design and methodology, modeling, and analysis
- Is timely because databases and IT resources, such as electronic health records (EHRs) are becoming more robust and include health information exchange at the aggregate, regional, and local level.
- The HMO Research Network may be leveraged to address specific objectives.
- Program would be grounded in rational science but the findings could affect policy for health care purchasers, payers, insurance entities, physicians, providers, hospitals, consumer advocates, and others.

Design: Conduct research across three levels of observation/analysis (see schematic below):

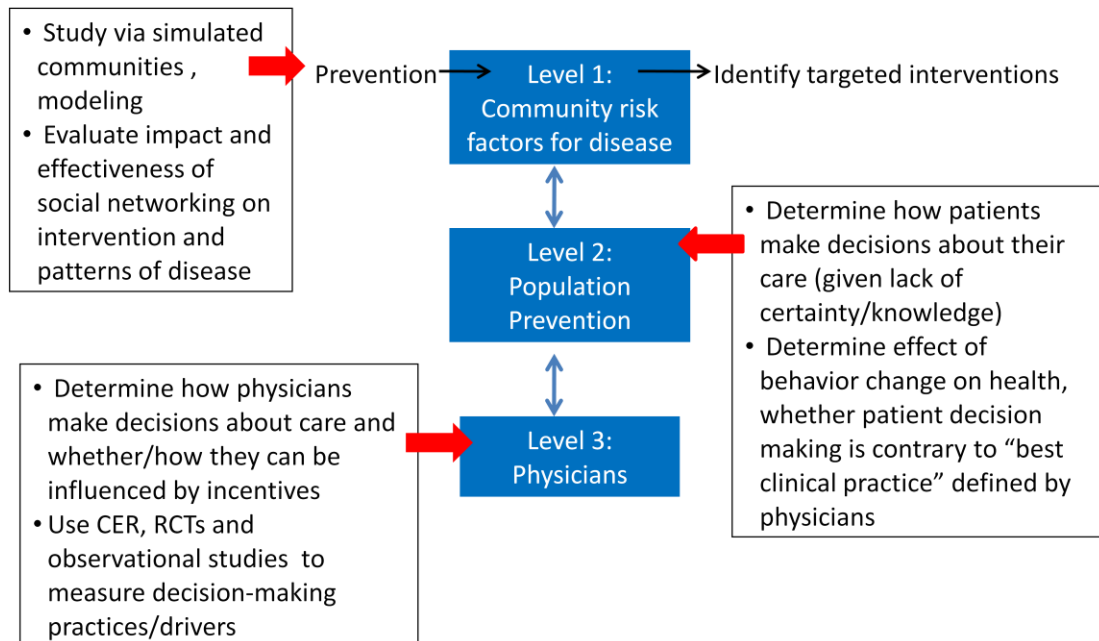
Level 1: Health care plans and communities

Level 2: Academic health centers and large medical centers

Level 3: Individual hospitals and networked physicians

Analysis: Use this framework to address questions related to health care decision making, delivery, and disease prevention, including:

- How do these units function normally and how are care and personal wellness decisions made?
- What are the optimal types of data/knowledge needed by patients and care providers to aid in decision making?
- What is the system's variation within and across units of analysis? Variations within and across units of analysis provide a basis for analysis of cause-effect relationships.
- What are the best practices?



Evaluation: Use “value equations” and other approaches to assess what we learn.

## Five Themes for Health Care Research

Research proposals would span five general themes:

### 1. Patients as Consumers in Decision Making

Although most patient care decisions are made by care providers, relatively little is known about how such decisions are made and whether they align with patient preferences, values and goals. Patients are not routinely involved in care decisions, and often lack the information they need to make informed choices either because the information does not exist or because it is not accessible or attractive to them.

Financial incentives exist for physicians to recommend specific types of care even when equally effective and less costly options are available. Patients often accept physician care recommendations out of desperation rather than informed choice and need. This creates inefficiencies because care decisions are driven by “average” health care needs as opposed to individual patient needs.

Research on the effects of patient education and financial incentive models could be conducted through a series of “natural experiments” or observational studies to determine how decisions are made at different care levels and in different care systems to identify the types of knowledge, education, system and culture changes, information delivery vehicles, and tools needed to align patients care with patients needs.

Randomized trials, natural experiments and observational studies could be used to address questions across multiple levels:

**Level 1:** What type of information do patients need, is it currently available, and what are the most effective ways to inform and educate patients?

- Is information about applicability, risk-benefits and costs of care options currently available?
- What are patient information needs by population subgroup (gender, age, race/ethnicity)?

**Level 2:** How are care decisions made and how can they be made more patient-centric?

- What approaches can improve patient-physician communication?
- How does patient literacy affect decision making and education?
- What do people think about their health and how can they be incentivized to adopt healthy behaviors and make healthy choices?
- What is the impact of the physician’s opinion on patient care decisions?

**Level 3:** Based on the findings from level 1 and 2 analyses, what types of systems changes (e.g., incentive and benefit designs) are needed to establish a more patient-centric system of care?

## **2. Health Systems Intervention**

Health care intervention focuses on developing new approaches to optimize the health care delivery system. These approaches could be identified through a series of randomized trials to assess the variability in processes and performance across health plans (largest), academic health centers and

medical centers (medium), and physicians at a given hospital or health care system (smallest). Assessing variability in relation to outcomes across centers will identify the “drivers” in health care delivery and costs. The network could be used to address a number of research topics including:

- What are the factors that destabilize small provider health systems that could be corrected to maximize cost-effective care?
- What corrective actions could be taken to convert a poor performing medical center into a high performing one?
- What is the impact and benefit of having standards and central support in areas such as consent and IRB, and standardized assays to measure performance?
- What is the minimal, optimal skill set required to deliver services in a given health care setting, and what are the cost savings when professionals other than primary care providers are used to deliver services?
- How do different patient/consumer behavioral, social and psychosocial models affect care and health?
- How can we assess and address extreme phenotypes in our medical system?

### **3. Chronic Disease Prevention and Wellness Promotion**

With chronic disease, the primary concern is prevention. Population-based research on prevention is fragmented and data collected across multiple studies cannot be compared and compiled. New approaches such as “value equations” are needed to assess the costs of care relative to multidimensional outcomes that may include clinical care, patient education, safety, health improvement, behavior, or other measures. Such research may require a new research mechanism that specifically encourages bold thinking and leadership by junior faculty.

Several research approaches are proposed:

- Create a network of “best practice” centers of clinical care, education, and research as care “hubs” to test best practices for prevention and treatment of common chronic diseases. The approach would address the issue of low patient recruitment in randomized trials and observational studies because it would encourage community enrollment in center activities. Efforts would need to be coordinated AHRQ and CMS. For example, CMS-funded demonstration sites could be leveraged to address specific NIH research questions.
- Conduct a series of randomization trials or simulation studies with mathematical modeling to evaluate different aspects of disease prevention and wellness programs.
  - Could randomize towns (or companies) to study effects of individual and environmental factors for health and disease, and identify best practices for community involvement and outreach.

- Could create simulated towns or randomize at the population level to study the impact of social networks on patterns of disease, education, behavior change, and patterns of care.
- Could assess the effectiveness of using EHRs in prevention research.

#### **4. Comparative Effectiveness Research (CER) and Related Activities**

NIH should take advantage of research opportunities afforded by recent advances in health information systems including EHRs and clinical registries which include both clinical and claims data. Randomized clinical trials and observational studies are needed to understand differences in effectiveness of care options and to assess health impacts, cost-effectiveness, processes and variability of care at the individual and systems level, and uncertainty of data. The findings could be made available to the clinical and research community.

- Clinical registries provide a good resource to study longitudinal patterns of disease and care, and enable observational studies at the patient, physician and community level, and randomized clinical trials, that bridge basic genomic sciences and translation.
- Research studies should leverage existing databases and infrastructure, including the NIH Clinical and Translational Science Award Centers (CTSAs) and longstanding Institute research programs.

Research efforts should exploit the heterogeneity in CER data to create clinical prediction models to improve decision making. NIH could require investigators of randomized trials to collect and report data to a central repository on heterogeneity of response to treatment.

NIH should expand existing CER studies funded through Recovery Act to address topics that beyond biomedical products and include health service models (e.g., academic health center vs. provider groups), practice variation at the institutional and individual level, and policies.

#### **5. Using IT to Implement Reform**

Electronic Health Records (EHRs) are a rich source of clinical and claims data for research. There are challenges to using EHRs for research purposes, although this is likely to improve, especially if physicians are required to respond to performance measures.

- NIH research can inform best practices for EHR data recording and extraction, and establish standards for defined outcomes across medical systems. Using standardized approaches to data reporting in EHRs could be used to create “indices of disease” across a “wellness scale” so that individuals would know what is considered a “standard normal” range and then know when to adjust their behavior when they fall out of the norm, thereby empowering individuals to take responsibility for their wellness.

- This approach will require a deep level of data specificity within segments of the population (across gender, age, race/ethnicity, geography) to know what types of health information individuals understand and appreciate.

Standardized patient recruitment processes and services, and research information infrastructure (e.g., for consent, institutional review board approvals, data reporting, EHRs) should be developed at a national level to facilitate CER and clinical studies broadly. CTSAs and other NIH-supported research centers could be incentivized to use these research platforms.

Studies are needed to assess the costs of medical documentation in health care and to develop approaches to reduce this burden. Research could identify specific types of information that can be removed from the medical record without adversely affecting the quality of care.

Costs for post-acute and long-term care have skyrocketed over the past decade and payment systems are focused on financial incentives as opposed to quality patient care. Research could assess current payment systems and develop new models based on a patient-centered system of care.