

Common Fund Concept Clearance

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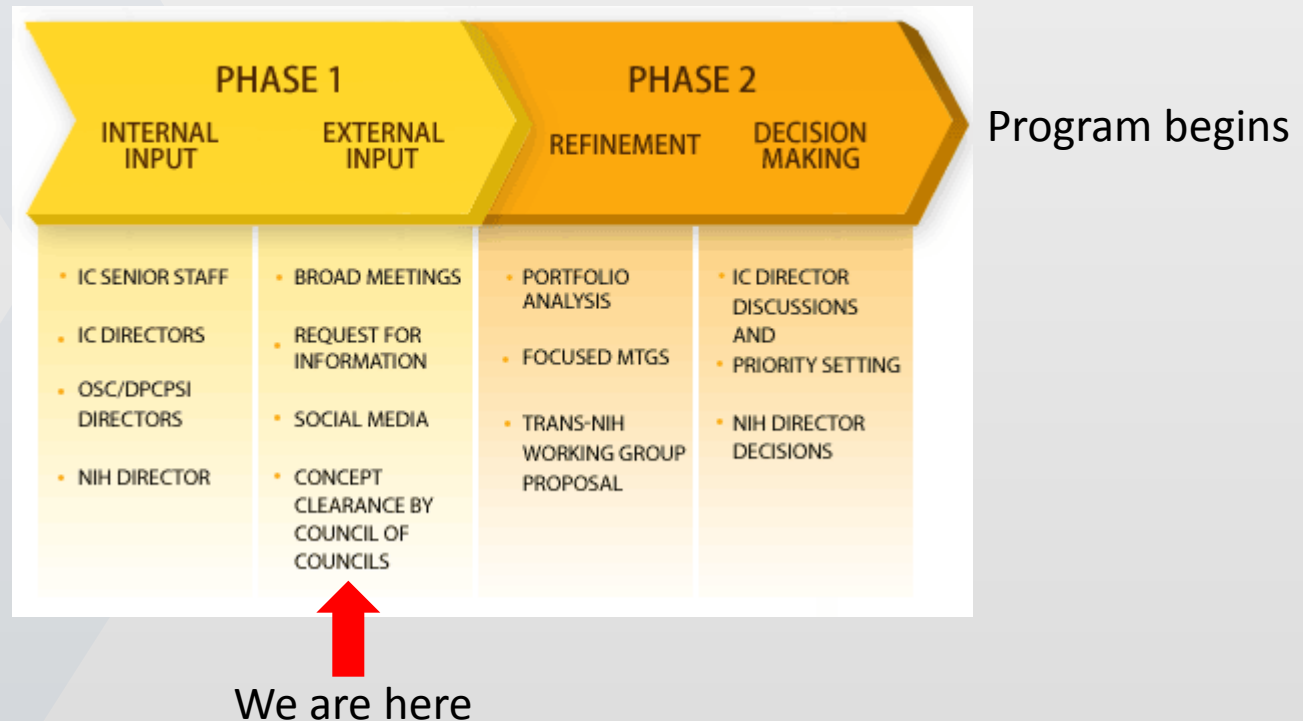
Director, Office of Strategic Coordination
Council of Councils Meeting, June 20, 2014



Common Fund Strategic Planning Process

Phase 1: Identification of ***broad topic areas*** that address the biggest challenges and greatest opportunities in biomedical research

Phase 2: Refinement of broad areas into ***well-defined programs and initiatives***

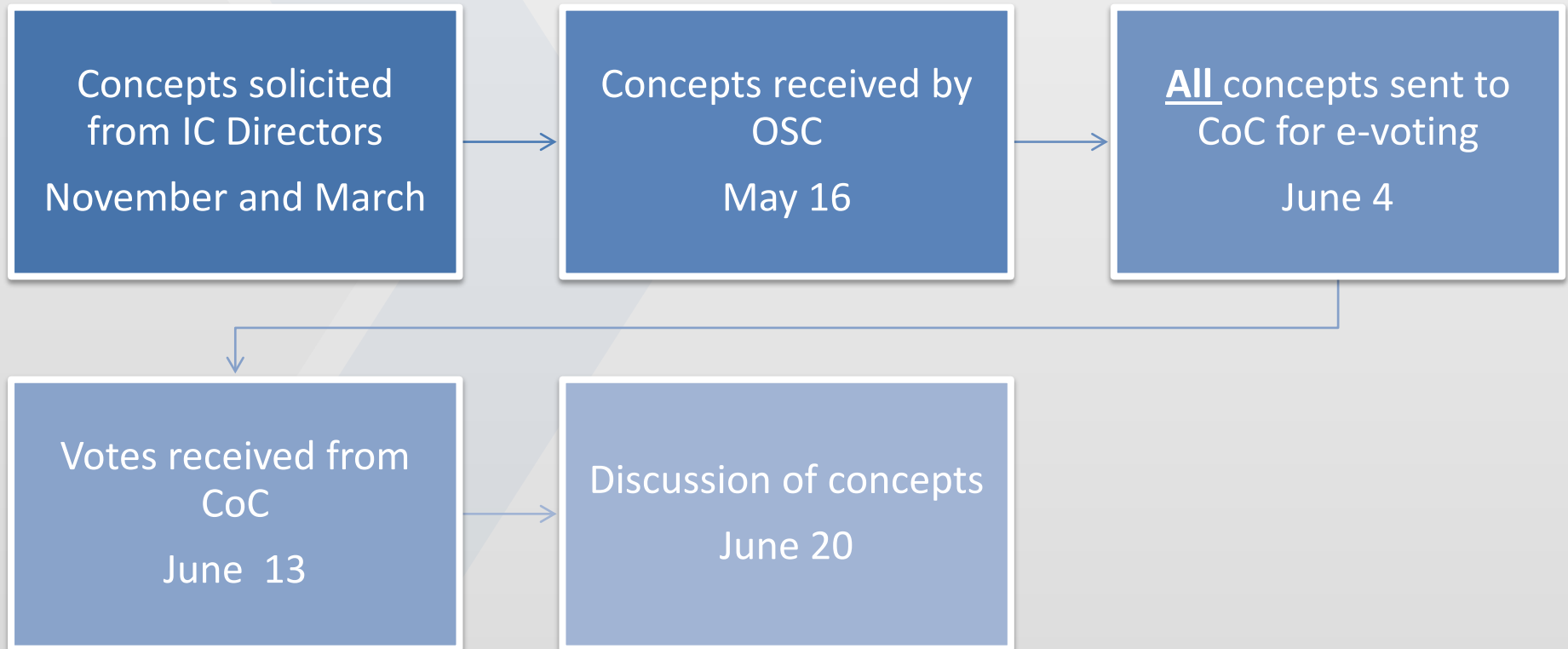


- We are at an early stage in the process— Working Groups have not formed, portfolio analysis has not been conducted, and budgets have not been established
- We are asking for your input on whether just the broad CONCEPT meets the Common Fund program criteria

Criteria for Common Fund Programs

- **Transformative:** Must have high potential to dramatically affect biomedical and/or behavioral research over the next decade
- **Catalytic:** Must achieve a defined set of high impact goals within 5-10 years
- **Synergistic:** Outcomes must synergistically promote and advance individual missions of NIH Institutes and Centers to benefit health
- **Cross-cutting:** Program areas must cut across missions of multiple NIH Institutes and Centers, be relevant to multiple diseases or conditions, and be sufficiently complex to require a coordinated, trans-NIH approach
- **Unique:** Must be something no other entity is likely or able to do

Process for FY16 CF programs



Concepts Pre-Cleared or Combined

Cleared by electronic pre-voting:

- A Structural Basis for RNA Therapy
- Integrative Geroscience Project
- Next-Generation Cell Engineering

Combined Ideas:

- Research to Facilitate Aging in Place: can combine with pre-cleared idea “Integrative Geroscience Project during Phase 2 planning
- Multiple Chronic Conditions: can combine with ongoing multiple chronic conditions initiative within Health Care Systems Research Collaboratory program

Challenges Addressed by Common Fund Strategic Planning

“...identification of research challenges is easy; identifying those where recent advances – perhaps in unrelated fields – create an opportunity to overcome the challenges within five to ten years is more difficult. Similarly, identifying exciting areas of science is easy; identifying areas where a coordinated, goal-driven, trans-NIH approach is required to reveal new paradigms is more difficult.”

Collins, Wilder, and Zerhouni, Science in press, 2014

Enabling Exploration of the Eukaryotic Epitranscriptome (E⁴)

Challenge/Opportunity: The main obstacles hampering our efforts to better understand RNA modifications and their role in both healthy and diseased biological processes are fundamentally technical in nature. Presently, we lack user-friendly tools and technologies for investigating the epitranscriptome.

Program Goals:

- Generate tools/technologies to monitor and manipulate eukaryotic RNA modifications
- Survey the diversity of known RNA modifications
- Discover previously unknown RNA modifications and modifying enzymes
- Generate a Mammalian Epitranscriptome Catalog
- Develop computational strategies to predict the presence of RNA modifications
- Explore the biogenesis and mechanistic functions of modified RNAs
- Develop small molecule modulators as probes and potential therapies

Enabling Exploration of the Eukaryotic Epitranscriptome (E⁴)

Proposed Initiatives:

Phase 1

- Generate tools and technologies to monitor and manipulate RNA modification
- Survey the diversity of known RNA modifications in a defined number of disease –relevant mouse and human tissues and in different RNA classes
- Discover novel RNA modifications in mRNA and regulatory RNAs, and the protein and/or RNA enzymes that write, erase, or read these modifications

Phase 2

- Generate a Mammalian Epitranscriptome Catalog of mRNAs and regulatory RNAs from a defined number of disease-relevant mouse and human tissues
- Develop computational strategies to understand the relevant features of a given RNA substrate to understand and predict how RNA modifications are targeted
- Explore the biogenesis and mechanistic functions of modified RNAs and the readers, writers, and erasers of these modifications
- Develop small molecules as probes and early stage validation of new therapeutic targets

Potential Impact:

This program will generate tools and resources to explore the biological functions of epitranscriptomic modifications; identify the role of RNA modification in biological and disease processes; and provide information about novel druggable targets.

Fibrotic Diseases: causes, consequences, prevention, and treatment

Challenge/Opportunity: The biology and pathophysiological progression of fibrotic diseases, which represent a major cause of morbidity and mortality worldwide, are poorly understood. Major obstacles, challenges, and opportunities lie in developing validated approaches to reduce the incidence and mortality attributable to the broad range of fibrotic diseases.

Program Goals: To advance our understanding of the various risk factors that contribute to the pathogenesis of fibrosis; to improve primary and secondary prevention of these risk factors; and to determine the degree to which successful secondary prevention can reduce the risk and progression of fibrosis.



Pulmonary Fibrosis

Fibrotic Diseases: causes, consequences, prevention, and treatment

Proposed Initiatives:

- Determining the degree to which interventions reverse prevalent risk factors for specific fibrotic diseases
- Improving understanding of the pathogenesis of fibrosis, including determinants of progress common to multiple organ-specific fibrotic diseases
- Tissue engineering to develop artificial organs

Potential Impact:

This program could set the stage for increased understanding of the pathogenesis of fibrosis, together with a reduction in incidence and mortality attributable to fibrosis and its downstream consequences in a variety of organ systems.

Mobile Health (mHealth) Technologies for Medical Diagnostics in NIH Mission Areas

Challenge/Opportunity: Although mHealth is an emerging field, there have been very few devices developed that can monitor health vital signs in the field, capture medically actionable physiologic measurements, and are regulated as medical diagnostic devices. However, there are great opportunities for mHealth with the high computing power and inherent connectivity of low-cost mobile devices, especially in resource-limited settings.



LUCAS (Lensless, Ultra-wide-field Cell monitoring Array platform based on Shadow imaging): holographic microscope that can be attached to a cell phone camera.

Named 2011 Top Innovation by The Scientist Magazine.

Program Goals: to support mHealth medical device projects for screening, early detection, risk assessment, exposure analysis, diagnosis, treatment monitoring or other medical applications.

Mobile Health (mHealth) Technologies for Medical Diagnostics in NIH Mission Areas

Proposed Initiatives:

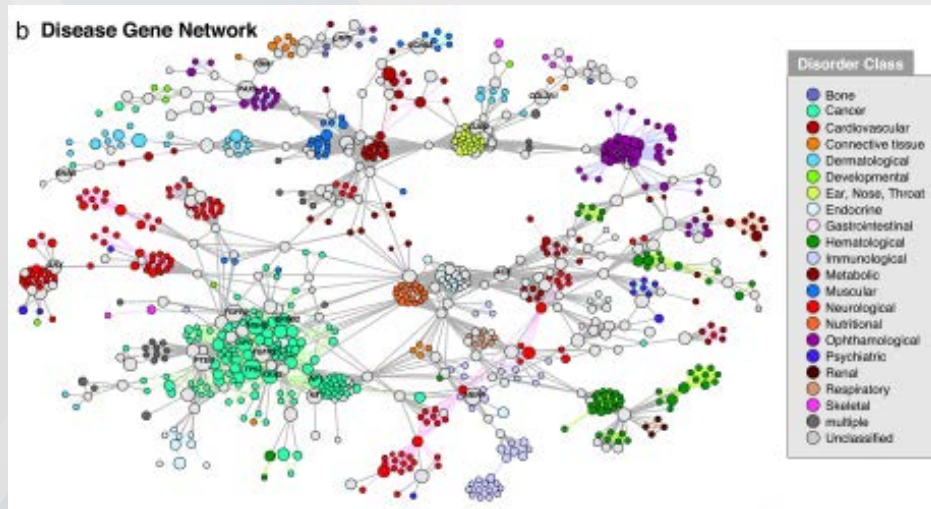
- Multi-disciplinary teams will be supported, containing the following types of expertise:
 - Technology
 - Clinical
 - Translation
 - Computation, communication, and remote analysis
 - Health disparities (optional)
 - Behavioral (optional)
- Teams will develop mHealth devices, test the utility and effectiveness of these devices, and bring the technologies to the clinics and users
- Follow-on projects could address IC-specific technology development and/or target later stages of product commercialization

Potential Impact:

The new low-cost mHealth technologies created will have the potential to change management and care practices and to reduce the cost of health care. Importantly, the program will significantly improve access to medical diagnostics devices for disease screening, detection/diagnosis, and monitoring, especially in low-resource areas.

The Network-based Taxonomy of Disease (NetTD)

Challenge/Opportunity: There is a need for a new taxonomy based upon diseases' molecular basis. However, the information of intermediate/subclinical phenotypes are missing for most complex diseases, presenting a major obstacle to identifying subphenotypes of disease and developing a new disease taxonomy based on individual patients' molecular makeup.



PNAS, 2007, 104(21)

Program Goals: To develop a diseases network focusing on intermediate and subclinical phenotypes of complex diseases that will provide molecular bases to discover new disease subtypes, novel biomarkers for early diagnosis, more accurate prognosis, and therapeutic targets, and eventually lead to the development of a new taxonomy of disease.

The Network-based Taxonomy of Disease (NetTD)

Proposed Initiatives:

Phase I:

- Leverage existing clinical and molecular data and tools to identify potential intermediate, preclinical, and subclinical phenotypes
- Develop high throughput technologies to measure and characterize phenotypes

Phase II:

- Support multiple centers for the generation of new data and validation of predictions regarding intermediate and subclinical phenotypes made in Phase I
- Support a knowledge base center to integrate all data generated from centers

Potential Impact:

This program will integrate research on the molecular bases of diseases with clinical data, and will break the artificial boundaries created by decades of organ- or single-disease centric research. It will drive the development of a new and more precise disease taxonomy that will enable early diagnosis, more accurate prognosis, discovery of novel therapeutic targets, and aid drug repurposing efforts.

New Technologies to Accelerate Therapeutic Synthesis

Challenge/Opportunity: As fundamental understanding of disease biology advances and the number of therapeutic targets increases, there is a need for technologies and methodologies that will accelerate synthesis and formulation of drugs.



Program Goals:

- Develop methodologies/technologies to accelerate synthesis and formulation aspects of drug development
- Develop low-cost synthetic process for drugs
- Developed improved formulations that result in improved compliance
- Provide open access to synthetic processes and formulations for existing off-patent drugs for neglected tropical diseases (NTDs)

New Technologies to Accelerate Therapeutic Synthesis

Proposed Initiatives:

- Development of practical synthetic methodologies to accelerate drug manufacture and lower manufacturing costs
- Optimization of engineering design of new technologies to allow easy and low-cost implementation
- Development of low-cost synthetic processes for manufacture of off-patent drugs for NTDs, as well as newer, more convenient formulations
- Open access database of synthetic processes and formulations of for drugs for NTDs

Potential Impact:

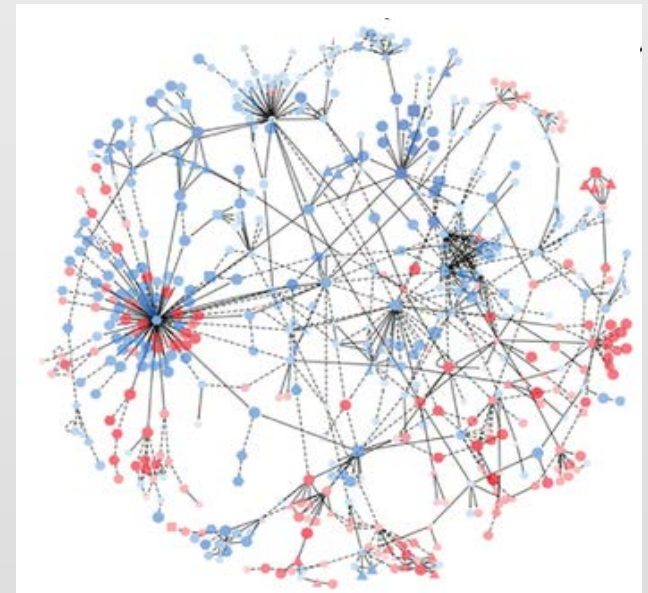
Development of new practical synthetic methodologies and low-cost manufacturing technologies will lower the cost of drug development and medical care.

SaME Therapeutics: Targeting Shared Molecular Etiologies underlying multiple diseases

Challenge/Opportunity: Therapeutics development focuses on one disease at a time. A more efficient approach would be to identify diseases with Shared Molecular Etiologies (SME) and screen for therapies targeting these common pathways, potentially impacting several diseases at once.

Program Goals:

- To streamline and accelerate the number of new therapeutics across a wide range of diseases
- To identify new therapeutics that target SME underlying multiple diseases
- To anticipate and address potential scientific and regulatory hurdles
- To undertake pre-clinical/clinical studies that underlie therapeutics development targeted to SME



Nature Genetics (2013), 45

SaME Therapeutics: Targeting Shared Molecular Etiologies underlying multiple diseases

Proposed Initiatives:

- Identify and screen for new therapeutics to target SME
 - Therapeutics could include small molecules, devices, and biologics
- Undertake pre-clinical and early stage clinical studies of therapeutics targeted to SME
 - These studies would be fundamentally different than current approaches focused on single diseases

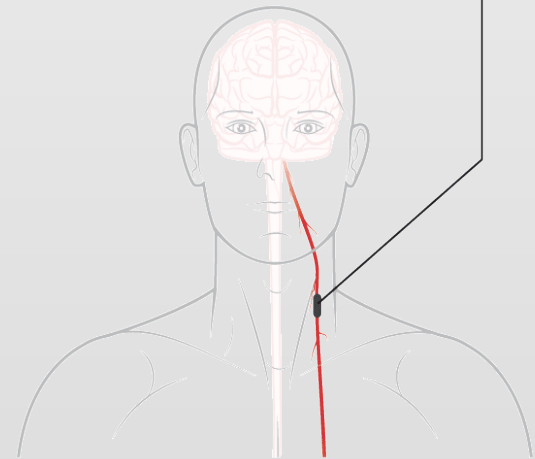
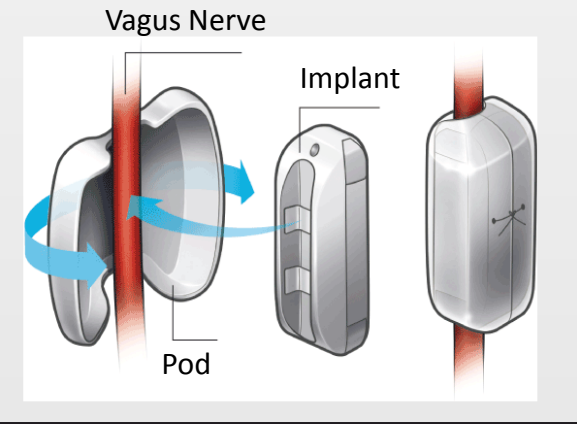
Potential Impact:

This program would fundamentally change the paradigm for pre-clinical and clinical studies and therapeutics development, from the current focus on individual diseases to SME. It would also address regulatory challenges that are associated with changing the concept of disease and therapeutics development.

SPARC- Stimulating Peripheral Activity to Relieve Conditions

Challenge/Opportunity: Neuromodulation of end-organ function holds promise in treating many diseases/conditions, but the mechanisms of action for therapies remain poorly understood.

Program Goals: To deliver detailed, integrated functional and anatomical neural circuit maps in five organ systems. The maps would be leveraged directly to develop and pilot five novel electrode designs, with corresponding stimulation protocols and minimally invasive surgical procedures, to improve existing neuromodulation therapies or pursue new indications.



New York Times Magazine, May 23, 2014

SPARC- Stimulating Peripheral Activity to Relieve Conditions

Proposed Initiatives:

- Biology: Anatomic and Functional Mapping: Deliver a detailed, integrated functional/anatomical neural circuit map in five organ systems; develop/pilot novel electrode designs, surgical procedures, and stimulation protocols leveraging insights from the functional maps
- Next Generation Tools: Develop next-generation tools for visceral nerves (optogenetics, stimulating/recording electrodes, cell-type specific tracing, etc.) needed to complete aims in the Biology initiative.
- Off-label Use of Existing Market-Approved Technology for Small Market Indications: Partner with industry and FDA to explore utility of existing, approved devices to address new, small-market indications.
- Data Coordination: Assemble data from all SPARC biology/technology projects into a coordinated data resource, develop user-friendly computational tools, and incorporate new computer modeling methods.

Potential Impact:

A successful SPARC Common Fund program would catalyze development of new and more efficacious therapies utilizing neuromodulation of end-organ system function, improve our ability to stratify patients by identifying likely responders to neuromodulation, and expand the number of organ systems amenable to neuromodulation.

Using Pharmacogenomics to Improve Opioid Pain Management

Challenge/Opportunity: Opioid analgesics are widely used to treat pain; however, large individual differences exist in opioid analgesic efficacy and adverse effects. The identification of genetic factors affecting the efficacy of opioid analgesics and their adverse effects will greatly improve and personalize pain management by maximizing analgesia and decreasing side effects.

Program Goals:

The goal of the program is to personalize opiate analgesics pain management using pharmacogenomics to maximize treatment efficacy while decreasing adverse events.



Using Pharmacogenomics to Improve Opioid Pain Management

Proposed Initiatives:

One initiative would include awards to address the following:

- Assess treatment efficacy of different types of opioid analgesics for chronic pain
- Assess adverse side effects of opioid analgesia, such as hyperalgesia, nausea, respiratory depression, withdrawal, drug interactions, and others
- Measure PK/PD of prescription opioids
- Identify gene variants associated with efficacy of treatment and occurrence/severity of adverse effects

A second initiative would support:

- Physician training courses on opioid pain management
- Integration of pharmacogenomics of opioid pain management into curriculum of medical/nursing schools and medical residency programs

Potential Impact: The use of pharmacogenomics to optimize opioid pain management would enable clinicians to give opioids to those who will benefit and reduce unwarranted side effects, thus increasing the efficacy of pain treatment and decreasing the number of deaths and hospitalizations due to overdose.