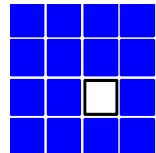


International SAE Consortium, Ltd

An International Industrial Biomedical Consortium Researching the Genetic Basis of Drug Related Serious Adverse Events

Brookings / FDA event on Sentinel Initiative

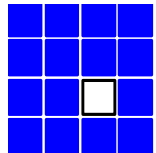
January 11, 2009



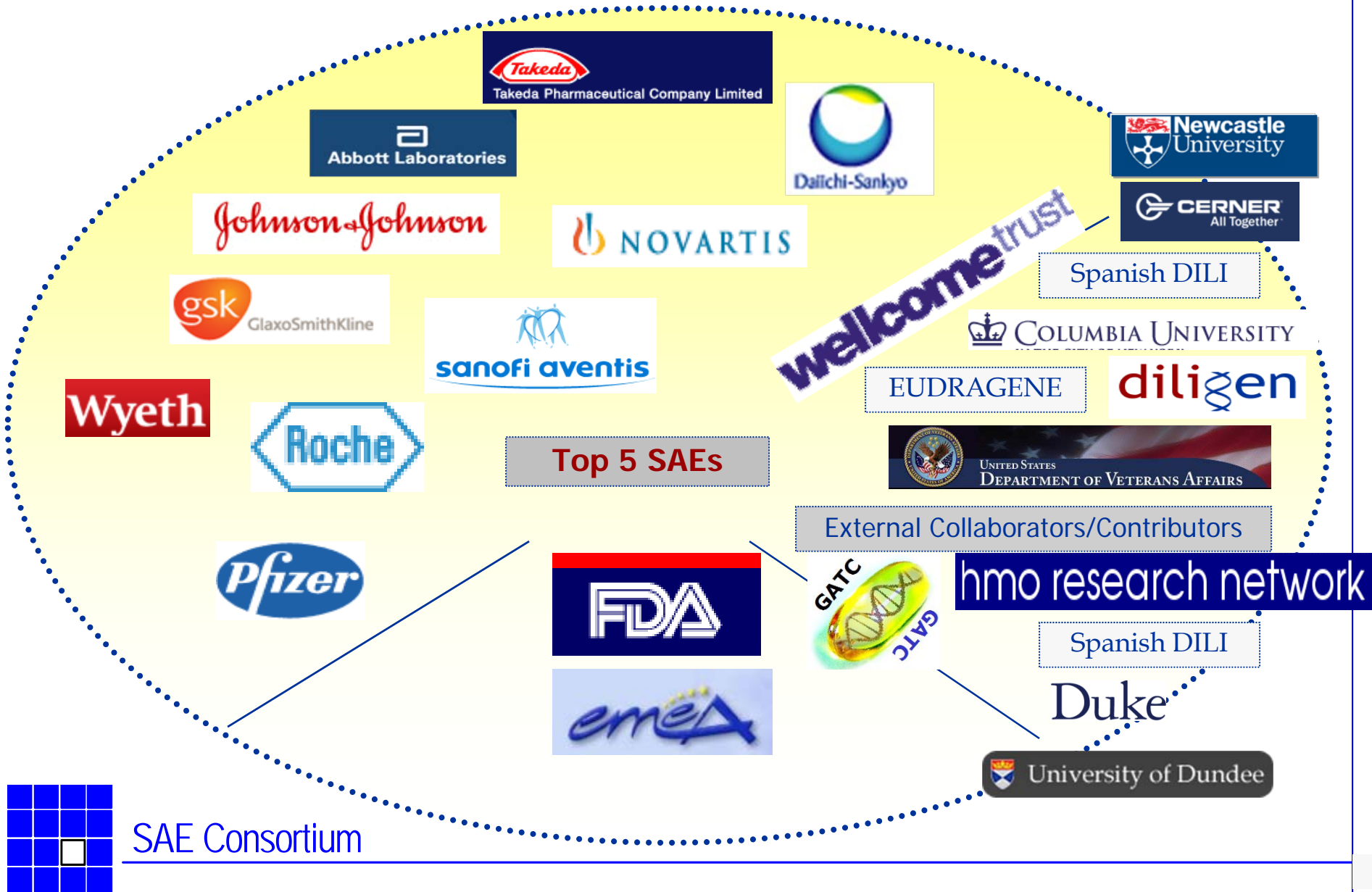
SAE Consortium

SAEC's Mission

"The SAEC will identify and validate DNA-variants useful in predicting the risk of drug induced serious adverse events."

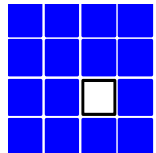


Current SAEC's Membership [11]



SAEC - Phase 1 Goals

- Support international network[s] in obtaining well phenotyped cases and controls for SAE PGx research [*discovery and validation*]
- Develop optimal genotyping and sequencing approaches for SAE research
- Evolve the computational methods necessary for effective GWAS analysis
- Create a publicly available “knowledge base” of PGx markers predictive key SAEs
- Manage IP relating to PGx markers useful in predicting SAEs to ensure broad and open access



iSAEC Phase 1 Operational "Dividends"

Core Investments

SSR GWAS,
Paper &
DR1

DILI GWAS,
Papers (3) &
DRs 2 & 3

Dividends!

TdP GWAS,
Paper (1) &
DRs 4

A-E
GWAS,
Paper (1) &
DRs 6

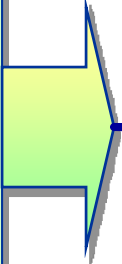
SAE Cohorts
Members
Pilots (3)

DILI &
Agranulocytosis
Sequencing
Pilots

EMR SAE
Case Sourcing
Pilots (3)

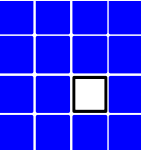
Phase 1 Execution

- DACC development
- SJS characterization & analysis
- DILI network expansion
- DILI characterization & analysis
- Data release[s]



■ Phase 2 planning

09/07-6/10



SAE Consortium

SAEC Web Site

- <http://www.saeconsortium.org>



International SAE Consortium FRIDAY, JANUARY 16, 2009

References | Newsroom and Connections | Collaborators | About SAEC | The Science of Drug Safety

The Serious Adverse Event Consortium (SAEC) is a nonprofit organization comprised of leading pharmaceutical companies, and academic institutions with scientific and strategic input from the U.S. Food and Drug Administration (FDA). The mission of the SAEC is to help identify and validate DNA-variants useful in predicting the risk of drug-related serious adverse events (SAEs).

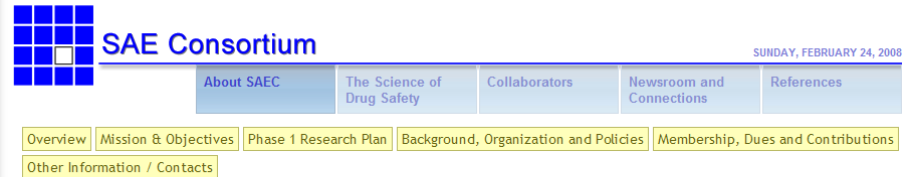
Patients respond differently to medicines and all medicines can have side effects in some people. The SAEC's work is based on the hypothesis that these differences have a genetic basis, and its research studies will examine the impact genes can have on how individuals respond to medicines. The SAEC's initial studies are focused on identifying the genetic markers associated with drug-related liver toxicity (the leading cause of acute liver failure) and Steven Johnsons Syndrome (SJS, a severe form of skin necrosis).

All research results are made available publicly within 12 months of the completion of the study group's genotyping. The SAEC has developed a [data portal](#) to provide the research community with free and unencumbered access to study data. Results obtained in initial studies can thus be reevaluated by researchers who can determine their validity as predictive markers.

Examples of severe adverse drug reactions

A number of severe adverse drug reactions are known. These include the conditions which are the initial focus of the Consortium's efforts:

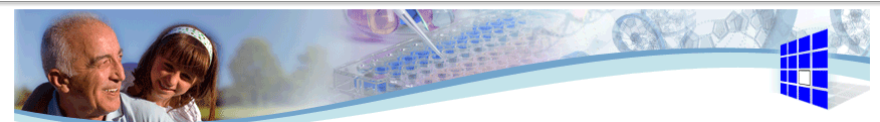
- Serious Skin Rashes: Stevens-Johnson Syndrome (SJS) and Toxic Epidermal Necrosis (TEN) - related, rare, severe, mucocutaneous blistering disorders that are associated with over 200 medicines.
- [Drug Induced Liver Injury \(DILI\)](#) - Hepatotoxicity caused by more than 30 different drugs in more than seven different classes, including NSAIDs, various antibiotics, analgesics and



SAE Consortium SUNDAY, FEBRUARY 24, 2008

About SAEC | The Science of Drug Safety | Collaborators | Newsroom and Connections | References

Overview | Mission & Objectives | Phase 1 Research Plan | Background, Organization and Policies | Membership, Dues and Contributions | Other Information / Contacts



Letter from the Chairman

November 2007

Dear Colleagues:

Welcome to the website of the International Serious Adverse Event Consortium [SAEC]. We're delighted you chose to spend a few minutes with us.

We launched the SAEC in August of 2007, as an industrial biomedical consortium, focused on identifying and validating DNA-variants useful in predicting the risk of drug induced, rare serious adverse events [SAEs]. Drug-induced, rare SAEs can be a



SAE Consortium

“Pathways” to SAE Cases and Controls

SAE Research → Discovery, Validation and Outcomes

Academic Networks

- ❖ DILI → EUDRAGENE, DILIGEN, Spain, Scotland
- ❖ SSR → Eudragene, SCAR, GATC, Pharmcos, etc
- ❖ PQT/TDP → Roden, DARE, Montreal Heart
- ❖ AHSR → European Network with MP

Pharmaco Safety Cohorts

- ❖ Global, Cross Industry
- ❖ Key SAEs → Existing & New

IHS EMR based research

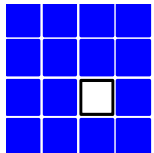
- ❖ VA
- ❖ PSP Project
- ❖ HMO Research Network
- ❖ Kaiser
- ❖ European Mkts [Scotland/Nordic/Finland]

LS EMR/CDW based research

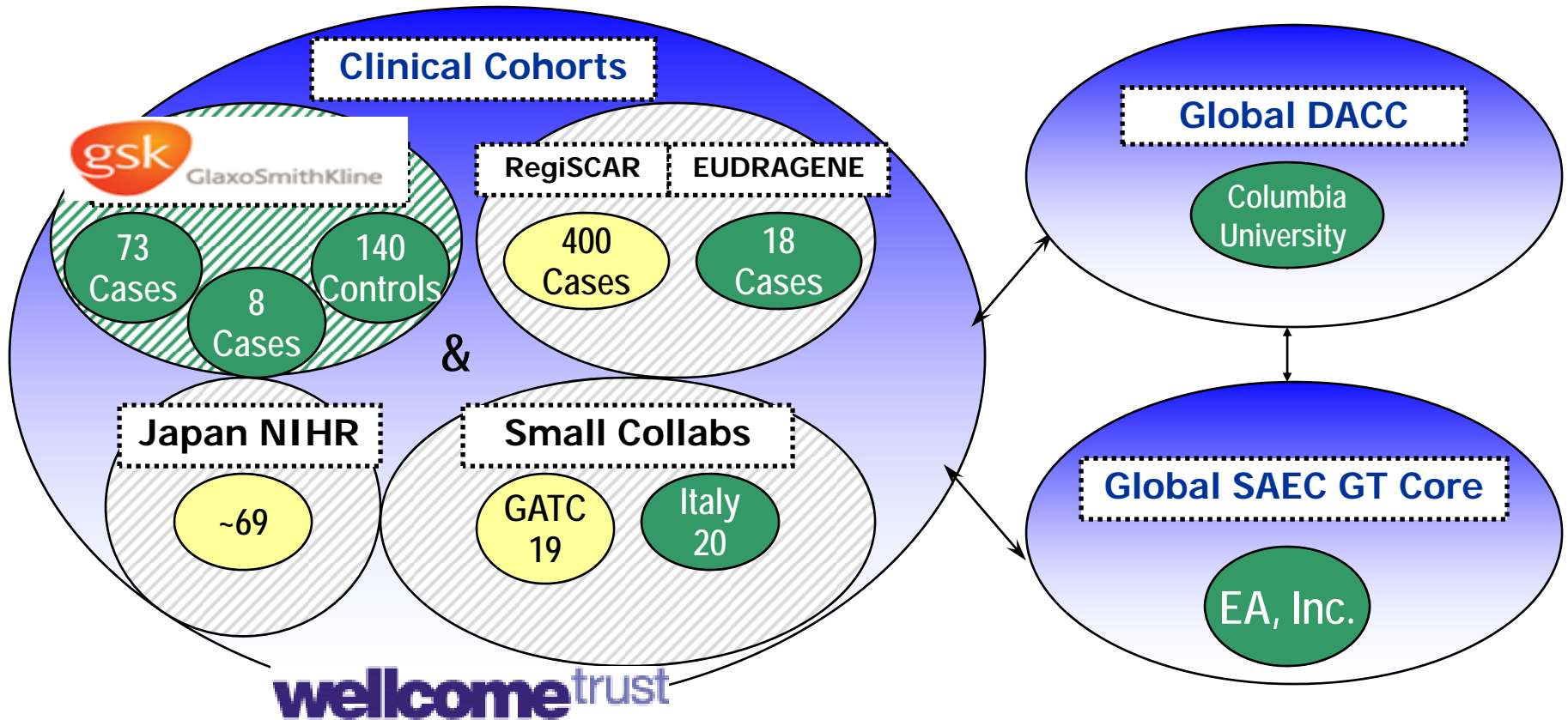
- ❖ SAEC [Cerner] Feasibility Project
- ❖ Cerner Patient Recruitment [1,500 → 4,000 hospitals]
- ❖ EMR - CDW mining and enrollment [real time]

Scalability & Breadth of Safety PGx Research

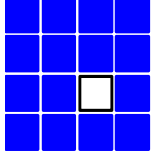
SAE Consortium



Phase 1 SSR Discovery Project - June`09

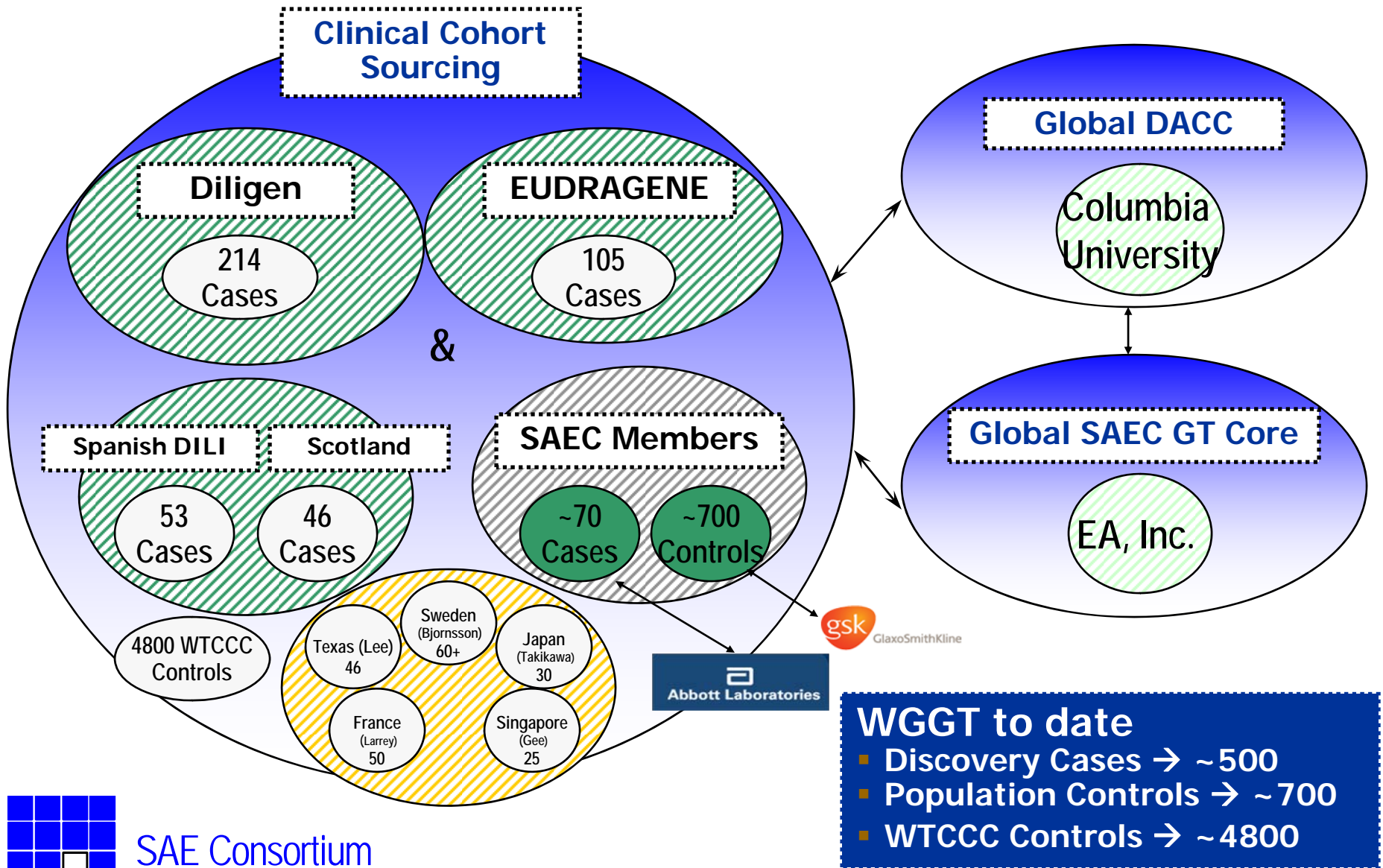


Discovery Cohort → 81



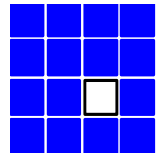
SAE Consortium

Phase 1 DILI Discovery Project - as of 06/09



WGGT to date

- Discovery Cases → ~500
- Population Controls → ~700
- WTCCC Controls → ~4800



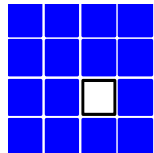
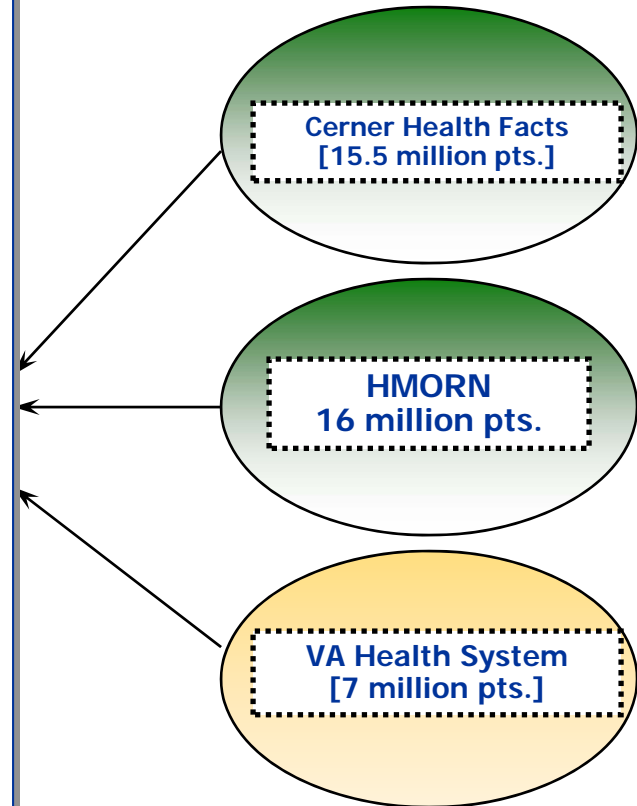
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Sourcing SAE cases via Providers & EMRs

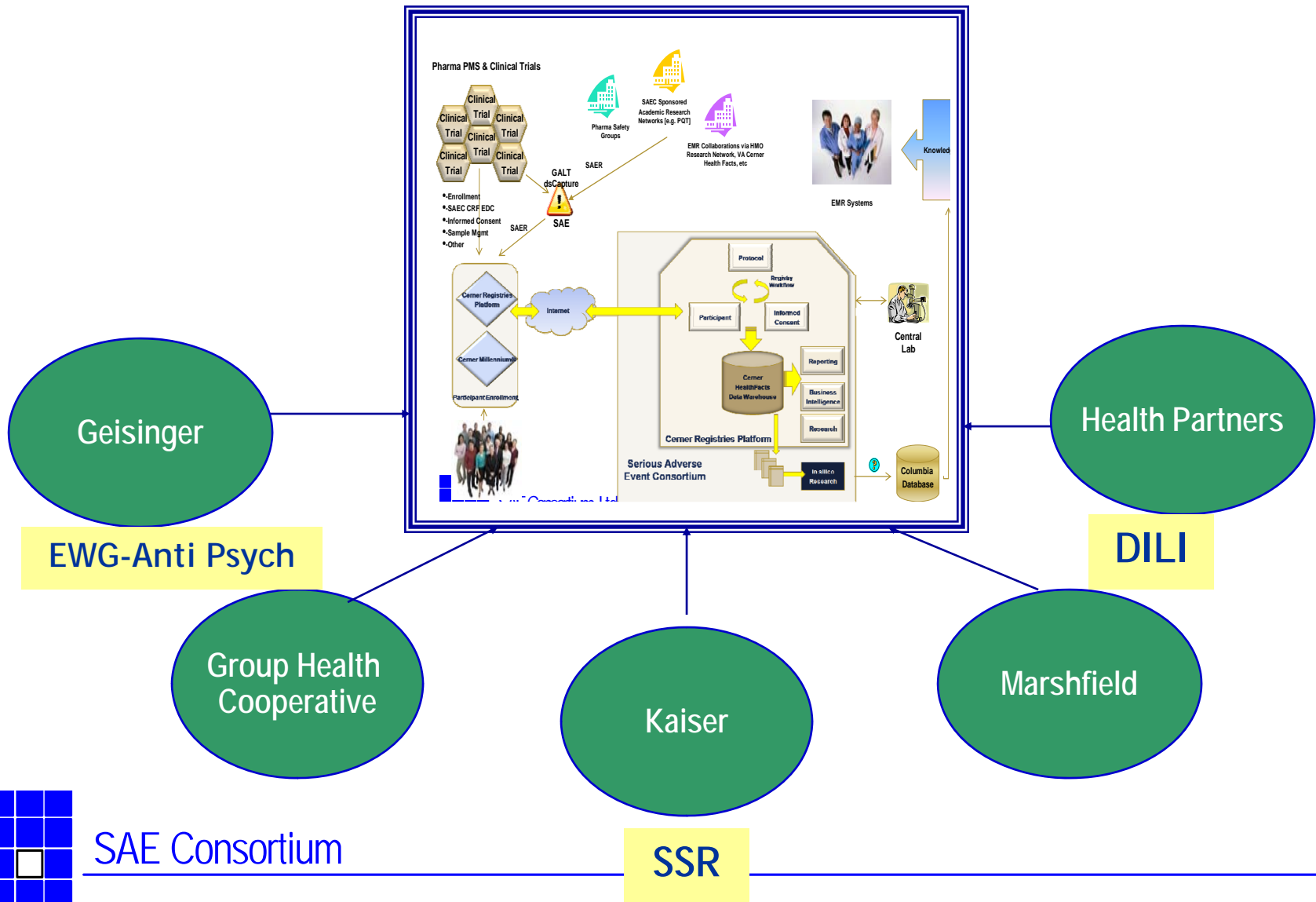
Phase 1 Feasibility Project

- 2009-10 Feasibility Projects
- Focus: Using EMR and associated research systems to determine the feasibility of yielding high quality SAE cases.
- SAE targets/3/collaboration [*of joint interest*]
 - Cerner → Hepatotoxicity, TdP/PQT, and SSR
 - HMORN → Hepatotoxicity, EWG, and SSR
 - VA → Hepatotoxicity and Rhabdo/Myopathy
- Standardized phenotype translated into EMR data ontology – feasibility of (retrospective) case detection in CDW
- Determine how many potential cases and key clinical data gaps

EMR SAE Case Sourcing



HMORN Sourced SAE Cohorts (Pilot)



SAE PSP Project Phase 1 - EMR ID of SAE Cases

- ADR research challenges → lack of phenotype standards and “coding” into EMR data ontologies
- PSP 1 Focus: Immunologic Related SAEs (SSR, DILI & AHHS) and TdP/PQT
- 2009-10 Project → Munir Pirmohamed, Chairman; Julian Arbuckle, Project Consultant
- EWG Steering Committee → Munir Pirmohamed (Liverpool), Ann Daly (Newcastle), Paul Watkins (UNC), Guru Aithal (Nottingham), Dan Roden (Nashville) & Dr. Elijah Behr (London)
- Organizing committee → Arthur Holden (SAEC), Michael Dunn (WT), Munir Pirmohamed (Clinical Chairman), and ShaAvhree Buckman (FDA)
- Expert Working Committees (3) → AHHS/SSR, DILI, and TdP/PQT
- Q4`09 - Member CRF inputs solicited; representative involvement in 2010 consensus conference
- Pooled funding → SAEC project management and working group meetings, WT 2010 consensus conference, and FDA scientific writing consultants for proceedings write-up

1. Draft phenotype definitions (staff)

2. Formation & EWGs initial meetings/drafts

3. PSP Consensus Conference (UK)

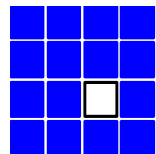
4. Scientific Write Up & Publication

Q3`09

Q4`09 -
Q1`10

Q1`10 -
Q2`10

Q3`10



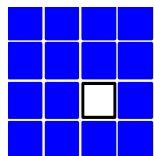
SAE Consortium



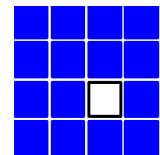
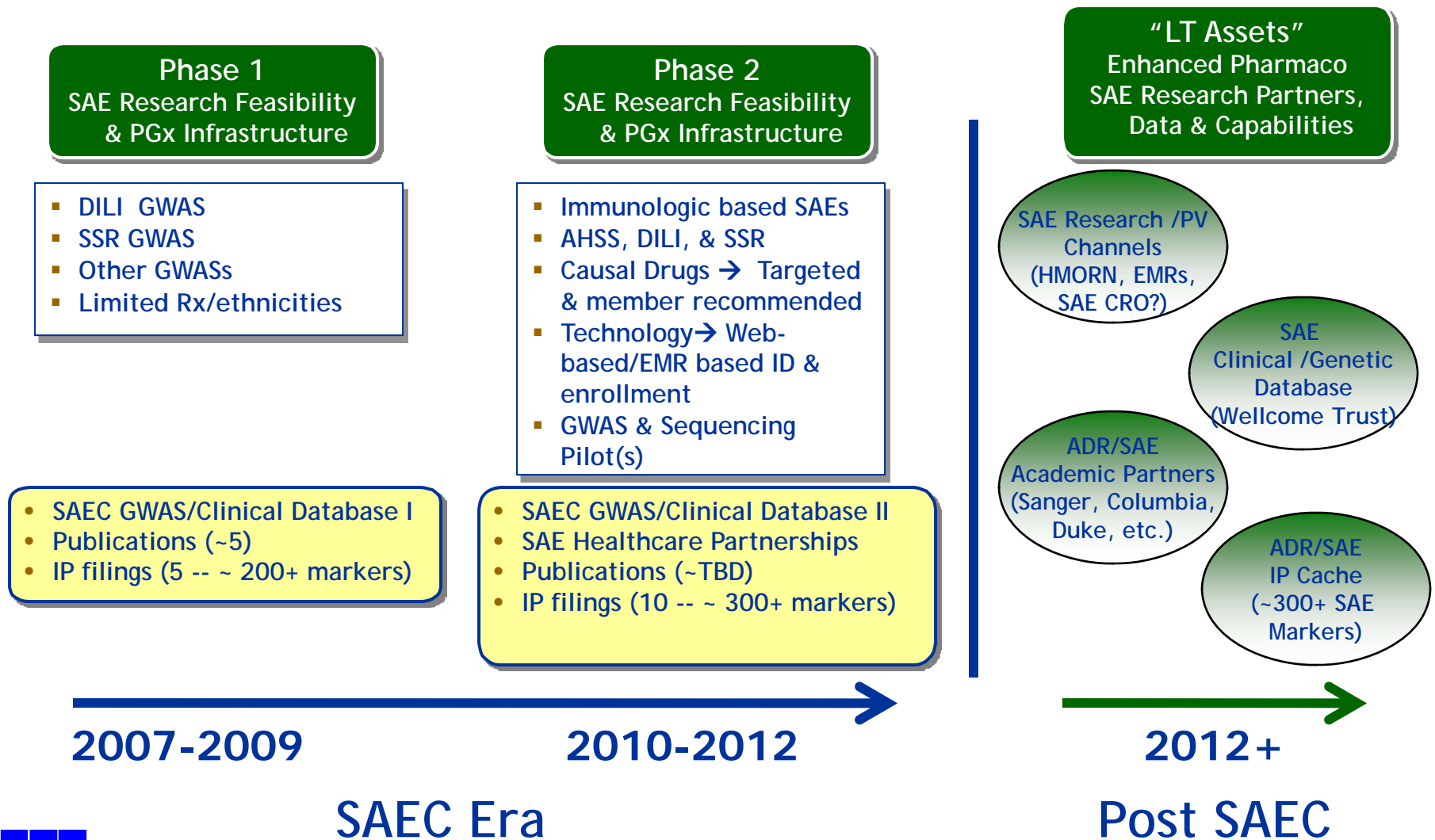
wellcome trust

Key Points from SAEC's Phase 1

1. Genomic technology and the scope of the SAEC's collaborative networks are helping to enable basic genomic research on drug induced SAEs ... a significant public health and drug industry/FDA challenge ... faster and more efficiently.
2. Robust statistical inference is possible from relatively small SAE cohorts [e.g. DILI research] and larger, well constructed control cohorts
3. DNA variants may be useful in predicting and mitigating SAE risk for some drugs in some patients → certainly supportive of safety PGx studies as part of clinical development or post market surveillance studies
4. There are important genetic effects at root of many SAEs, but many of these effects will likely be drug and ethnicity specific, and vary in terms of their predictability and clinical utility
5. At the same time, we are finding genetic risk alleles [e.g. HLA B*5701] that predispose certain individuals to drug induced SAEs [e.g. SSR, Acute hypersensitivity reaction, or DILI] across multiple drugs.

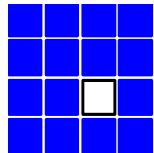


SAEC Evolutionary Perspective



EMR based drug safety PGx science

- “Standardization” of phenotype
- “Functional/ compatible” ontology/ies
- Drug and ethnic diversity
- High quality phenotyping → real time
- Adequate case & control numbers (e.g. 50 cases X drug X ethnicity/3X control)
- Supporting genomics skills and infrastructure
- Committed partners, with “results orientation”



The SAEC Has Established an Ideal Collaborative Framework for SAE Research ¹

- ✓ Global orientation to deal with ethnic diversity
- ✓ Driving standardized phenotyping across SAE/ADRs
- ✓ Strong research design skills via Scientific Management Committee
- ✓ Strong network development skills → adequate size cohorts & optimal controls [*from academia, providers and companies*]
- ✓ Strong genomics “core”
- ✓ Excellent Data Analysis & Coordinating Center [*@ Columbia*] with state-of-the-art analysis pipeline and public website for data release
- ✓ Efficient IP pipeline to ensure all discovered markers are placed unencumbered into the public domain
- ✓ Strong, focused management
- ✓ Strong integration → industry, academia, providers & regulators

