



## *Uniting Rare Diseases*

### *Advancing Rare Disease Research: The Intersection of Patient Registries, Biospecimen Repositories and Clinical Data*

*Keynote address:*

## *The Contribution of large Healthcare Systems to Improving Treatment for Patients with Rare Diseases*

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**KAISER PERMANENTE**

# Why Is Kaiser Permanente Here?

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- KP represents the largest defined healthcare population covered by a single electronic health record in the US
- KP uses EPIC, a leading multi-specialty EHR with great potential for expanded data collection and attention to standardization
- More than 120 KP-based researchers have a long history of conducting research, including registry building, patient surveys, clinical trials, and building of biorepositories
- In its larger regions, KP has an organized group of clinical geneticists, counselors, specialized clinics where members with many of the rarest diseases are seen and tracked.



# Goals for Today

- Registry and Biorepository Building
- Collaboration and Access
- IRB Concerns – patient contact, data sharing

# So, How Big Is Kaiser Permanente??

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## Current Enrollees

Kaiser Permanente  
No. California Region

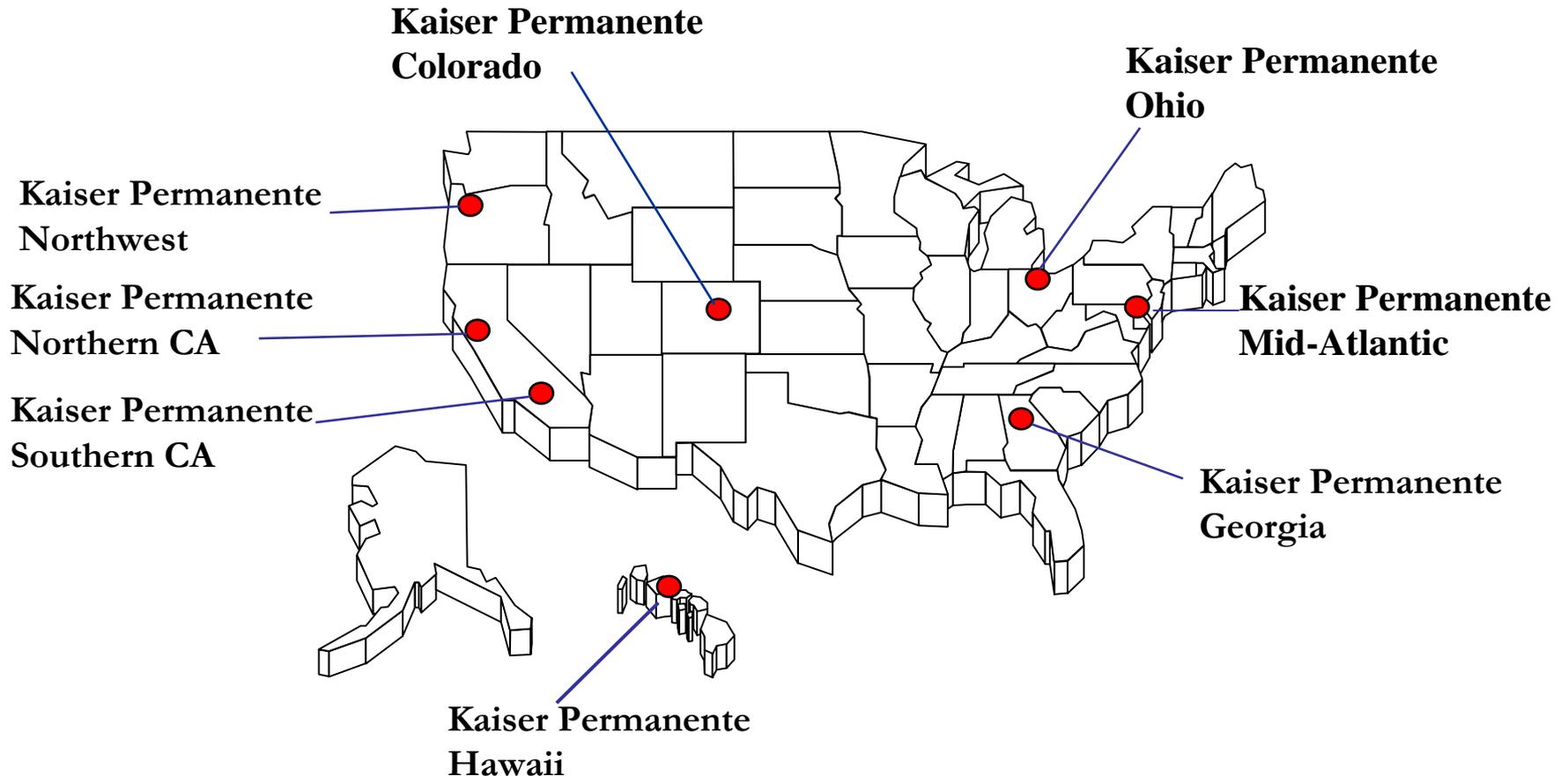
**3.2 million**

Kaiser Permanente  
Program (Nationwide)

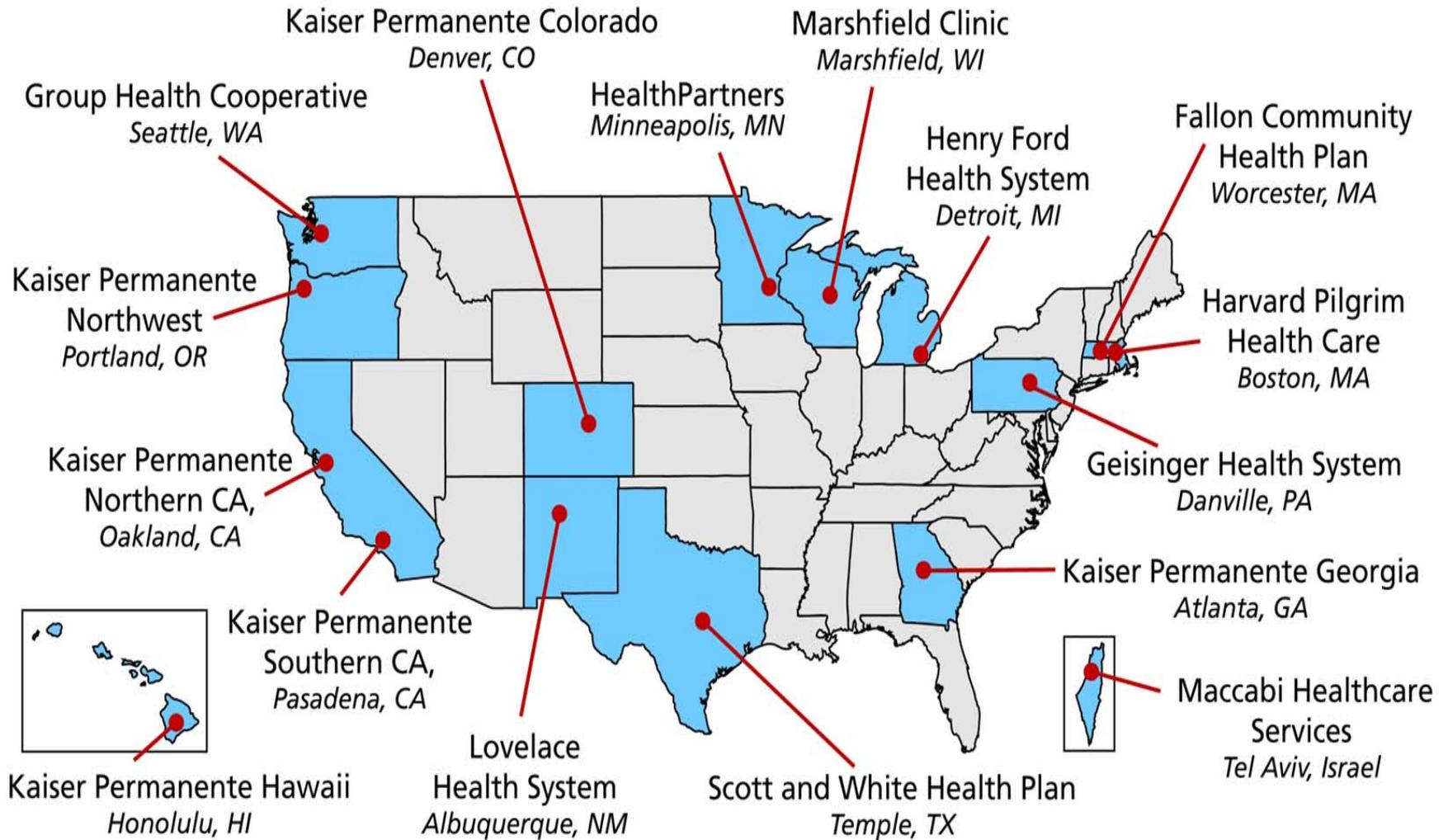
HMO Research  
Network

# Kaiser Permanente Medical Care Program – 8 Regions

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# HMO Research Network Members



# So, How Big Is Kaiser Permanente??

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## Current Enrollees

Kaiser Permanente  
Northern California

**3.2 million**

Kaiser Permanente  
Program (Nationwide)

**8.2 million**

HMO Research  
Network

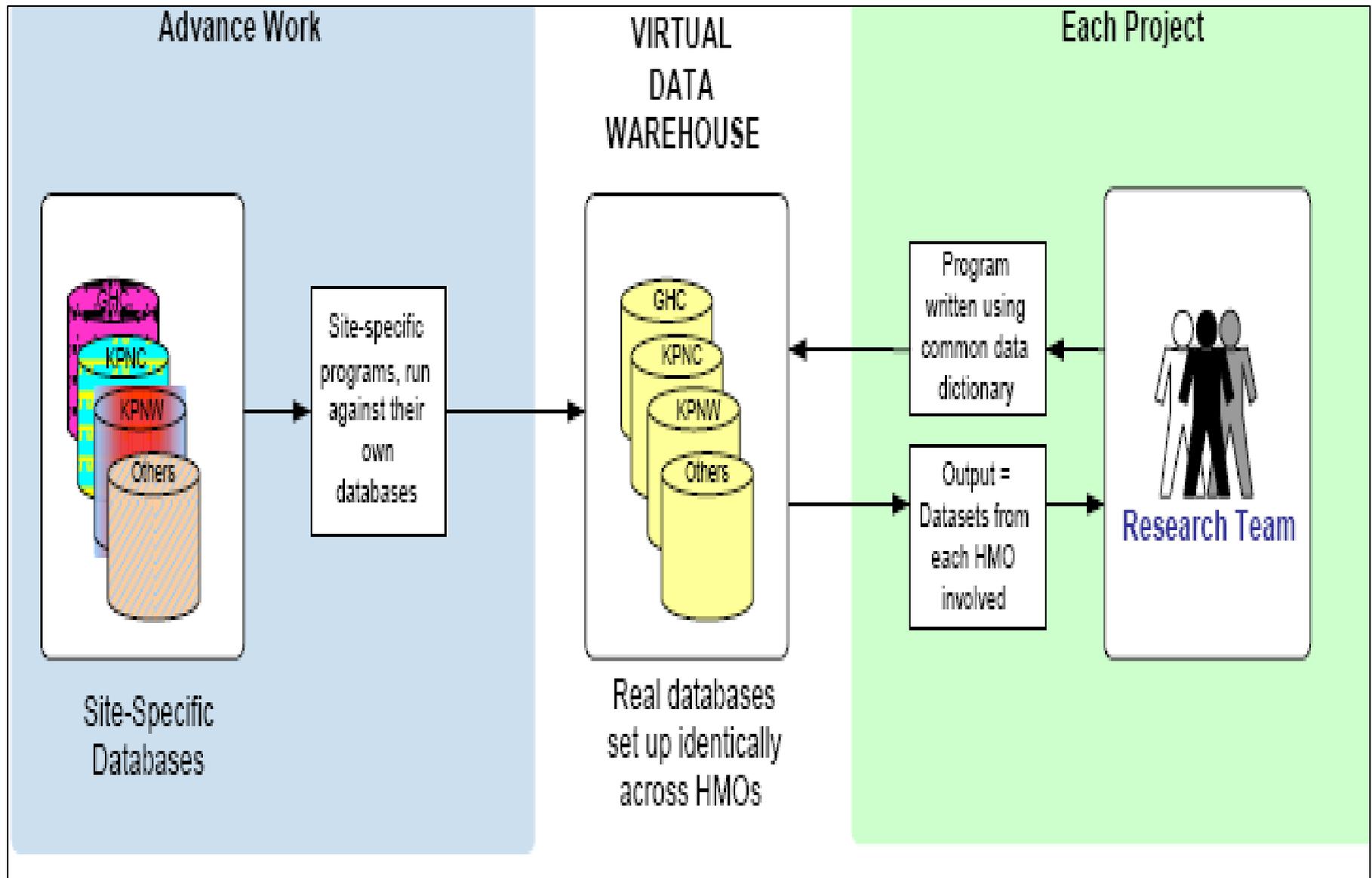
**12 million**

# HMORN Data Standardization

- All members now have established EHRs, at least 9 of 16 use EPIC
- 5 major federally funded collaboratives, each supporting multiple projects
- Virtual Data Warehouse: standardized, distributed dataset used in 12 of 16 HMOs.
- Governance: local ownership, shared data; exploring federated models

| <b>HMORN Collaborative</b>   | <b>Funder</b> | <b>Yr funded</b> | <b># of Sites</b> |
|--|---------------|------------------|-------------------|
| Cancer Research Network <b>(CRN)</b>   | NCI           | 1998             | 14                |
| Center for Education and Research on Therapeutics <b>(CERT)</b>              | AHRQ          | 2000             | 13                |
| Developing Evidence to Improve Decisions about Effectiveness <b>(DEcIDE)</b> | AHRQ          | 2005             | 15                |
| Epidemiologic Studies of Adverse Drug Effects                                | FDA           | 2005             | 10                |
| Cardiovascular Research Network <b>(CVRN)</b>                                | NHLBI         | 2008             | 15                |

# The HMORN Virtual Data Warehouse



# KP Center for Effectiveness and Safety Research (CESR)

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- \$5 million KP award to advance inter-regional research within KP – involves all 8 regions
- Will build on and greatly expand the VDW within KP, with spillover to HMORN
- A single EHR provides hope of somewhat greater data standardization
- Because governance issues are somewhat less within KP, can move toward more efficient federated data model

# **Kaiser Permanente Research Program on Genes, Environment and Health**

## Goals of the RPGEH

To build the largest and most comprehensive resource in the U.S. for research on genetic and environmental influences on health and disease. Ultimately the resource will include at least 500,000 participants with survey and genetic information. The resource links:

- Clinical data from EPIC EHR and from KP legacy systems
- Member survey data (over 400,000 KP members to date)
- Environmental data (GPS data: e.g., neighborhood air quality, crime, built environment, socioeconomic status)
- DNA specimens (saliva, blood) – currently 125,000 biospecimens have been obtained

# Timeframe and Funding

## **Kaiser Permanente Support (2005-2010)**

\$6M from National Community Benefits

\$3M from N. Ca. Regional Community Benefits

\$1.5M from other KP sources

## **Private Foundation Support (2005 – 2008)**

\$1.2M Ellison Medical Foundation (2005 – 2008)

\$3.5M Wayne and Gladys Valley Foundation (2005-2008)

\$8.6M Robert Wood Johnson Foundation (2008-2010)

## **NIH “GO” Grant**

\$24.8M Grand Opportunity Grant (9/30/2009-9/29/2011) awarded to KP and UCSF

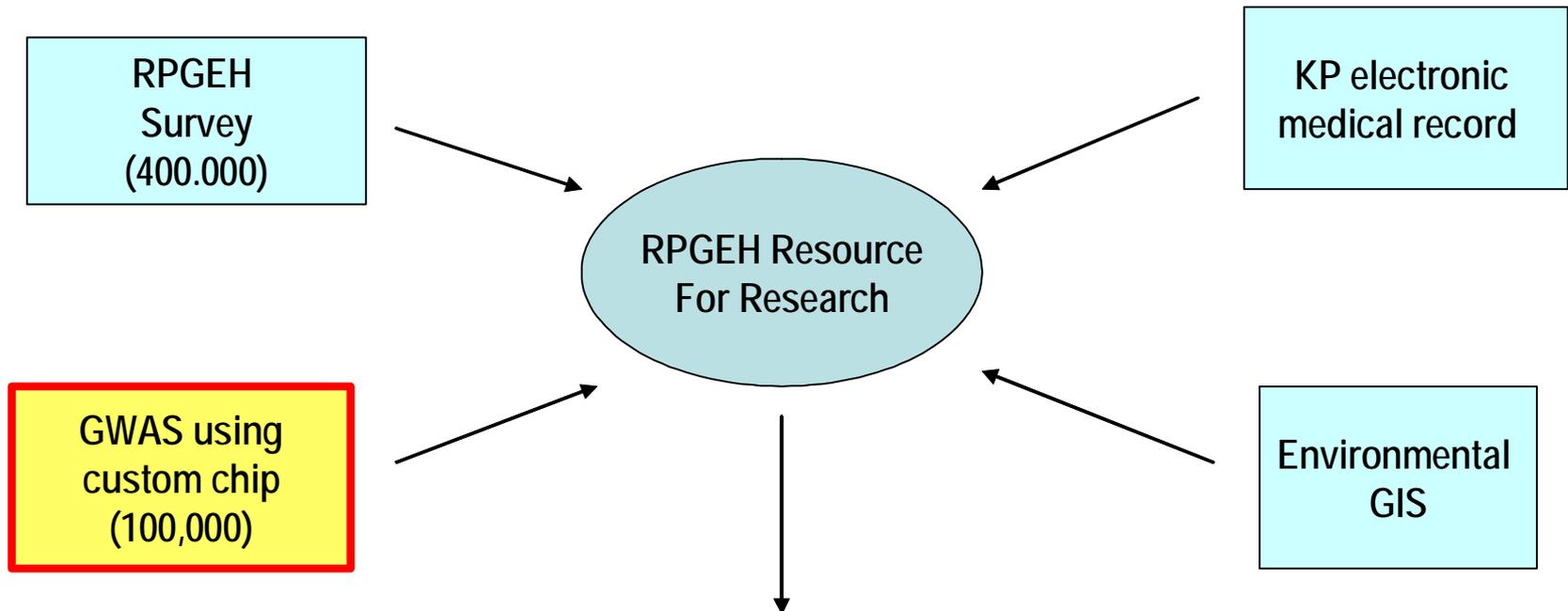
- **Phase I (Jan 2005- Dec 2007)**
  - **(Funded by KP and private foundations)**
  
- **Inform Membership**
- **Convened Community and Scientific Advisory Panels**
- **Build Database -- >50 disease specific “registries”**
- **Surveyed Membership -- to obtain demographic, environmental, and behavioral data**

## **Phase II (2008-2012)**

- **Establish KPNC Biorepository**
  - Develop laboratory, acquire samples (n~500,000), process samples for immediate use and long-term storage
  - Informed consent process for biospecimen collection
  
- **Build database of environmental exposures**
  
- **Launch research studies funded by NIH, foundations, industry**

# Research Program on Genes, Environment, and Health (RPGEH)

The GO Grant will create a resource with rich data from each of these domains -- a resource within a resource



Research studies, as approved by the KP Institutional Review Board (IRB) and the RPGEH Access Review Committee;

Genotypic and selected other data will also be used through dbGaP

## Examples of Several RPGEH Disease Registries (Counts through 2004)

|                            |         |
|----------------------------|---------|
| Asthma                     | 639,362 |
| Autism                     | 3,397   |
| Acute Coronary Syndrome    | 89,945  |
| Bipolar Disorder           | 53,153  |
| Diabetes Mellitus          | 207,098 |
| Heart Failure              | 42,289  |
| Inflammatory Bowel Disease | 10,317  |
| Stevens-Johnson Syndrome   | 69      |

# Why Doesn't KP Study More Rare Diseases?

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- The researchers who come to work at KP are attracted by the ability to do definitive studies (of more common disorders) within the KP population
- Funding supports definitive studies, studies that can be conducted within a single system
- KP as an organization takes an approach based on population “disease burden” and is more attracted to studies of more common conditions

# Finding Rare Diseases Within KP

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- Diagnoses, but also laboratory tests, laboratory results, disease-specific medications help identify patients
- ICD-9-CM, the usual diagnostic system used by KP researchers is not detailed enough to specifically identify many rare diseases
- However, EPIC has its own, much more granular diagnostic coding system; both EPIC and KP are engaged in mapping these codes to SNOMED

# Example: non-specific ICD-9 code

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## **270.3 Disturbances of branched chain amino-acid metabolism**

- Disturbances of metabolism of leucine, isoleucine, and valine
- Hypervalinemia
- Intermittent branched-chain ketonuria
- Leucine-induced hypoglycemia
- Leucinosi
- Maple syrup urine disease

# Search Using EPIC Dx Codes (KP Northern CA Only)

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| Disorder  | ICD-9 code | EPIC DX Code | # Identified |
|---|------------|--------------|--------------|
| Adrenal hyperplasia virilizing congenital Salt-losing | 255.2      | 12137010     | 56           |
| Adrenal hyperplasia virilizing congenital Salt-losing | 255.2      | 12137009     | 55           |
| Maple Syrup Urine Disease                             | 270.3      | 12015224     | 10           |
| Galactosemia  | 271.1      | 12018152     | 45           |
| Galactosemia (Duarte variant)                         | 271.1      | 12137012     | 12           |

# *Collaboration and Access*

# RPGEH Collaboration Policy

- RWJF funding focuses on supporting collaborations and access; will evaluate our success in this area.
- An Access Committee (AC) is established
- AC reviews, prioritizes applications from external scientists for use of the resource
- High priority given to proposals with an internal collaborator – because it will usually be difficult to support external researchers without an internal partner
- Nevertheless, policies recognize that such requests will sometimes merit access and support

# *IRB Concerns*

# The RPGEH Consent

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- CF is currently mailed along with request to provide a biospecimen. Saliva kit or blood test order then sent to persons who've returned the CF.
- IRB now considering a web-based consent process too.
- CF covers long-term nature of study, multiple potential uses, lack of any individual financial return if research leads to commercialized product
- CF explains that since we're looking for genes for common diseases, finding major gene effects is unlikely. But states that if we do, pts will be notified and asked whether they'd like to have the results.
- CF states that *de-identified* information, including genetic information may be shared with scientists outside of KP. We believe the IRB will concur that this language covers placement of genotypic information on DbGaP.

# KP IRB Practices

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- IRBs recognizes the safety and value of “database only” studies, including complete registries, and usually waives need for informed consent
- IRBs review patient contact materials with extreme care – these patients are also “members.” Particular concerns when patients are contacted on basis of having a condition.
- Does NOT usually require physician approval prior to contact, except for clinical trials – but this may differ for rare diseases
- Never approves direct contact of patients by non-KP researcher, but does allow KP researchers to identify and contact eligible patients to inform them of an outside study

# Conclusions

- Integrated delivery systems have potential for rapid and complete identification of patients with rare disorders
- They can serve as a vehicle for initial contact of patients and for conducting follow-up or recruitment for longitudinal studies
- Ideally, collaboration with health system-based researchers should be pursued, but this may not always be possible
- Large investigator networks – CESR, the HMORN are likely the best places to start.

***Thank You!***