The Public Health Approach to Pharmacogenomics

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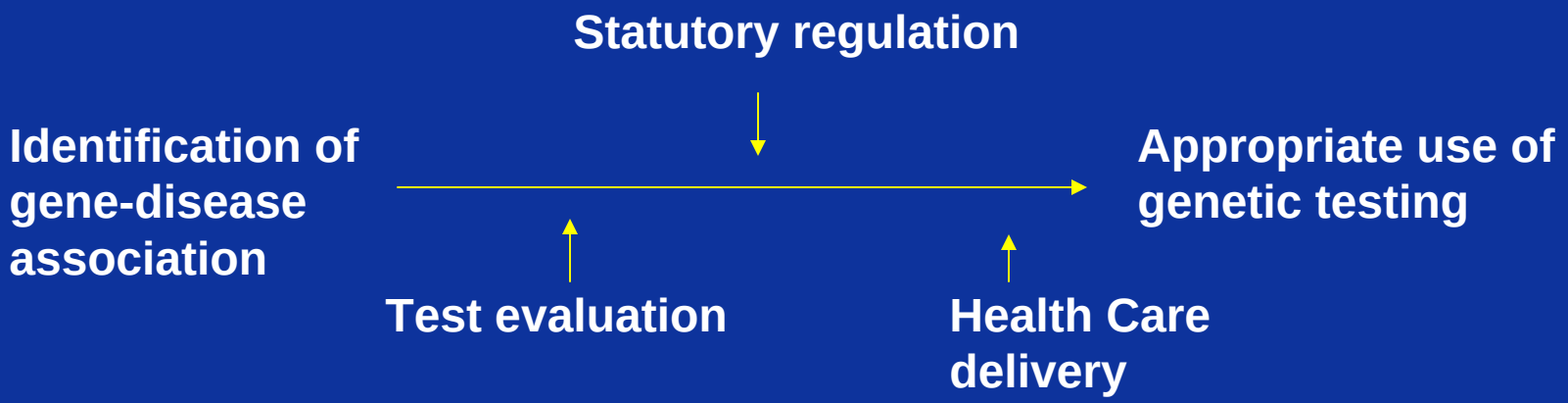
The Public Health Approach to Pharmacogenomics

Goal: Personalized delivery of therapeutics that accounts for the genetic variation of the patient

The Public Health Approach to determine the real world effectiveness of pharmacogenomics and monitor its applications

Genetic Tests



Pharmacogenomics

The Public Health Approach to Pharmacogenomics

Clinical development (Basic science)

- **Bench research**
  - **Phase I,II, III trials**
  - **Response, safety, efficacy**
  - **Clinical trials**

Clinical application (Public health)

- **Effectiveness in ‘real-world’ (including generalizability)**
- **Monitoring of real world applications**

The Public Health Approach to determine the real world effectiveness of pharmacogenomics and monitor its applications

Evidence Of Effectiveness → **Integrating Evidence** → **Surveillance**

What is evidence?

The basic science approach:

- **Inhaled beta-adrenergic agonists most commonly used medication for asthma treatment**
- **Regular use may produce adverse effects in some patients.**
- **Polymorphisms of the beta(2)-adrenergic receptor (beta(2)-AR) appears to play role in responsiveness**
- **Pts homozygous for arginine at B(2)-AR-16 (Arg/Arg) appear to respond differently (poorly) to regular use of albuterol (Israel, Drazen, Liggett, et al. Am J Respir Crit Care Med. 2000 162:75-80)**

- **The basic science approach addresses the evidence about how albuterol and genes work together to affect lung function**

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What is evidence?

The public health approach:

- Polymorphisms of the beta(2)-adrenergic receptor (beta(2)-AR) appear to play role in responsiveness

- Does this polymorphism affect measurable clinical outcomes?
  - Increased morbidity/mortality among treated asthmatics?
  - Increased costs of health care among treated asthmatics?
  - Decreased quality of life among treated asthmatics?

- The public health approach asks, given that albuterol and genes work together to affect lung function, does it matter?

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The public health approach:

- **Do polymorphisms of beta(2)-AR affect measurable clinical outcomes?**
  - **Increased morbidity/mortality, costs, and/or decreased quality of life**

- **What happens**
  - **With drug interactions** — **i.e. albuterol and prednisone/fluticasone**
  - **Elderly** — **i.e. diminished lung function**
  - **Pediatrics** — **i.e. different disease?**
  - **Different ethnic groups** — **i.e. gene-gene-drug interactions**

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The public health approach:

How would we go about collecting information on measurable clinical outcomes (morbidity/mortality) in a diverse population (elderly, children, different ethnicities)?

- **Observational studies**
- **Randomized clinical trials (RCTs)**
- **Large practical trials (PCTs)**
- **(Biobanks)**

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Observational (cohort or case-control) studies

beta(2)-AR ++

	Asthma (Rate of) good outcome	Asthma (Rate of) bad outcome
(%) albuterol +	a	b
(%) albuterol -	c	d

beta(2)-AR --

	Asthma (Rate of) good outcome	Asthma (Rate of) bad outcome
(%) albuterol +	a	b
(%) albuterol -	c	d

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Observational (cohort or case-control) studies

beta(2)-AR ++		Asthma	
		(Rate of) good outcome	(Rate of) bad outcome
	(%) albuterol +	a	b
	(%) albuterol -	c	d
beta(2)-AR --		Asthma	
		(Rate of) good outcome	(Rate of) bad outcome
	(%) albuterol +	a	b
	(%) albuterol -	c	d

Advantage : Data is easily available (relatively)
Comparison by gene group is relatively unbiased

Disadvantage: Sample size limitations when stratifying additionally by elderly, by children, by other medications, by ethnic groups, etc

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Randomized Clinical Trials allow you to enroll based on gene status

beta(2)-AR ++ — **Asthma**

	(Rate of) good outcome	(Rate of) bad outcome
(%) albuterol +	a	b
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beta(2)-AR -- — **Asthma**

	(Rate of) good outcome	(Rate of) bad outcome
(%) albuterol +	a	b
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Randomized Clinical Trials allow you to enroll based on gene status

Disadvantages:

- **typically RCTs have enrolled healthy patients, often limited to those on monotherapy.**
- **Often minimal generalizability**
- **Can stratify additionally by elderly, by pediatrics, by other medications, by ethnic groupings, etc, but size requirements may get very large**

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Randomized Clinical Trials allow enrollment based on gene status

Problems with generalizability and sample size requirements has led to concept of
Large Practical Clinical Trials

Objective: To enroll many (>100,000) people in trial randomized at patient (or clinic/provider) level

Will allow for head to head comparisons of commonly used medications

For pharmacogenomics, can study not only

"does statin A work better than statin B", but also

"are there haplotypic 'groups' whereby statin A works best for haplotypic group A, while statin B works best for haplotypic group B"?

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Large Practical Clinical Trials

Head to head comparisons of commonly used medications

- **Can study not only "does statin A work better than statin B", but also**
  - **"are there haplotypic 'groups' whereby statin A works best for haplotypic group A, while statin B works best for haplotypic group B"?**

Utilizing the natural experiments among large numbers:

- **Can also study these genetic differences in drug effectiveness among risk groups (elderly, pediatrics, etc)**
- **Can look at interactions with other genes, other medications**

Advantage: studies looks at drug, gene and system effects

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Evidence Of Effectiveness → **Integrating Evidence** → **Surveillance**

- All types (observational, RCT, LPCT) have benefits and drawbacks
- What type of system is necessary for collecting evidence of effectiveness?

NEEDS:

Network of Researchers	Organizations	IRBs	Data
Clinical researchers	MCOs		
Epidemiologists	BCBS/United	Standards	Standards
Biostatisticians	Medicare/aid		
Trialists	VA		

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Systematic analyses of drug/test effectiveness

- Relies primarily on format of systematic reviews/meta-analyses
- Incorporating evidence from RCTs, observational studies

NEEDS:

EGAPP (Evaluation of Genomic Applications in Public Practice)

- Priority setting for topics
- Standardized format for collecting, analyzing and publishing findings

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Evidence Of Effectiveness → Integrating Evidence → Surveillance

U.S. research enterprise has failed miserably in integrating evidence into clinical practice (Califf, 2005)

Cochrane Collaboration – synthesis and collection of evidence

AHRQ TRIP program – translating research into practice

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Evidence Of Effectiveness → **Integrating Evidence** → **Surveillance**

Assuming evidence is strong that knowing beta(2)-AR status among asthmatics improves outcome, what is the best way to get this evidence integrated into practice?

Old way: Doctor education – better testing
Patient education – better knowledge
Academic detailing – high cost, temporary effects
Private detailing – directed change, not PH focused

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Evidence Of Effectiveness → **Integrating Evidence** → **Surveillance**

Assuming evidence is strong that knowing beta(2)-AR status among asthmatics improves outcome, what is the best way to get this evidence integrated into practice?

New movement (long overdue) to perform RCTs or quasi-experimental designs as a means to test the best way to integrate evidence into practice

Example: Usual care vs.

Electronic reminder within electronic health record (EPIC) with automatic ordering of gene status based on diagnosis or prescribing behavior

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Evidence Of Effectiveness → **Integrating Evidence** → **Surveillance**

- RCTs or quasi-experimental designs
- What type of system is necessary to get evidence integrated into practice?

NEEDS:

Network of Researchers	Organizations	IRBs	Data
↓	↓	↓	↓
Clinical researchers	MCOs		
Health care researchers	BCBS/United	Standards	EMR development
Biostatisticians	Medicare/aid		
	VA		

Public Health Approach to the real world effectiveness of pharmacogenomics

Evidence Of Effectiveness → **Integrating Evidence** → **Surveillance**

- **Quality measures**
- **Ethics**
- **Safety**

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Evidence Of Effectiveness → Integrating Evidence → Surveillance

- Quality measures
  - Example: Among subjects with asthma,
    - % tested for beta(2)-AR
    - % placed on appropriate medications (conditional on genetic results)

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Evidence Of Effectiveness → Integrating Evidence → Surveillance

- Ethics
  - Genetic discrimination/exceptionalism
    - Decreased access to/timeliness of service
    - Loss of insurance
  - Inappropriate use of tests
    - Wrong population
    - Incomplete counseling
  - Unintended outcome(s)

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Evidence Of Effectiveness → **Integrating Evidence** → **Surveillance**

- **Safety**

Vaccine model:

- VAERS reporting
- VSD (population & denominator based collaborative project)
- Future: registry
  - buccal swabs for DNA
  - candidate gene generation

Pharmaceutical model

- AERS reporting
- CERT and other population based collaborative projects
- Future?: registry
  - buccal swabs for DNA
  - candidate gene generation

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Evidence Of Effectiveness → **Integrating Evidence** → **Surveillance**

- Quality measures; safety; ethics
- What type of system is necessary to for proper ‘surveillance’?

NEEDS:

Network of Researchers	Organizations	IRBs	Data
↓	↓	↓	↓
Safety researchers	MCOs		
Health care researchers	BCBS/United	Standards	EMR development
Ethics researchers	Medicare/aid		
	VA		

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Have assumed availability of data in electronic format

- to collect evidence
- to conduct trials of integrating evidence into care
- to provide information to guide/monitor clinical care
  - prescribing – pop-up alerts
  - family history – “”
  - high risk conditions – “”

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Electronic Health Record

Have assumed availability of data in electronic format

- to collect evidence
- to study integration trial
- to provide information to guide/monitor clinical care
  - prescribing – pop-up alerts
  - family history – “”
  - high risk conditions – “”

Standardization of data

- collection
- processing
- structure
- security
- transmission

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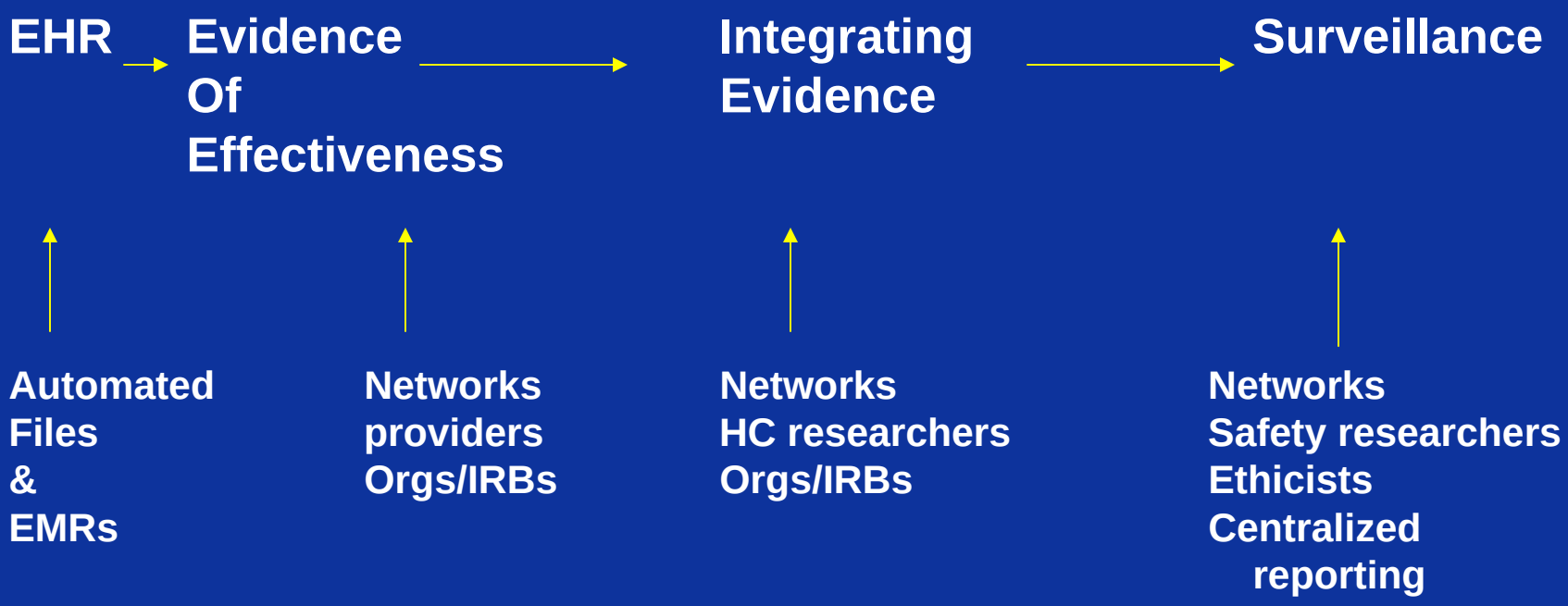

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Creating the system:

Funding: FDA, AHRQ, NIH, CDC, Pharma, Insurers

Legislation/Standards: FDA/CDC, Insurers

EHR → **Evidence Of Effectiveness** → **Integrating Evidence** → **Surveillance**

- **Automated Files & EMRs**
- **Networks providers Orgs/IRBs**
- **Networks HC researchers Orgs/IRBs**
- **Networks Safety researchers Ethicists Centralized reporting**

There are no challenges, only solutions