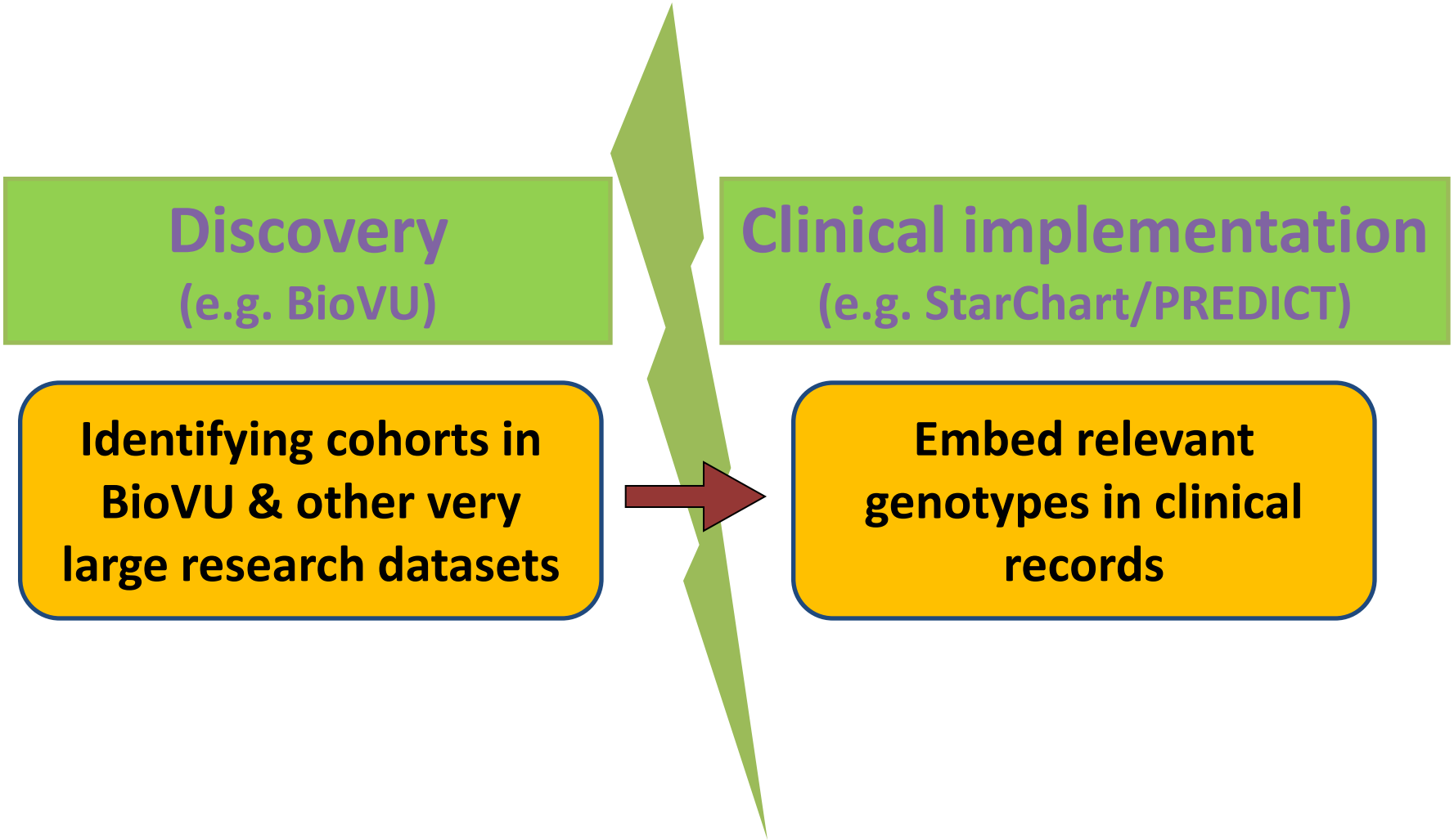
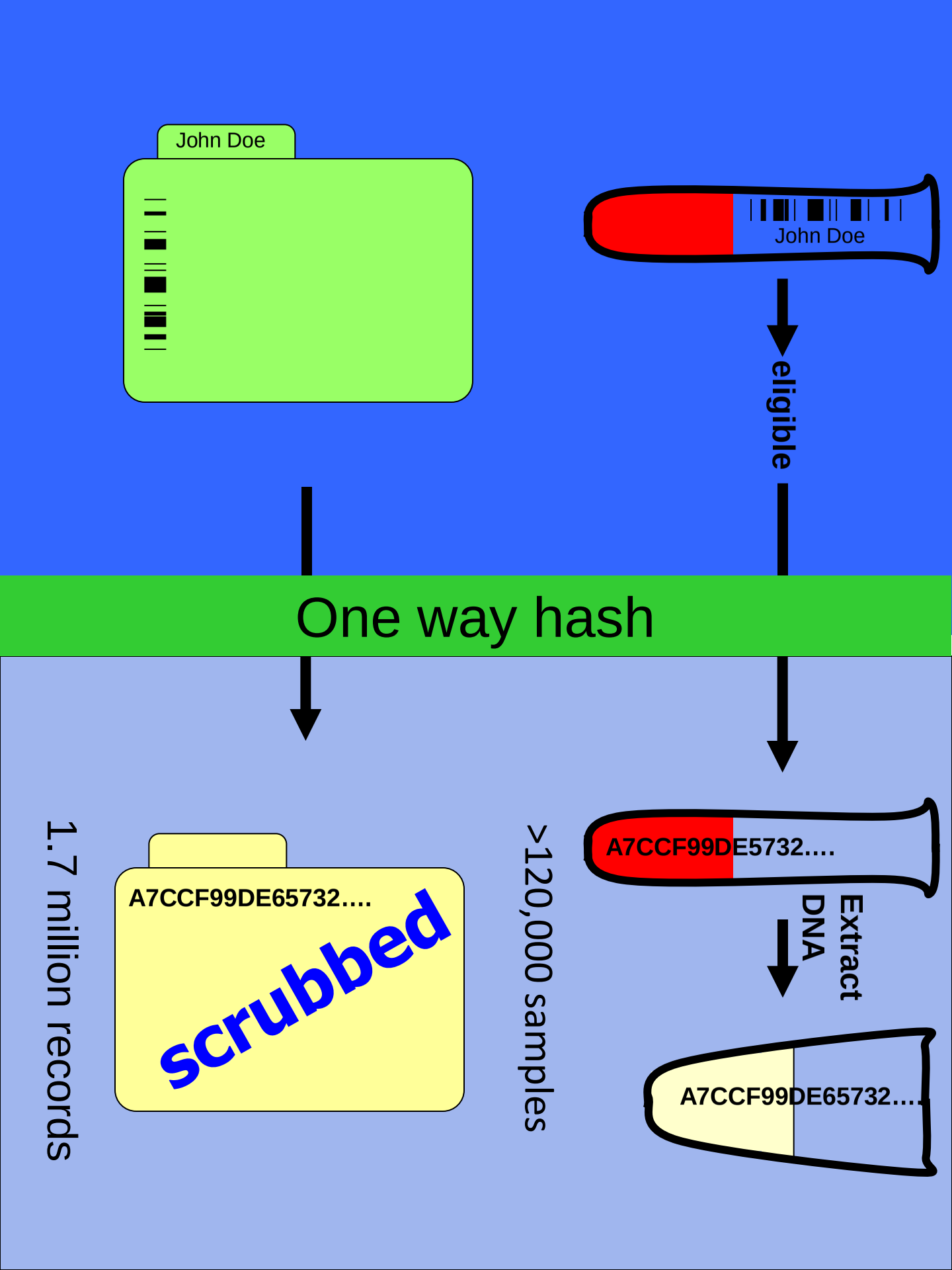
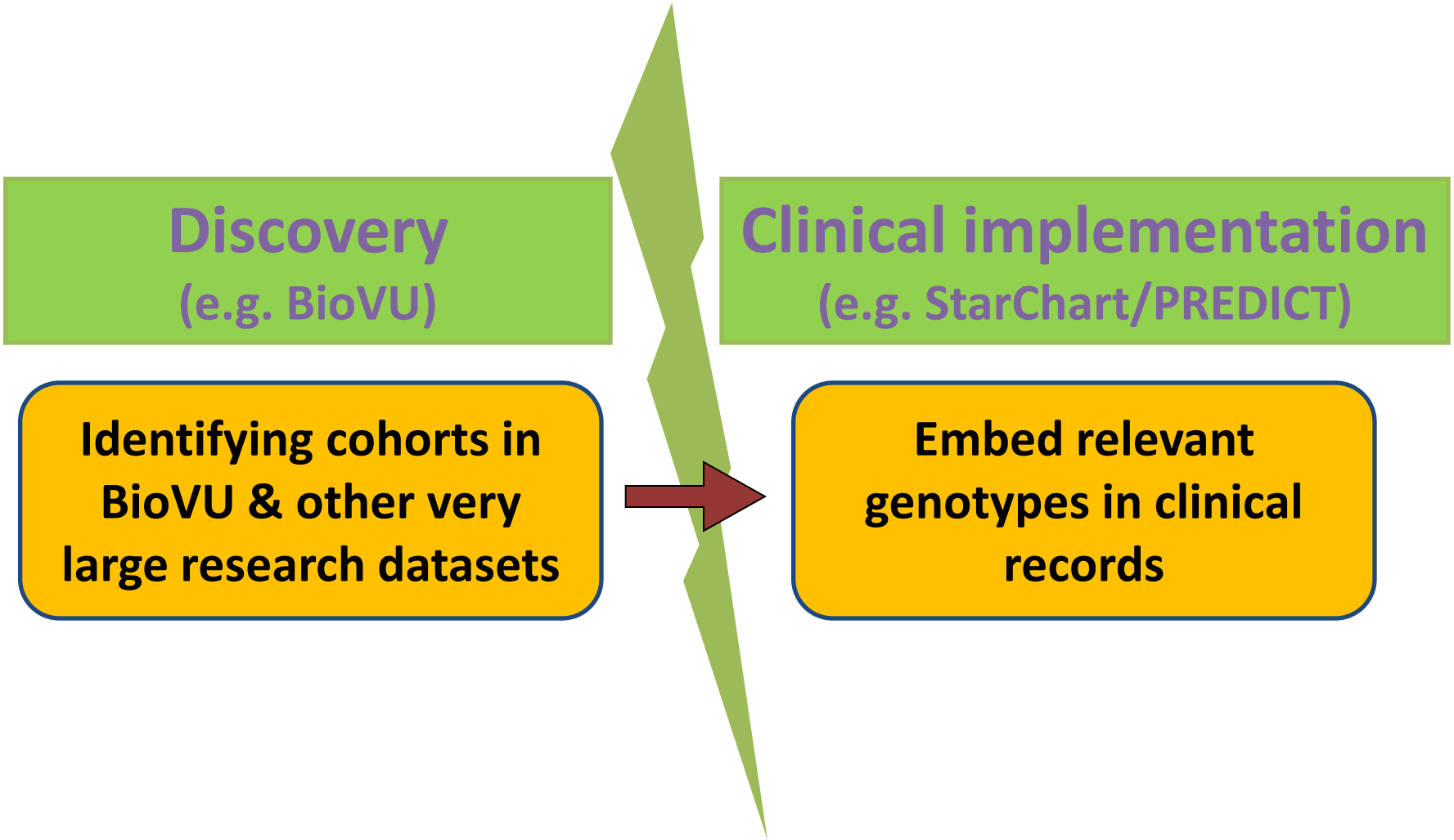
Genomics and Personalized Medicine at Vanderbilt University: Goals, Challenges, and Successes

Ellen Wright Clayton, MD, JD


Discovery
(e.g. BioVU)
Clinical implementation
(e.g. StarChart/PREDICT)
Identifying cohorts in BioVU & other very large research datasets
Embed relevant genotypes in clinical records

(bright line….)


John Doe
John Doe
eligible
One way hash
A7CCF99DE65732....
scrubbed
1.7 million records
>120,000 samples
A7CCF99DE5732....
Extract DNA
A7CCF99DE65732....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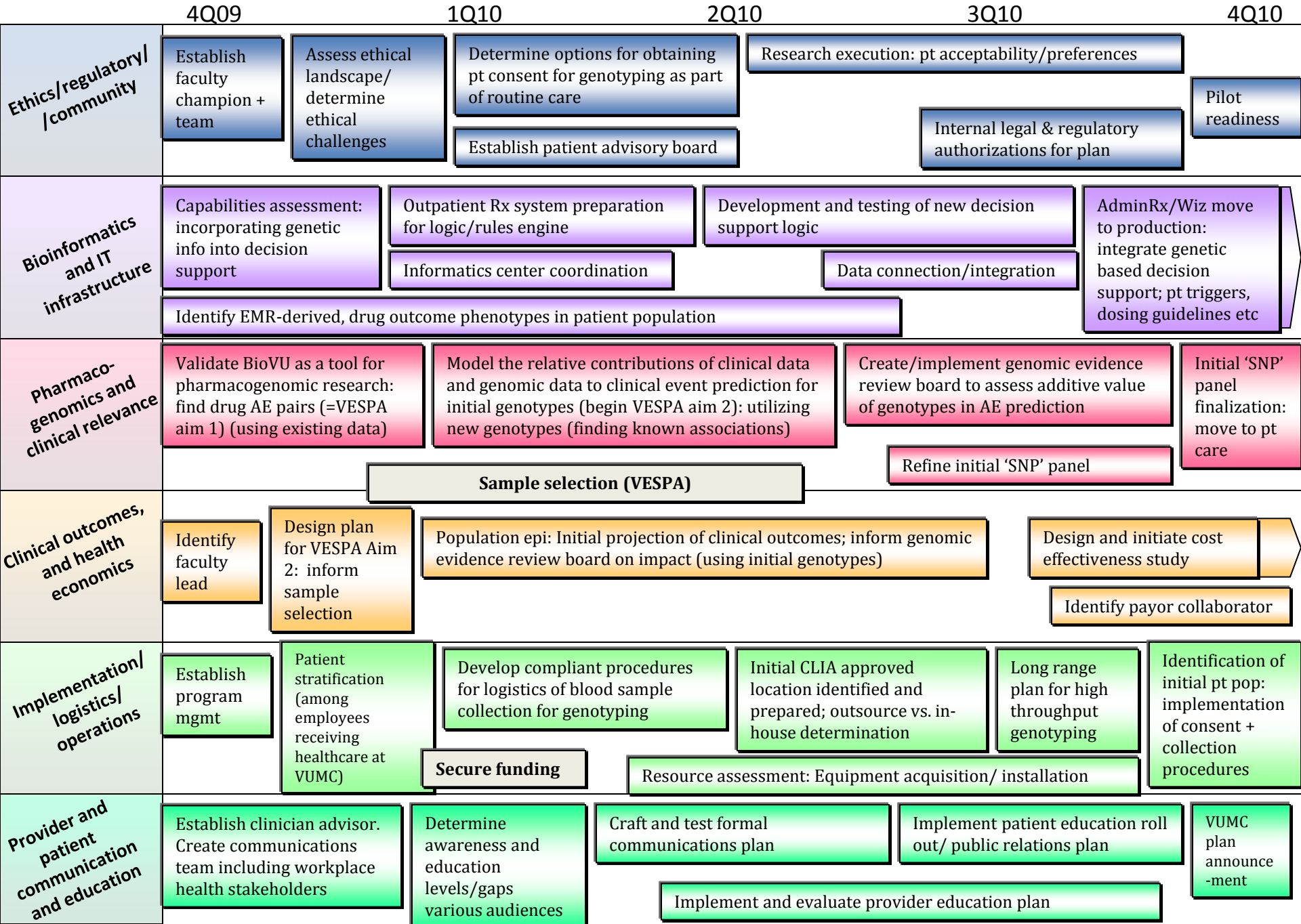
What does clinical implementation take?

- Commitment by health care system
- CLIA approved test
- IT support
- Clinician education
- Patient education and acceptance
- Follow up for both clinicians and patients

Large scale, real world pilot of personalized prescribing



Clopidogrel (Plavix) label revision March 2010

WARNING: DIMINISHED EFFECTIVENESS IN POOR METABOLIZERS

See full prescribing information for complete boxed warning.

- **Effectiveness of Plavix depends on activation to an active metabolite by the cytochrome P450 (CYP) system, principally CYP2C19. (5.1)**
- **Poor metabolizers treated with Plavix at recommended doses exhibit higher cardiovascular event rates following acute coronary syndrome (ACS) or percutaneous coronary intervention (PCI) than patients with normal CYP2C19 function. (12.5)**
- **Tests are available to identify a patient's CYP2C19 genotype and can be used as an aid in determining therapeutic strategy. (12.5)**
- **Consider alternative treatment or treatment strategies in patients identified as CYP2C19 poor metabolizers. (2.3, 5.1)**

CYP2C19*1/*2 and CYP2C19*2/*2

Implementation for clopidogrel

- Patients who are undergoing cardiac catheterization
- Focus groups with patients
- Education of providers
- Development of IT support
- Clinical consent

PREDICT Focus Group Study

- Phase 1 Focus Groups
  - Patients really like pharmacogenomics
  - Genetics → susceptibility, cost
  - GINA → Does not reassure patients
  - Detail of consent
    - Pharmacogenomics = quick verbal consent
    - Genetic susceptibility = formal written consent

PREDICT Focus Group Study

- Phase 2 Focus Groups
  - Range of perspectives on learning about genetic disease susceptibility
    - Family history goes both ways
    - Many patients want “everything.”
    - Definition of “everything” is *very* unclear.
  - Patients want to get to have control over which results they find out
  - Understanding of statistical risk varies, understanding of quality of evidence varies

Displaying results

- Caution
- Slow metabolizer
- Recommend use prasugrel

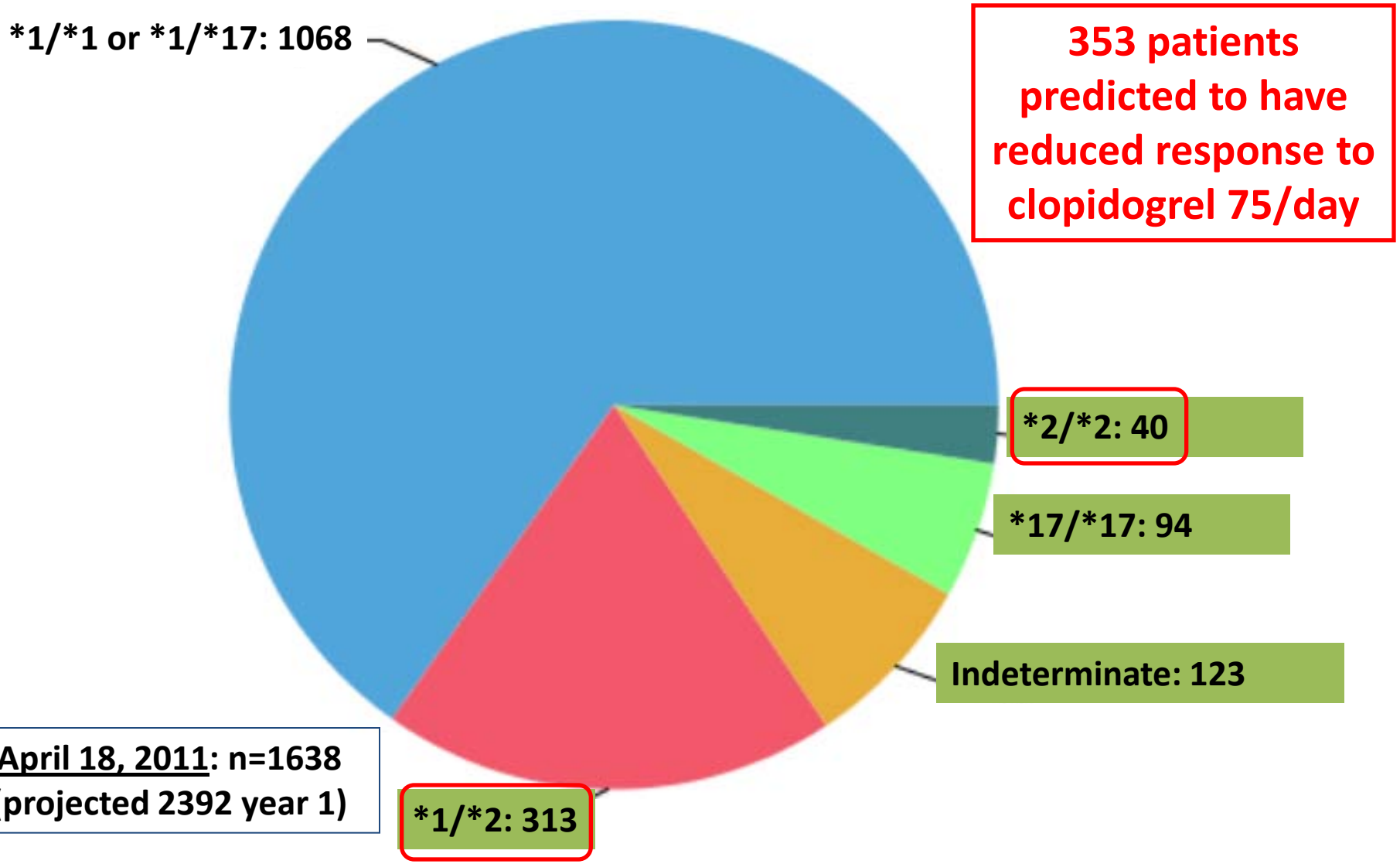
OR

- Caution
- Slow metabolizer
- CYP2C19*2/*2
- Recommend use prasugrel

Why might this matter?

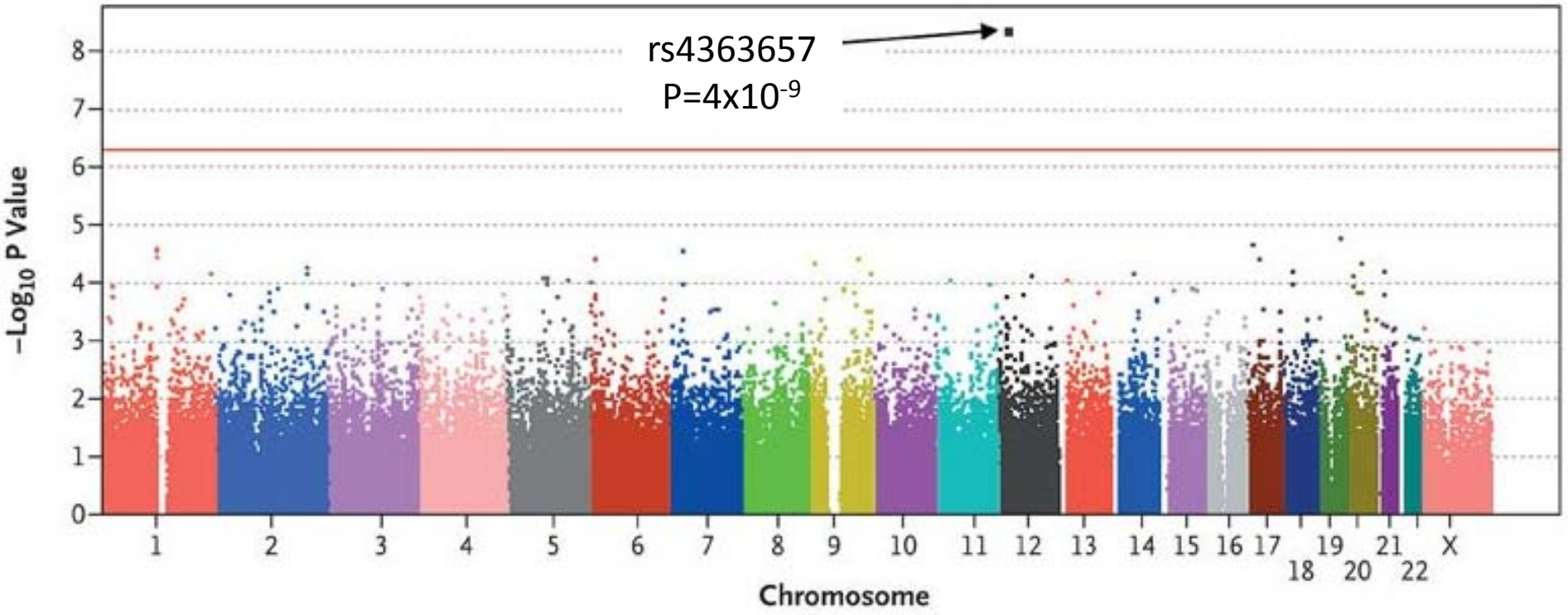
*2/*2 may be associated with esophageal cancer and AML as well as essential tremor

Startup Sept. 22, 2010 initial *CYP2C19* data



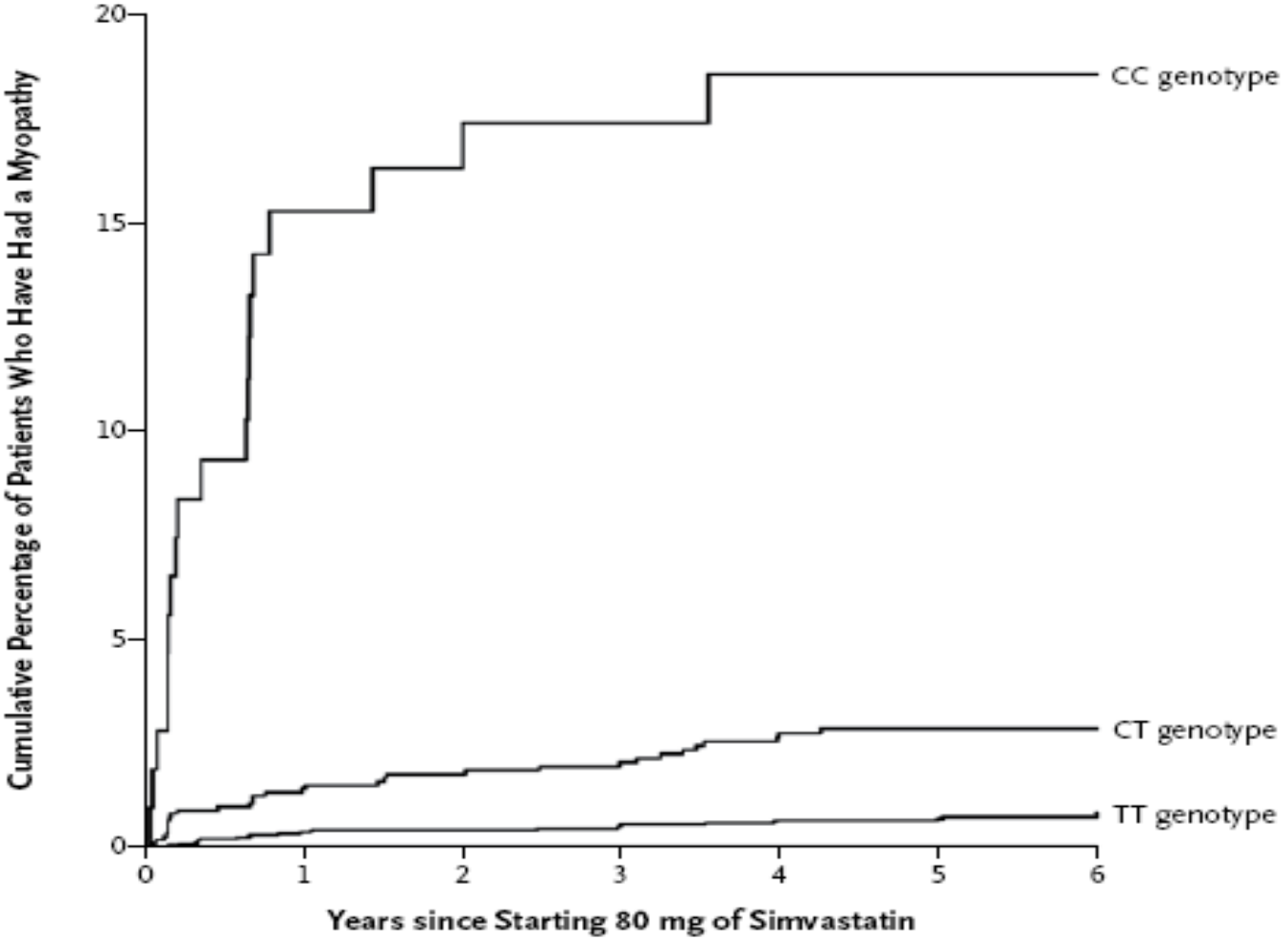
A next step

A GWA marker for statin-induced myopathy



rs4363657 is close to, and "tags" (i.e. is in the same linkage block as), a non-synonymous SNP in the drug transporter gene *SLCO1B1*. The encoded transporter is known to be responsible for simvastatin uptake into the liver.

SEARCH collaborative group
NEJM, August 2008



Genotype	Population Frequency	Cumulative No. and Percentages with Myopathy							
		Year 1				Year 5			
				Attributable to gentoype				Attributable to gentoype	
		no.	%	*no.*	*% of total*	*no.*	%	*no.*	*% of total*
TT	0.730	12	0.34	0	0	21	0.63	0	0
CT	0.249	17	1.38	12.8	75	32	2.83	24.9	78
CC	0.021	16	15.25	15.6	98	19	18.55	18.4	97
All genotypes	1.000	45	0.91	28.4	63	72	1.56	43.3	60

Early steps in implementation for simvastatin

- CTSA studio
- New challenges include
  - Expansion to primary care setting
    - Differential use of high doses of simvastatin
  - Less obvious action for patients with high risk genotype
    - What to do about people who had been on 80 mg for a while?

Some predictions

- Genome wide tests will become part of clinical care in the near future
- Access to this information will be difficult, if not impossible, to limit
  - Attributable only in part to DTC tests
- Interpretation will not be limited to medical settings or to clinicians well versed in genetics
  - Democratization of knowledge

The future?

- Francis Collins is “almost certain . . . that complete genome sequencing will become part of newborn screening in the next few years.”

  The Language of Life: DNA and the Revolution in Personalized Medicine. New York, NY, Harper Collins (2010) at 208

- “If you have the [sequence in the EMR], it will be hard, I think, to say that this is not a good thing. And once you've got the sequence, it's not going to be terribly expensive. And it should improve outcomes and reduce adverse events.”

  NEJM 2009; 361:1321-1323

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The real issues –
When the information is available

- Developing a policy consensus about when not to act upon research results and genomic information
  - More weight will need to be given to practice guidelines and comparative effectiveness analyses
  - These will be backed up by payer policies and economic incentives for clinicians

The real issues –
When the information is available

- Patients' and research participants' desires for medical interventions likely will not be determinative in many cases
  - Challenges the clinician-patient relationship
    - Increases likelihood of conflict rather than collaboration
  - Requires defining those domains in which clinicians ought to say no to requests and why
- These are not new issues but are raised with increased acuity