

The Sentinel Network

Development of a True Post-marketing Pharmacovigilance System

A Path Through the Forest

March 7-8, 2007

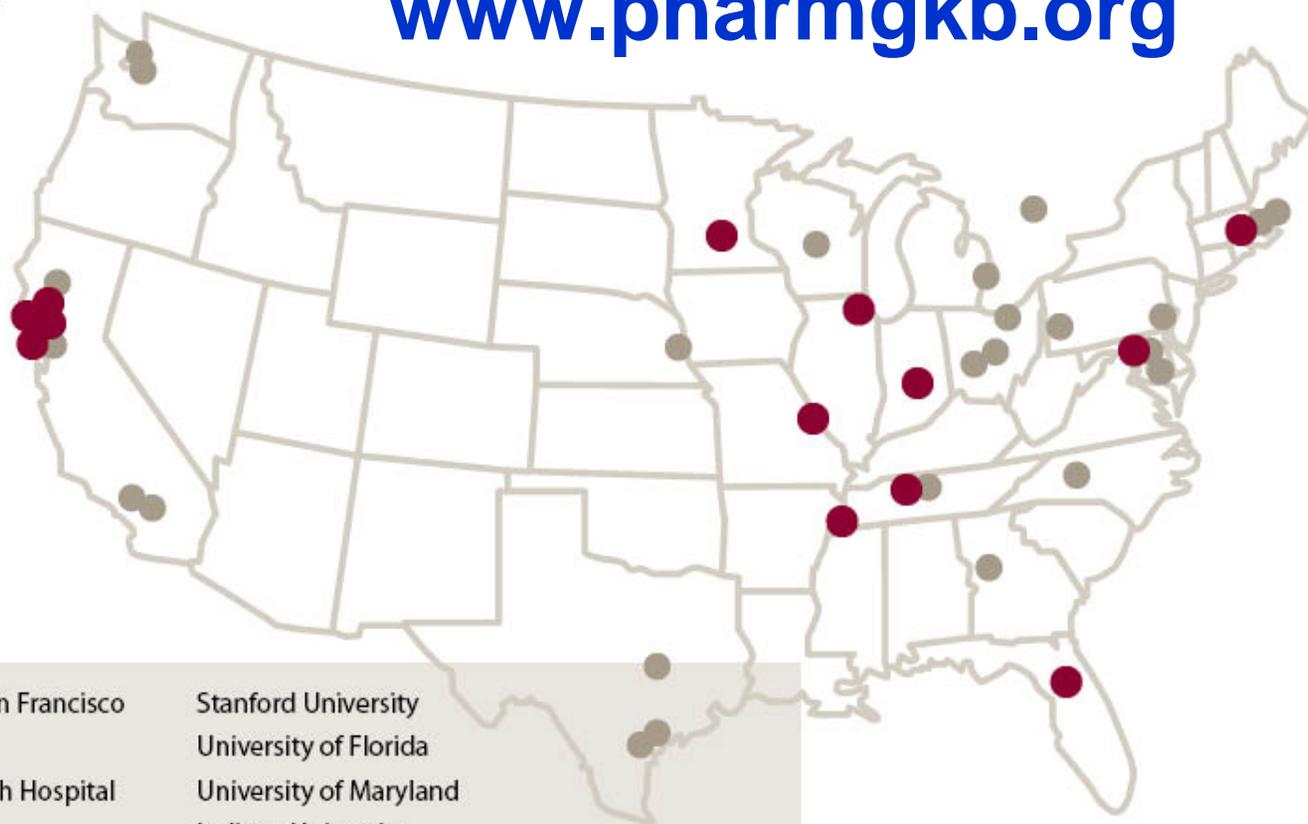
Requirements for Pharmacovigilant System

- **Electronic Definition of ADR**
- **Ongoing Population Based Estimate of Incidence of ADR's**
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NIH Funding Institutes

NIGMS
NHLBI
NIDA
NCI
NIEHS
NIMH
NHGRI
NLM
ORWH

www.pharmgkb.org



University of California, San Francisco
University of Chicago
St. Jude Children's Research Hospital
Mayo Clinic
Vanderbilt University
Washington University
SRI International

Stanford University
University of Florida
University of Maryland
Indiana University
Brigham and Women's Hospital
Children's Hospital of Oakland Research Institute

● Primary Investigator Site
● Co-Investigator Site



NIGMS leading the initiative, investing >\$16 M/ year

NHLBI major contributor, investing >\$9 M/ year

NIDA & NCI investing >\$1M/ year

**NIEHS, NIMH, NHGRI,
NLM & ORWH** contributors at \$0.5 M/ year or less

Research In PGRN Is Diverse



National Institutes of Health
U.S. Department of Health & Human Services

Areas of Research

Cardiovascular



Pharmacogenomic Evaluation of the Antihypertensive Response (PEAR)

Julie A. Johnson, Pharm.D., University of Florida

Pharmacogenomics and Risk of Cardiovascular Disease (PARC)

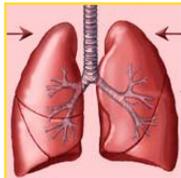
Ronald M. Krauss, M.D., Children's Hospital Oakland Research Institute

Pharmacogenomics of Arrhythmia Therapy (PAT)

Dan M. Roden, M.D., Vanderbilt University

Amish Pharmacogenomics of Antiplatelet Intervention Study (PAPI)

Alan R. Shuldiner, M.D., University of Maryland



Pulmonary

Pharmacogenetics of Asthma Treatment (PHAT)

Scott T. Weiss, M.D., Brigham and Women's Hospital



Addiction

Pharmacogenetics of Nicotine Addiction and Treatment (PNAT)

Neal L. Benowitz, M.D., University of California at San Francisco
Huijun Ring, Ph.D., SRI International

Cancer

Consortium on Breast Cancer Pharmacogenomics (COBRA)

David A. Flockhart, M.D., Ph.D., Indiana University

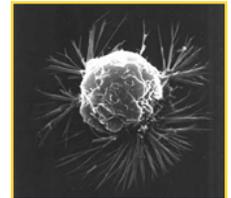
Comprehensive Research on Expressed Alleles in Therapeutic Intervention (CREATE)

Howard L. McLeod, Pharm.D., Washington University

Pharmacogenetics of Anticancer Agents Research Group (PAAR)

Mark J. Ratain, M.D., University of Chicago

Mary V. Relling, Pharm.D., St. Jude Children's Hospital



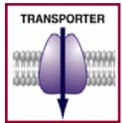
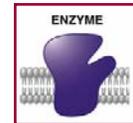
Metabolism/Transport

Pharmacogenetics of Membrane Transporters (PMT)

Kathleen M. Giacomini, Ph.D., University of California, San Francisco

Pharmacogenetics of Phase II Drug Metabolizing Enzymes (PPII)

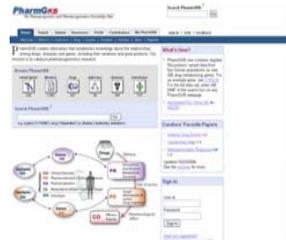
Richard M. Weinshilboum, M.D., Mayo Clinic



Informatics

PharmGKB: Catalyzing Research in Pharmacogenetics

Russ B. Altman, M.D., Ph.D., Stanford University



Establish Phenotypic Criteria To Ascertain Cases of Adverse Drug Reactions

Drug Induced Liver Toxicity

Statin Induced Myopathy

Drug Induced Renal Toxicity

Torsades de Pointes

PGRN Adverse Drug Reactions Working Group

Co-chairs: Dan Roden, M.D. and Ronald Krauss, M.D.

**Goal: To facilitate studies of genetic risk factors for
adverse drug reactions.**

Example:

Criteria For Ascertainment of Rhabdomyolysis

Discharge diagnosis code: (ICD-9-CM).

Admitting diagnosis: Evidence from medical record of severe muscle injury.

Elevation of creatine kinase level to more than 10 times the upper limit.

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Marshfield Epidemiologic Study Area

Resource for population-based health research

80,000 people, stable population

60-70% participation in studies

Northern European origin

Many families have lived in MESA for many generations

MESA CENTRAL

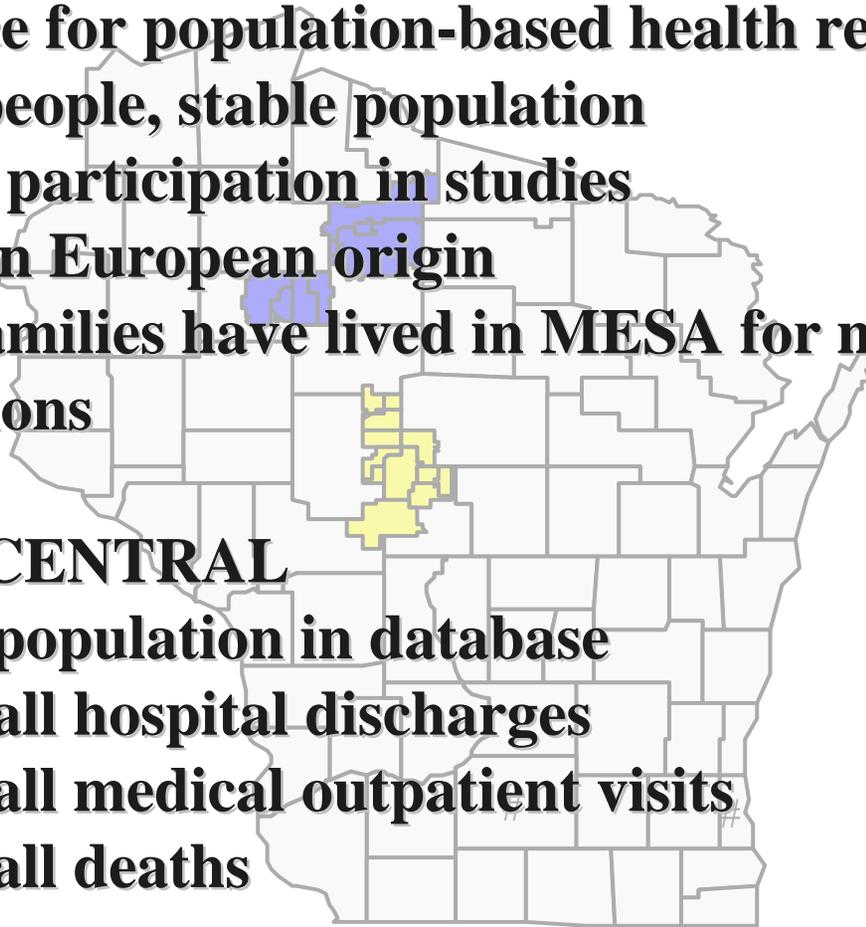
95% of population in database

94% of all hospital discharges

92% of all medical outpatient visits

99% of all deaths

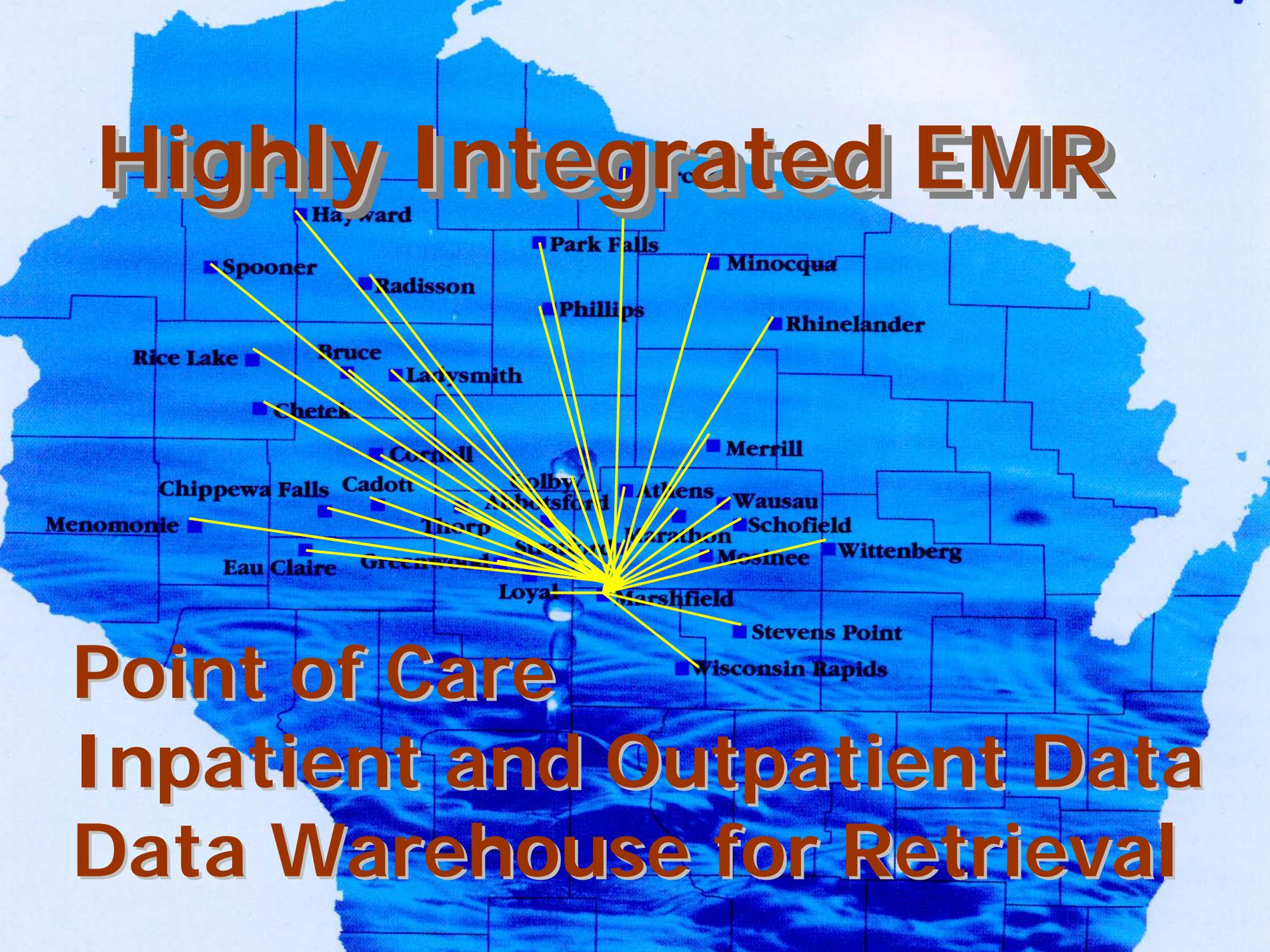
Central  North 



Marshfield Epidemiological Study Area

- Allows Accurate Evaluation of Population Based Incidence and Prevalence of Disease**
- “Syndromic Surveillance” Using the Highly Sophisticated and Integrated EMR**
- Ability to Detect a Change in the Incidence of a Defined Syndrome in the Clinic Population as Different from the Reference Population**

Highly Integrated EMR



Point of Care

Inpatient and Outpatient Data

Data Warehouse for Retrieval

Marshfield Clinic's EMR

- **Began in the early 1960's with electronic lab data**
- **Since 1975 joint inpatient and outpatient records**
- **All outpatient and inpatient healthcare tracked electronically since early 1980's**
- **Currently tracks all healthcare activities clinical data, FMH, patient medical history, lab, procedures, radiology, pathology, medications, etc, inpatient and outpatient.**
- **Event driven, updated with each new medical appointment**

EMR Status

- 1,623 total users system wide
- 2,376 procedure terms with 29,838 code rules
- 18,729 diagnoses with 44,920 code rules
- Over 1,800,000 visits in 2006
- Over 1,200,000 total electronic records

PMRP Population Construct



MARSHFIELD CLINIC

Where the future of medicine lives

Annual Unique Patients ~400,000

**All MC Health Care
Events Captured
Electronically**

**~1,800,000 Visits
~1,200,000 Electronic
Records**

**MESA
~80,000**

**PMRP
~20,000**

**All Health Care
At MC**

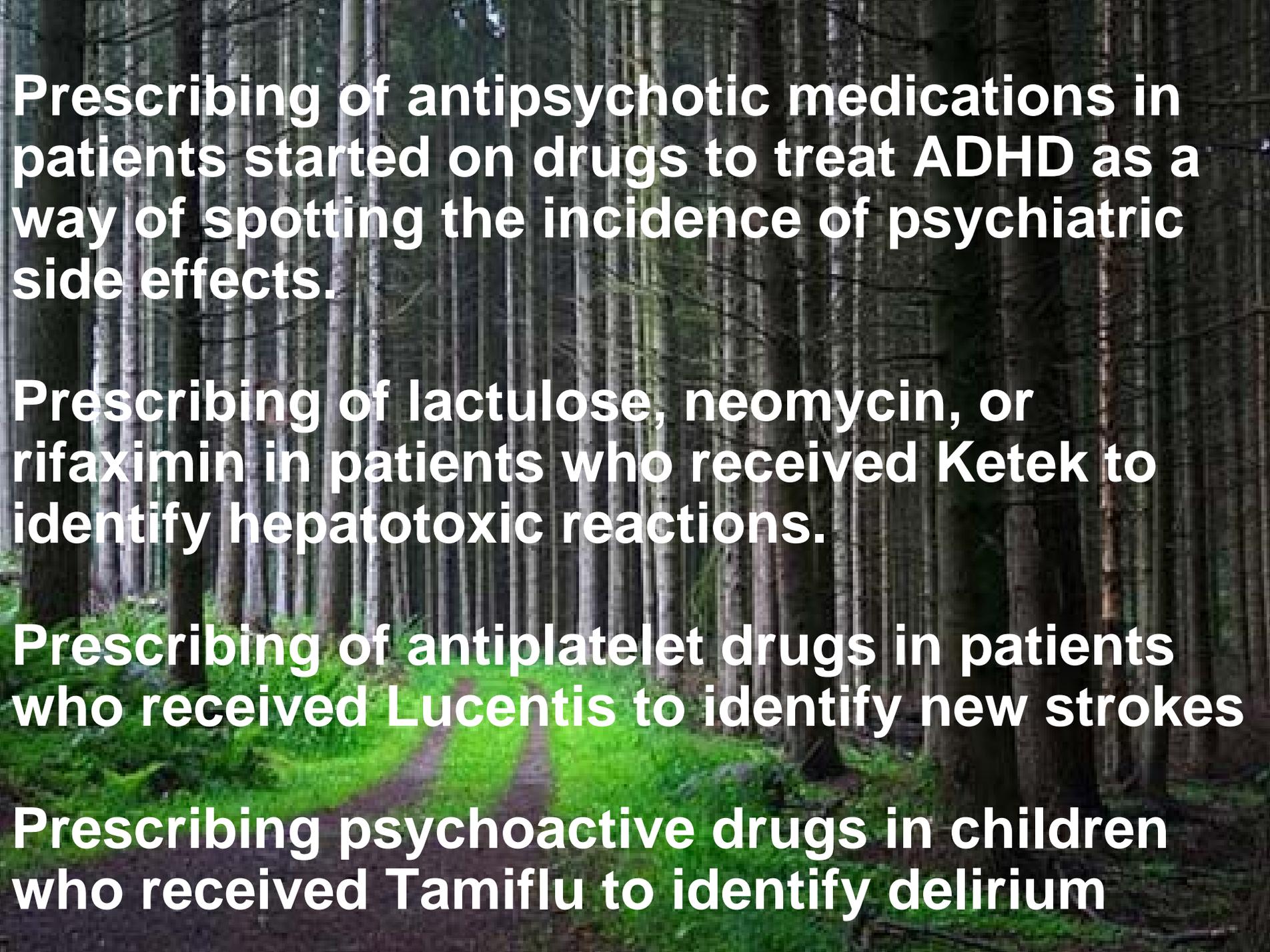
**Donated DNA,
Serum, Plasma
Access To Health
Records
IRB Approval of
Projects**

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- Administers public and private employer plans of all sizes, health plans, labor unions, government agencies and individuals served by Medicare Part D
- Medco serves approximately **60 million lives**
- Prescriptions filled in Medco mail service pharmacies in 2006 totaled **89 million**
- Prescription claims processed in 2006 totaled **553.4 million**
- About **60,000 pharmacies** participate in Medco retail pharmacy networks

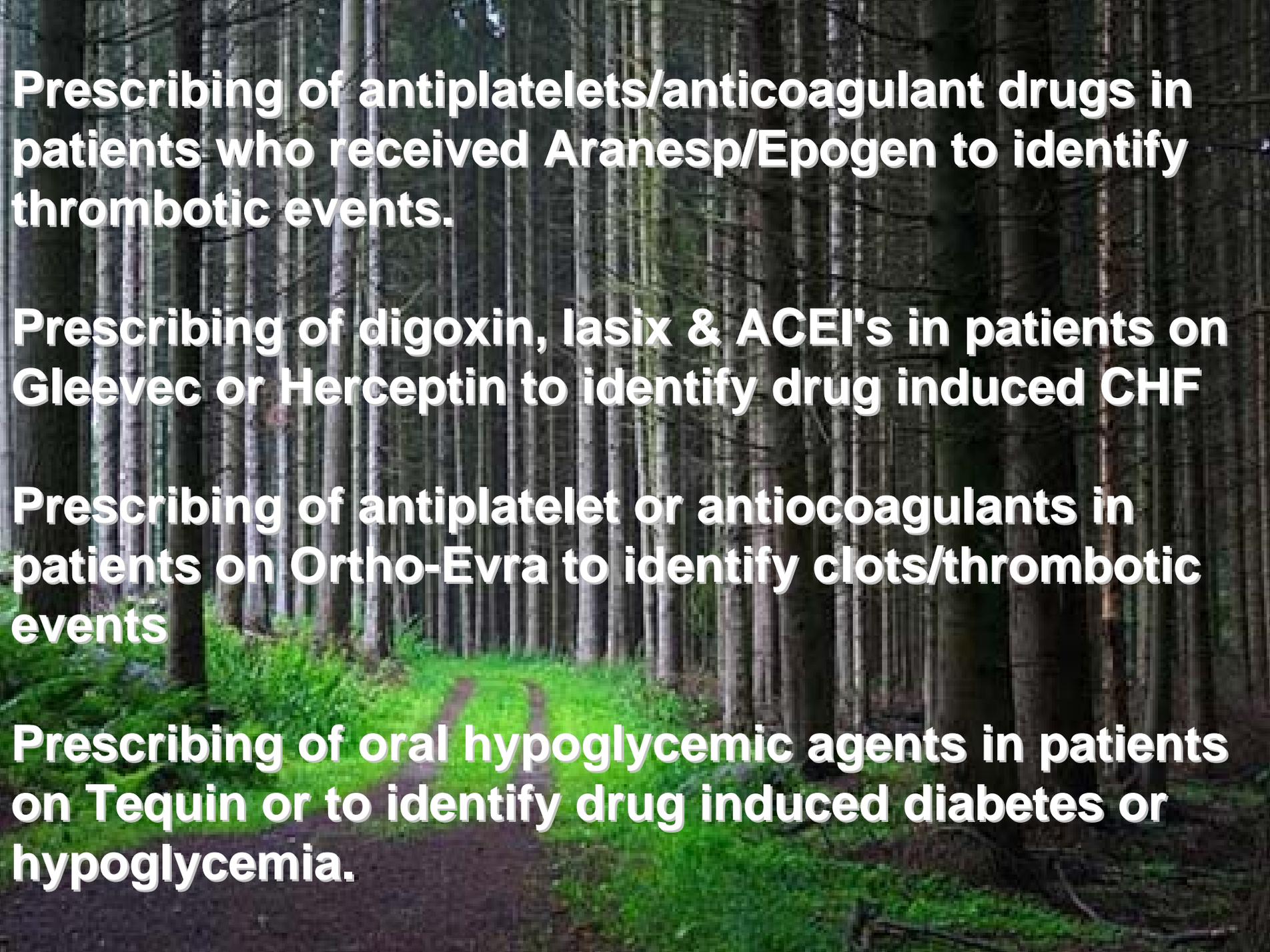
A photograph of a forest path. The path is a narrow, dirt trail that winds through a dense forest. The trees are tall and thin, with light-colored bark, possibly birches or aspens. The ground is covered in green moss and ferns. The lighting is soft, suggesting a slightly overcast day or a shaded forest interior. The path leads from the foreground into the distance, disappearing among the trees.

Prescribing of antipsychotic medications in patients started on drugs to treat ADHD as a way of spotting the incidence of psychiatric side effects.

Prescribing of lactulose, neomycin, or rifaximin in patients who received Ketek to identify hepatotoxic reactions.

Prescribing of antiplatelet drugs in patients who received Lucentis to identify new strokes

Prescribing psychoactive drugs in children who received Tamiflu to identify delirium

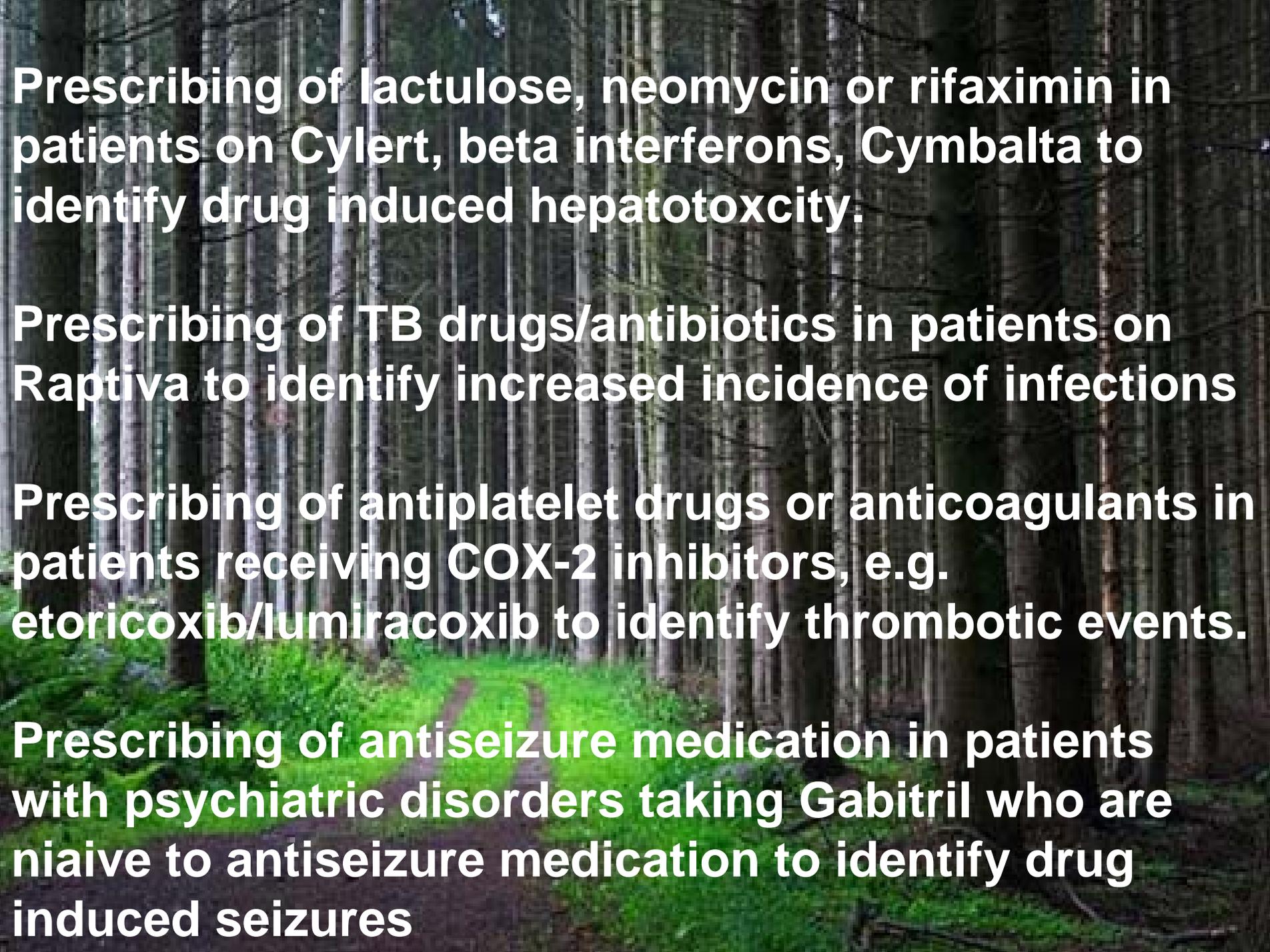
A photograph of a forest path. The path is a narrow, dirt trail that winds through a dense forest of tall, thin trees. The ground is covered in green moss and ferns. The lighting is soft, suggesting a shaded forest environment.

Prescribing of antiplatelets/anticoagulant drugs in patients who received Aranesp/Epogen to identify thrombotic events.

Prescribing of digoxin, lasix & ACEI's in patients on Gleevec or Herceptin to identify drug induced CHF

Prescribing of antiplatelet or antiocoagulants in patients on Ortho-Evra to identify clots/thrombotic events

Prescribing of oral hypoglycemic agents in patients on Tequin or to identify drug induced diabetes or hypoglycemia.

A photograph of a forest path. The path is a narrow dirt trail winding through a dense forest. The trees are tall and thin, with light-colored bark. The ground is covered in green moss and ferns. The lighting is soft, suggesting a shaded forest environment.

Prescribing of lactulose, neomycin or rifaximin in patients on Cylert, beta interferons, Cymbalta to identify drug induced hepatotoxicity.

Prescribing of TB drugs/antibiotics in patients on Raptiva to identify increased incidence of infections

Prescribing of antiplatelet drugs or anticoagulants in patients receiving COX-2 inhibitors, e.g. etoricoxib/lumiracoxib to identify thrombotic events.

Prescribing of antiseizure medication in patients with psychiatric disorders taking Gabitril who are naive to antiseizure medication to identify drug induced seizures

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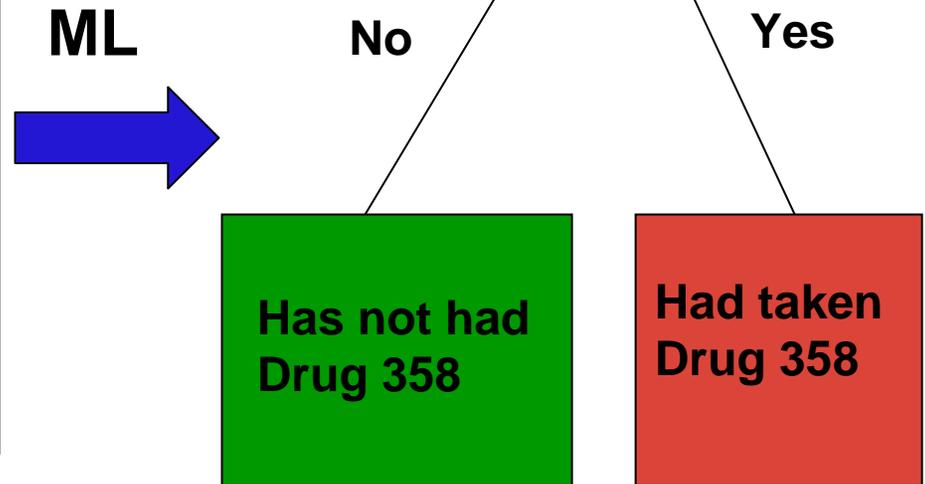
Supervised Learning Task

- **Given:** Clinical and genetic database as shown
- **Do:** Learn a model to predict drug response or adverse reaction

Machine Learning (ML)

Database

| Date | Patient | ICD9 | Drug |
|---------|---------|-------|------|
| 12/2/02 | P1 | 437.2 | 358 |
| 12/1/02 | P1 | 348.1 | |
| 1/20/03 | P1 | 258.3 | 256 |
| 3/19/04 | P2 | 568.0 | 784 |
| 4/29/04 | P3 | 129.5 | 654 |
| 5/10/04 | P3 | | 358 |
| 6/19/04 | P3 | 258.3 | 256 |



Input is a database, **output** is a predictive model. Many different types of models; simple decision tree shown is just one type of model. Model may not be completely consistent with the data, but ML's goal is to find a simple, nearly consistent model.

Specific Learning Task

- **Given:** Data for patients on Cox-2 inhibitors
- **Do:** Learn a model to predict elevated risk of MI
- Model might be a Bayes net where some variables are defined by learned rules, e.g.,
 - At least half of patient's last 2 years of blood pressures have been over 135 or 85 and patient has had at least one report of palpitations
 - Patient is AA for SNP4978 and either:
 - Not BB for SNP79252 or
 - AB for SNP97324

Proposal: A Machine Learning Approach to Pharmacovigilance

- **Given:** Data about prescriptions and diagnoses for patients.
- **Do:** *Learn* a model to distinguish patients on new drug **D** from patients not on **D**.
- If there is an adverse reaction **R** to drug **D**, then patients on **D** will be predicted better than chance (guessing), based on diagnoses related to **R** or prescriptions for drugs that treat **R**.

Additional Details

- Use only data *after* patient begins drug; otherwise, model might predict drug from the diagnosis for which drug is prescribed.
- Must test learned model on unseen (held-aside) patients, to see if truly better than guessing.
- Use an ML algorithm that gives a human-readable model, so analysts can determine whether the model really is indicating a potential adverse event.
- The control cases could be any patients not on the drug, or specifically patients on other drugs of the same class.

