Pharmacogenetics
The GSK Perspective

SACGHS June 16,2005

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Outline of Presentation

- Pharmacogenetics (PGx) at GSK
- Types of PGx
- Potential benefits of PGx to healthcare
- Examples of PGx and barriers to PGx application
- Areas for SACGHS to focus on?

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Genetics Research at GSK

- **Background**
  - 1997, formally established Genetics Research as a separate functional line in R&D
  - Allen Roses, MD, head of GSK Genetics Research
    - Previously head of Neurology at Duke University
    - Led team of researchers who found association of APOE4 Alzheimer disease

- **GSK Genetics Research**
  - 600 people worldwide with expertise in genetic/genomic science, data analysis, bioinformatics, education, research ethics and policy
  - Our research involves sample collections from individuals in all clinical trials, patients with disease, families, and healthy volunteers
  - Currently multiple on-going and committed PGx research projects

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Current Drug Development Process

- Current drug development and approval processes center on data collected from research participants
- Most drugs are effective in a majority of patients

(*Spear, B. Trends Mol Med May 2001 7 (5) 201-204*) :

Alzheimer	30%
Asthma	60%
Cardiac Arr.	60%
Depression	62%

- All drugs have side effects and some drugs produce major adverse reactions in small subset of patients

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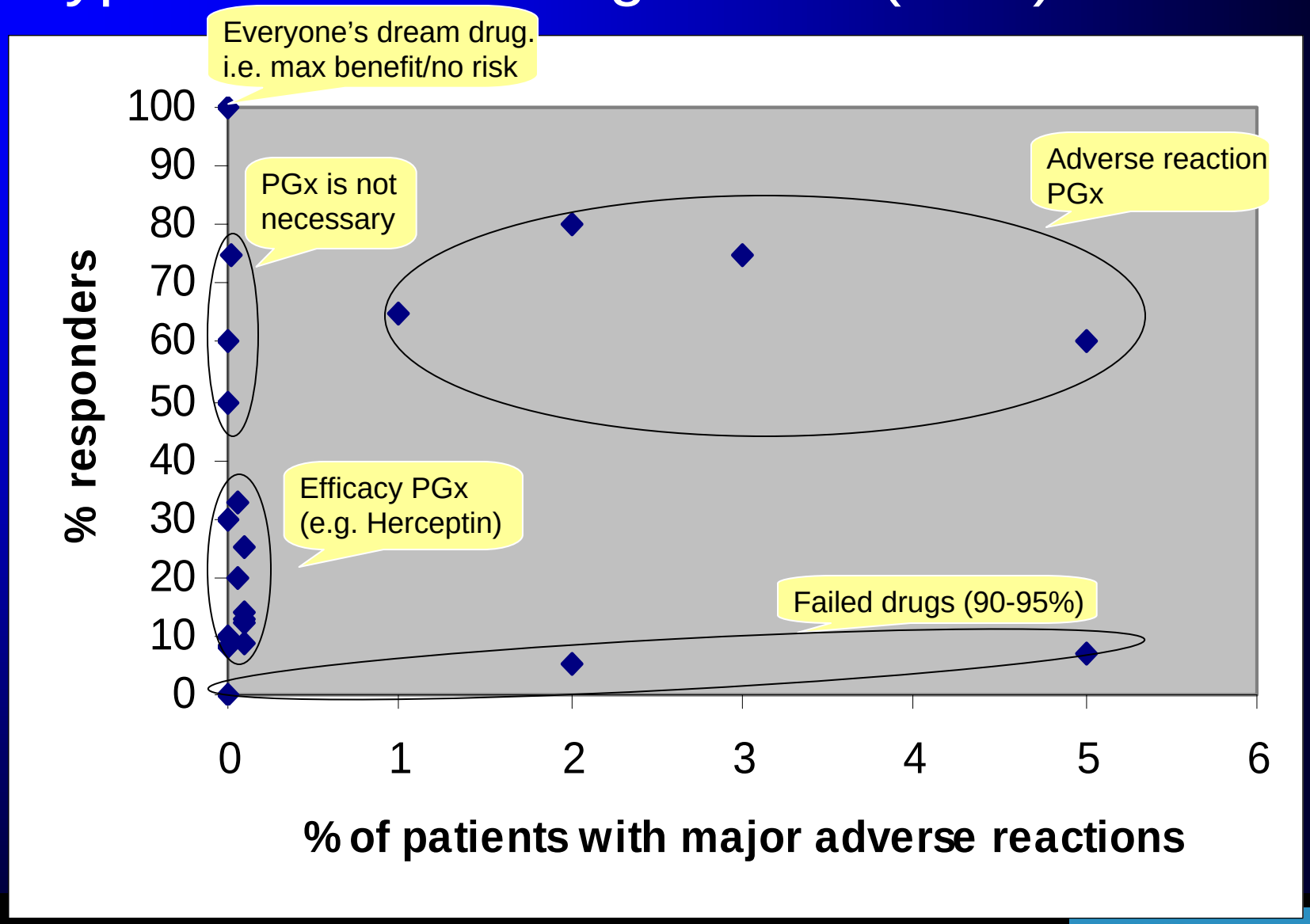
Types of Pharmacogenetics (PGx) Studies



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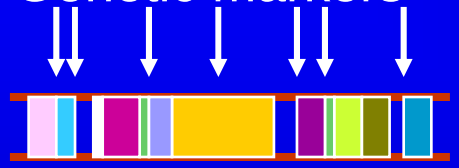
General Approaches to PGx

Genetic markers



Data Analysis
Compares the patients to the controls

Determine the genetic profiles of patients and controls

Collections of well characterized patients' samples and controls from clinical trials

- DNAs and tissues
- 200 - 1,000 per experiment

Marker discovery
Pharmacogenetics

Drug response (efficacy)
Adverse drug reaction

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Potential Benefits of PGx to Healthcare

- Positively impact the risk/benefit ratio by maximizing therapeutic benefits and minimizing risks.
- Target group of individuals most likely to benefit and least likely to experience an adverse event. (e.g. Iressa, Herceptin)
  - Modify the dosing regimen
  - Select an alternative therapy
- Ascertain more accurate, clinically-relevant information about the safety and efficacy profiles of medicines.
- Lead to a more evidence-based and efficient approach to drug development.
- Fill the gap between current drug development practices and our collective responsibility to improve the safety and efficacy profiles of medicines in the clinical setting.

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Current Application, example 1: HER2 testing in metastatic breast cancer

- The HERs proto-oncogene is overexpressed in ~25-30% of breast cancer patients
- Herceptin is a humanized monoclonal antibody that selectively binds to HER2, it has been shown that Herceptin inhibits the proliferation of human tumor cells that overexpress HER2, and is FDA approved for first-line use for the treatment of HER2 protein overexpressing metastatic breast cancer
- Testing for HERs status plays a key role in the management of metastatic breast cancer.

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Current Application, example 2
TPMT: To Test or Not to Test?

- For 20 years, doctors have been using 6 mercaptopurine as the first line of therapy for ALL (acute lymphocytic leukemia, a childhood cancer)

- Toxic to some patients: wipes out the patients' bone marrow

- **TPMT** (thiopurine methyltransferase) is the predominant inactivation pathway
  - 1/ 300 Caucasian individuals is enzyme deficient and the therapy is highly toxic to these individuals
  - CLIA testing available, but NOT standard of care to test prior to therapy

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2003: FDA's Pediatric Oncology Subcommittee recommended changing the 6 mercaptopurine label but not testing of patients prior to treatment. WHY NOT?

- Cost ? ($100-300)
- Change in practice ?
- Lack of physician awareness ?
- Lack of practitioners genomic knowledge / comfort with the testing ?

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The Long Road to P450 testing

- Cytochrome P450 proteins with well established common polymorphisms that affect drug metabolism have been described since 1950s and molecular basis for the polymorphisms have been known since 1980s.
- Potential predictors of optimum dose, drug choice and side effect response
  - Eg. CYP2D6 & codeine activation, CYP2C9 & warfarin inactivation
- Why have they not been taken up into clinical practice?
  - Complicated gene families and difficult assays
  - Limited awareness
  - Feasibility
    - Access to test
    - Genetic information required at point of prescribing decision?

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Comprehensive interpretation is key to P450 clinical application

June 1, 2005

LABCORP OF AMERICA
CMB&P
1912 ALEXANDER DR
RTP, NC 27709

Branch Number: NCB13
Account Number: 90001555
Specimen Number: 151-225-5001-0
Specimen Type: Blood

Physician: BROWN,T

Interpretive Information

The poor metabolizer (PM) phenotype is predicted by a homozygous or compound heterozygous genotype of any one of the following alleles: *CYP2D6**3, *4, *5, *6, *7 or *8 (formerly designated *CYP2D6* A, B, D, T, E and G alleles, respectively). Greater than 95% of PM phenotypes will be detected. The ultra-extensive metabolizer (UEM) phenotype is predicted by multiple copies of the *CYP2D6* gene (i.e., *CYP2D6* gene duplication).

Only the *CYP2D6* alleles listed above are identified in this test. Other alleles will not be detected.

Examples of *CYP2D6* Substrates	
Antihypertensives	Debrisoquine
Antiarrhythmics	N-propylamine
	Encainide
	Propafenone
Antidepressants	Amitriptyline
	Desipramine
	Imipramine
Neuroleptics	Haloperidol
	Perphenazine
	Thioridazine
Antianginals	Perhexiline
Opioids	Codeine
	Dextromethorphan

Frequency (%) of *CYP2C19* Alleles		
PM phenotype	Caucasians	5 - 10
	Asians	2
	African Americans	2
UEM phenotype	Caucasians	7

Quest Diagnostics®

***4 / *5**
ıbolizer

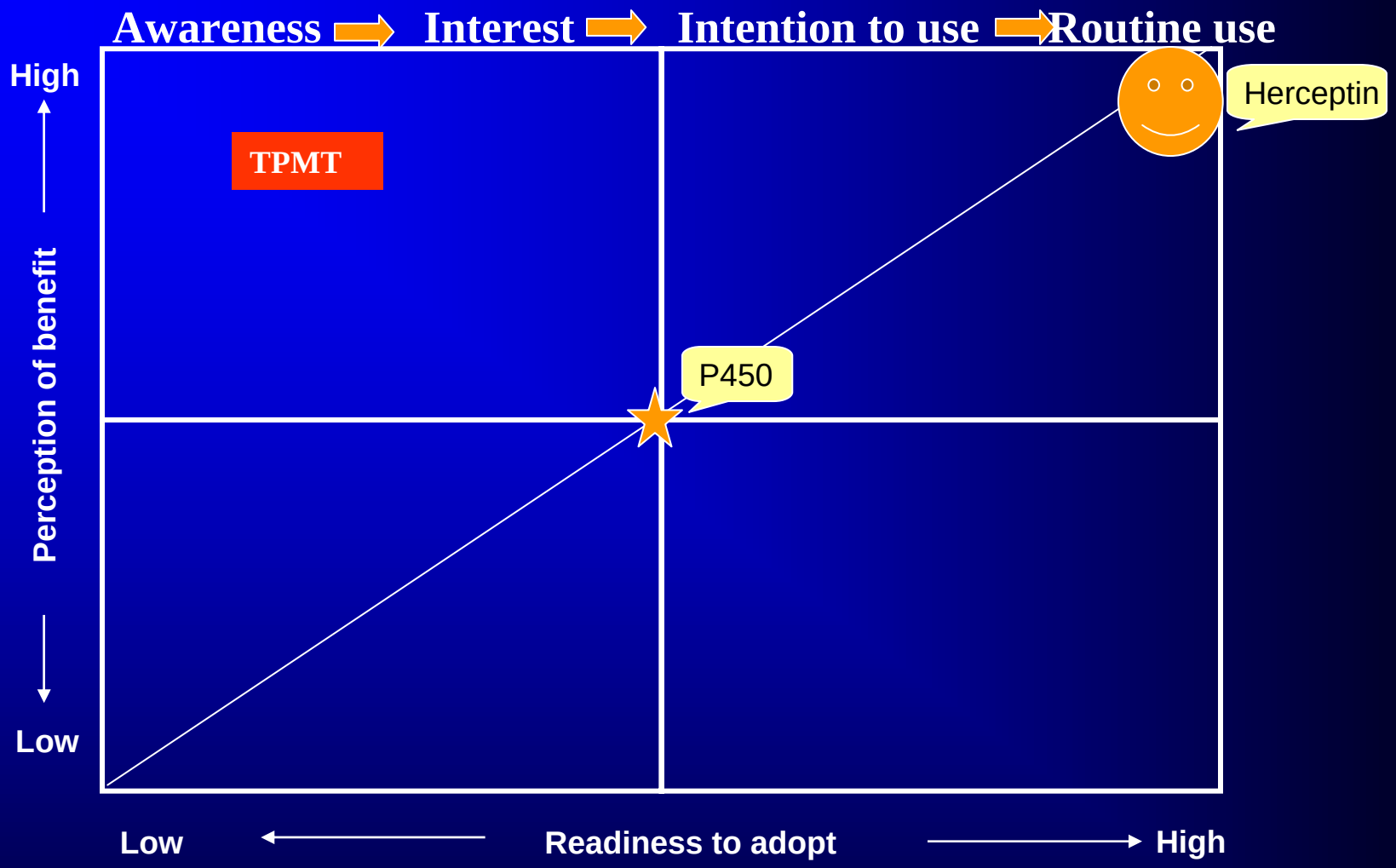
ıe. Poor metabolizers (PM) lack active enzymes and have reduced ɔlism can lead to increased concentrations of un-metabolized drug at increased risk for adverse effects and may not respond to usual :

nts	Antipsychotics	Others
	Haloperidol	Acetaminophen
:	Perphenazine	Codeine
	Risperidone	Dexfenfluramine
omers)	Thioridazine	Ondansetron
	Zuclopenthixol	Phenacetin
		Phenformin
		Tamoxifen
		Tramadol

Timolol	Perhexiline	Fluvoxamine
		Imipramine
		Maprotiline
		Nortriptyline
		Paroxetine
		Venlafaxine

This is not intended to be a comprehensive list of drugs metabolized by CYP2D6. Healthcare providers are encouraged to consult the current literature, the package insert of any medication considered, or contact the drug manufacturer for specific drug information.

PGx "Adoption Curve"



Scientific discovery → Validation → Demo Utility → Routine Clinical use

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Summary

- Over the next 10 years, there will be an increased application of genetic information prior to the prescription of some medicines.
- The integration of PGx into Medicine will help to accurately identify which group of people are likely to respond well or to experience a serious ADR in response to some—not all—medicines.
- PGx can be an effective intervention to improve health.
- PGx warrants consideration by policy makers to improve healthcare.

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Areas for SACGHS to Focus On?

- Education to change misperceptions
  - No medicine is totally effective and safe
  - PGx will improve the benefit/risk ratio of medicine. More effective medicine with less chance of major adverse reactions.
- Address fear of genetic testing/discrimination
  - PGx does not change the patient, the responses, or the disease.
  - Need protection and assurance from discrimination.
- Support of a research and health care environment conducive to using genetic information.

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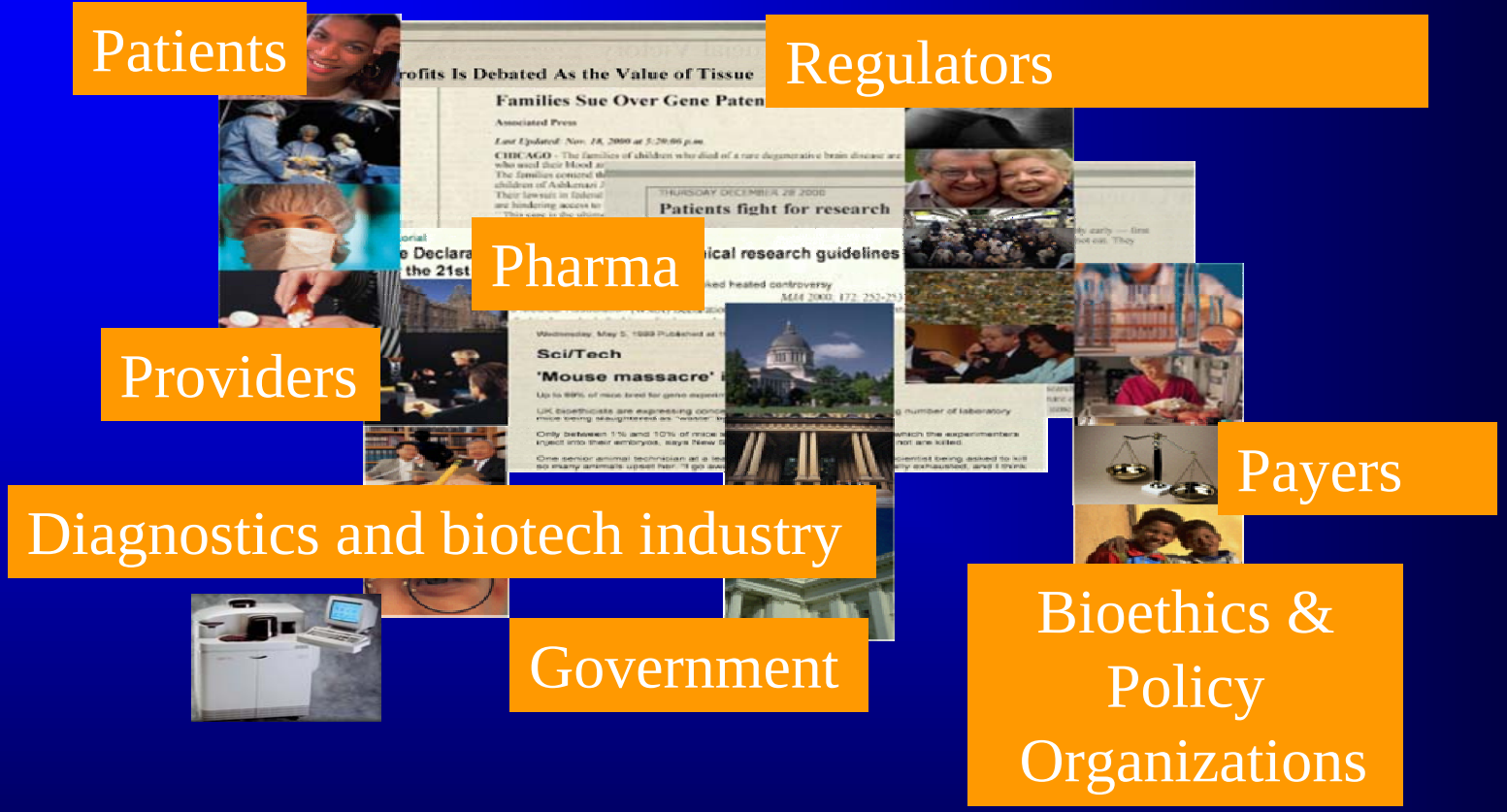
PGx: Key Stakeholders



Drug safety and efficacy are shared responsibilities

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