Growing National Concern About Adverse Drug Reactions

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:55

- IOM, Committee of Health Care in America Report: "To Err is Human: Building a Safer Health System", December 1, 1999.
- GAO, Report to Congressional Requestors, "Adverse Drug Events", January, 2000.
- FDA/CDER Spontaneous Reporting System (SRS) contains adverse drug reaction reports. Expanded Adverse Events Reporting System (AERS) under development.

Introduction

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- **Human Genome Project is accelerating genetic studies**
- **Human Genome Project has been accelerated**
- **Surrogate markers are expected to improve treatment efficacy**
- **Adverse reaction markers critical to understand toxicity**
- **Need for high information content diagnostic assays to address unmet clinical needs is increasing**
- **Examples of high information content assays include variant analysis, resequencing and expression (mRNA) profiling**

Challenges for Genetic and Cancer Diagnostic Testing

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Scientific: Correlation of disease phenotypes and treatment efficacy with pathogens and genes need to be established

Technological: Diagnostic assay formats and platforms that permit reliable, cost-effective testing with significant predictive value with high throughput and automation need to be developed

Clinical: Indications and defined utility need to be demonstrated

Regulatory: Timely approval of medicines and assays

Psychosocial: Acceptance of genetic testing

Many Drug-metabolizing Enzymes Exhibit Clinically Relevant Genetic Polymorphisms

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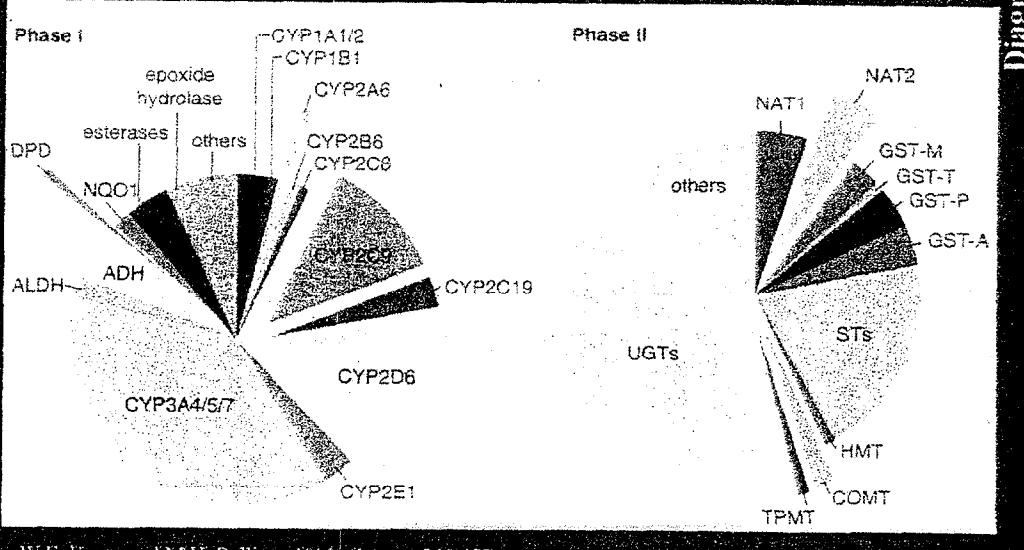

W.E. Evans and M.V. Relling (1999) *Science* 286:487

Examples of Drugs Impacted by Genetically-determined Interindividual Variation in CYP2D6 and CYP2C19 Metabolism

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CYP2D6 Substrates

Antiarrythmics
Propafenone, Encainide

Beta-blockers
Timolol, Metoprolol

Antidepressants
Desimipramine, Clomipramine, Imipramine, Amytriptyline, Fluoxetine

Neuroleptics
Haloperidol, Thioridazine, Risperidone, Venlafaxine

Miscellaneous
Codeine, Debrisoquine, Phenformin, Indoramin

CYP2C19 substrates

Omeprazole
Amytriptyline (in part)
Imipramine
Certain barbiturates
Chlorproguanil
Proguanil
Citalopram
Diazepam
Mephenytoin
Phenytoin
Propranolol
Cyclophosphamide

Impact of Human CYP450 Polymorphisms on Drug Treatment in Poor Metabolizers

Polymorphic enzyme	Decreased clearance	Adverse effects	Reduced prodrug activation
CYP2C9	*S*-Warfarin	Bleeding	Losartan
	Phenytoin	Ataxia	
	Losartan		
	Tolbutamide	Hypoglycaemia	
	NSAIDs	GI-bleeding (?)	
CYP2C19	Omeprazole		Proguanil
	Diazepam	Sedation	
CYP2D6	Tricyclic antidepressants	Cardiotoxicity	Tramadol
			Codeine
	Haloperidol	Parkinsonism (?)	Ethylmorphine
	Anti-arrhythmic drugs	Arrhythmias	
	Perphenazine		
	Perhexiline	Neuropathy	
	SSRIs	Nausea	
	Zuclopenthixol		
	S-Mianserin		
	Tolterodine		

Abbreviations: NSAIDs, nonsteroidal anti-inflammatory drugs; SSRIs, selective serotonin reuptake inhibitors.

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M. Ingelman-Sundberg, et al
TiPS 20: 342, Aug. 1999

GeneChip CYP450 Microarray:
A combination of controls assures validity

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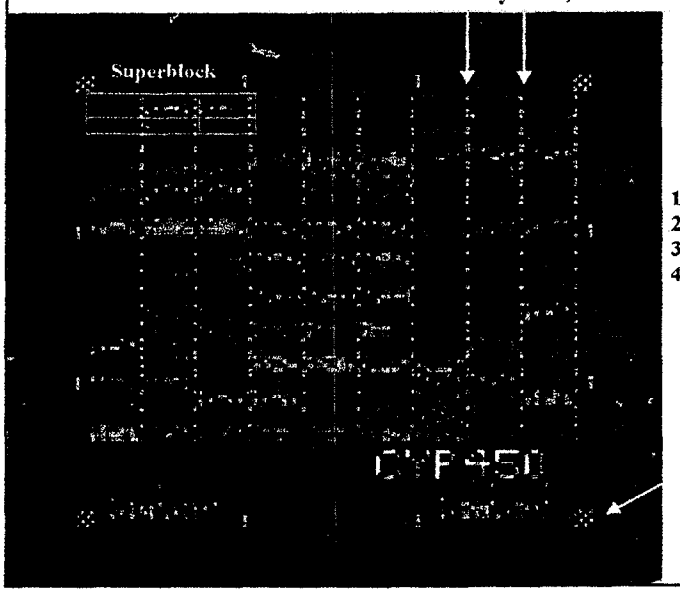
For every block, "Column 11" control probes



1) Hybridization Positive control probe
2) Hybridization Negative control probe
3) Exon sense strand control probe
4) Exon antisense strand control probe

Hybridization positive control probes

Issues Regarding Regulation of High Density Genetic Variation Diagnostics

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- What regulatory path is most appropriate for these new technologies?
  - CBER classification of HIV Resistance assays
    - Class II (Special Controls)
    - Guidance Document
  - Regulation of Genetic Tests
    - Classification based on Intended Use?

Issues Regarding Regulation of High Density Genetic Variation Diagnostics

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- Possible Intended Uses, Impact on Regulatory Requirements
  - Identification or measurement of a physical or biochemical parameter
    - Well-characterized mutations, phenotype predictions
  - Identification of the clinical use of the measurement
    - Treatment decisions based on antiviral resistance, drug metabolic profiles
  - Identification of or implication of an effect on clinical outcome
    - Treatment outcome

http://www.fda.gov/cdrh/modact/genspec.html

Analytical Performance of Human Genotyping Assays: Validation Samples

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- Establish reference panels of genomic DNA samples representative of common allelic variants, genotyped by independent method(s)
- When possible, obtain one or more genomic DNA samples representative of rare allelic variants (<1% allelic frequency)
- When samples carrying rare variants are available only in extremely limited quantity, clone by PCR to generate renewable resource
- When samples carrying rare allelic variants unavailable, generate relevant mutations in plasmids