Impact of Pharmacogenomices on Drug Development and Commercialization: An International Perspective

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Today's Roadmap

- Background
- Impact of PGx on global drug development
- Regulatory perspectives on PGx drugs
- Payer perspectives on PGx drugs
- Looking forward

What are PGx Drugs?

- Drugs with biological responses that are known to be influenced by patient genes
  - Efficacy
  - Safety
- Pharmacogenomics seeks to
  - Improve drug treatment by more accurately predicting efficacy or safety response in a given patient, or subgroup of patients

In Drug Development, PGx Can be Thought of Two Ways

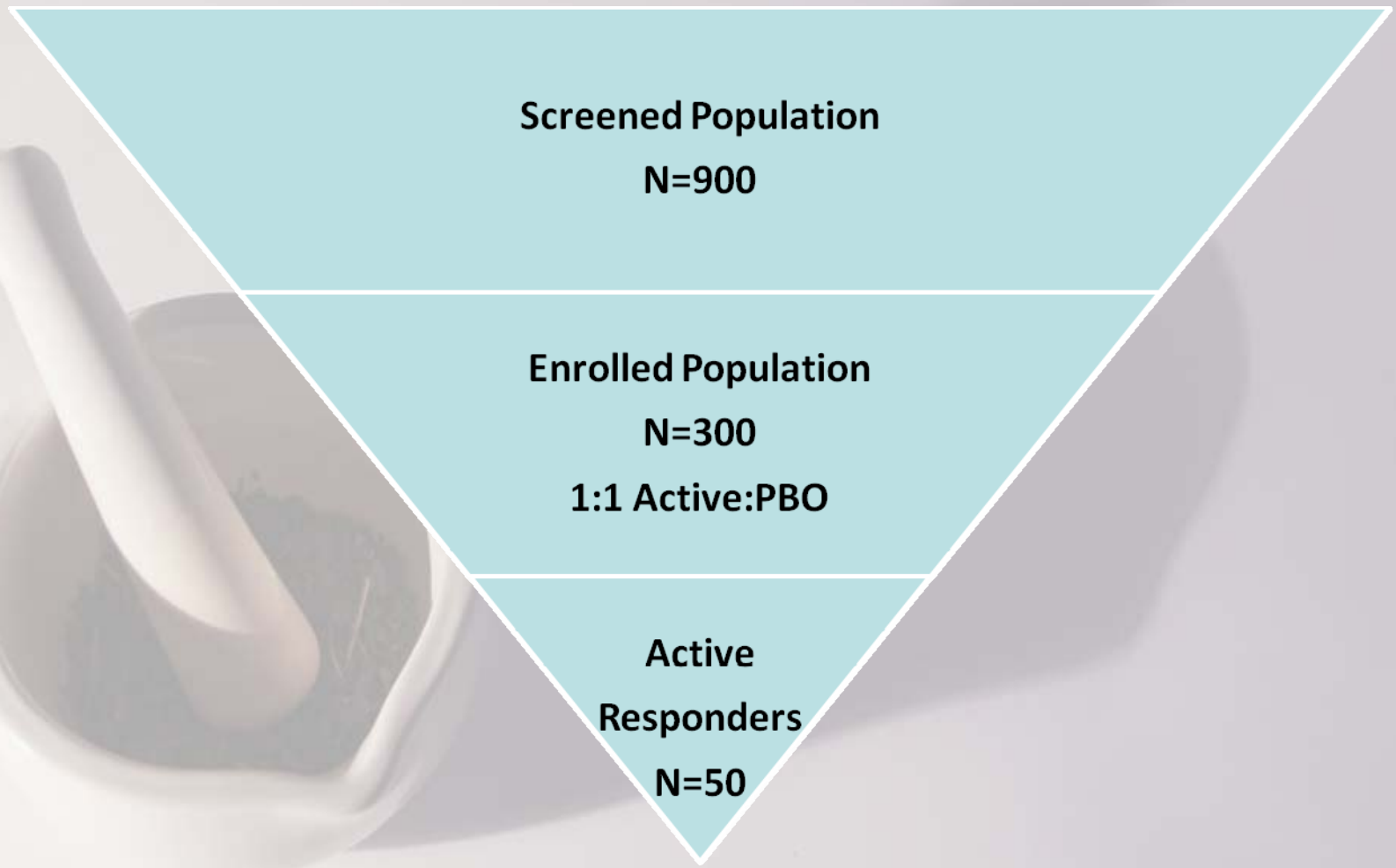
1. "After market" PGx tests developed for marketed drugs
   - > Warfarin—to identify potential PK issues and initial dose adjustments

2. Drugs that are co-developed with PGx tests
   - > Herceptin—to identify patients who will respond to treatment

➡ Much of the interest in the drug development industry is in co-development
   - > More efficient clinical trials
   - > Improve drug target identification

Traditional Clinical Trials Can Have Low Yields

Recent clinical trial



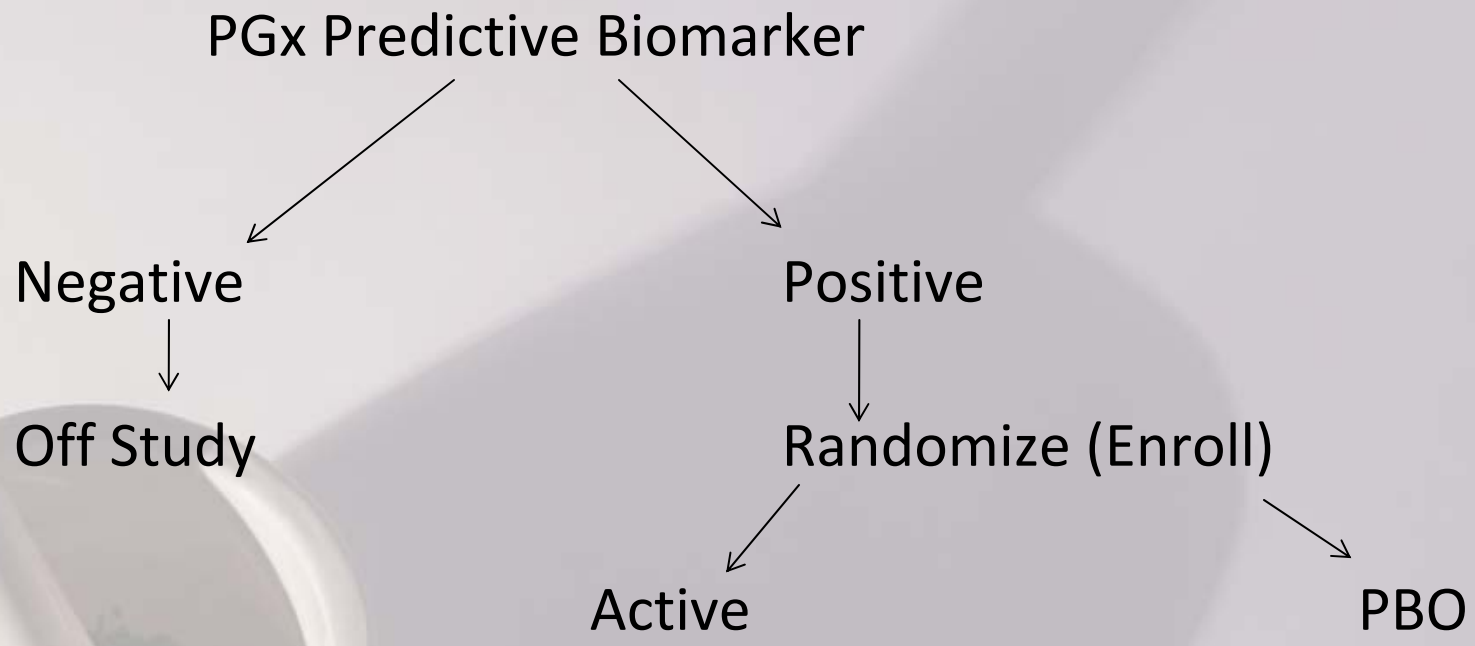
Enrollment Time is Often Rate Limiting in Conduct of Traditional Clinical Trials

Proposed timelines for clinical trial w/o PGx

Discussions with sites, investigators	Sept 2007
Final protocol	Nov 2007
FDA feedback	Jan 2008
First Patient In (FPI)	**Q1 2008**
Last Patient In (LPI)	**Q3 2009**
Last Patient Out (LPO)	Q3 2010
Database lock	Q4 2010
Draft tables	Q4 2010
Final Clinical Study Report	Q1 2011

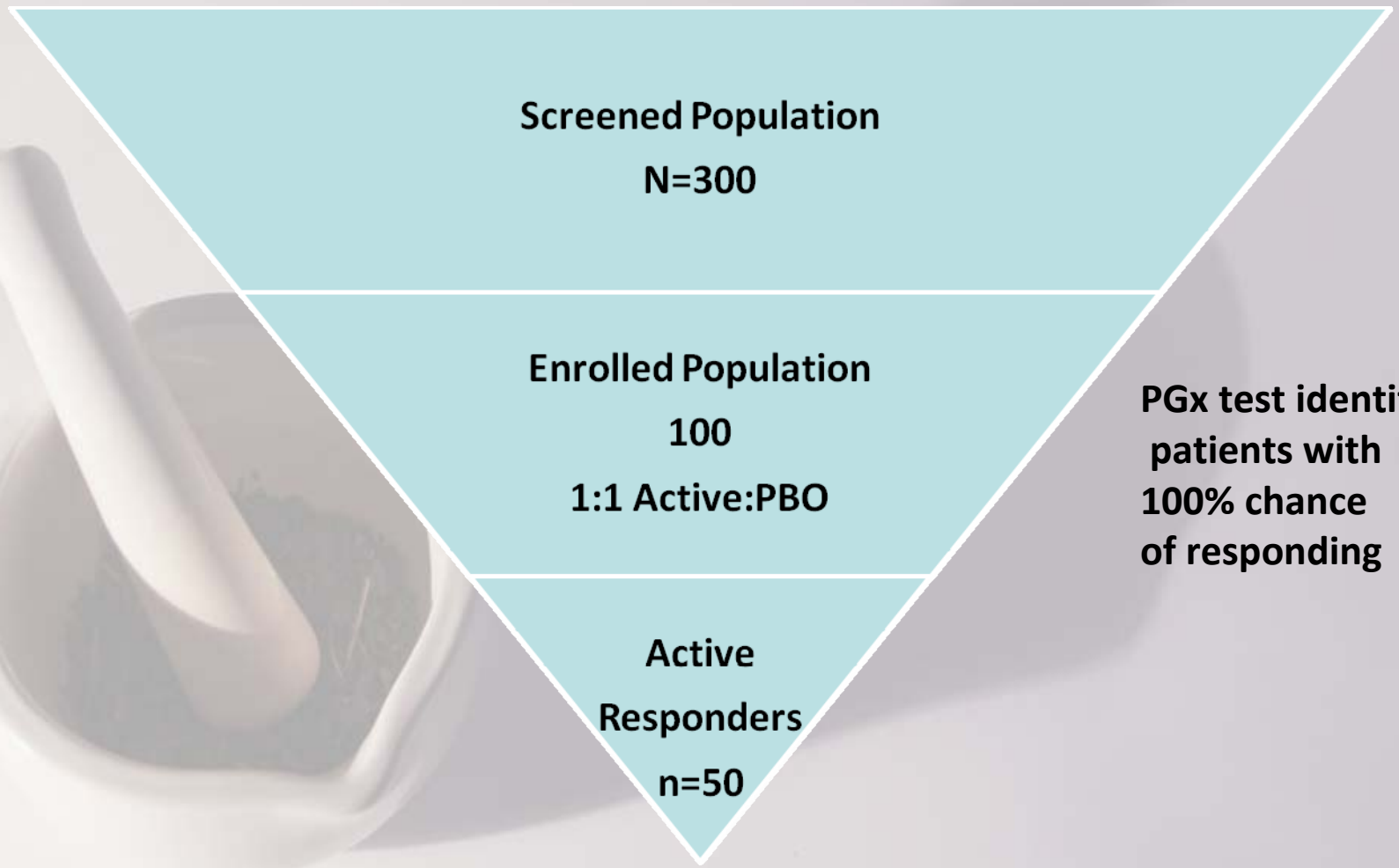
Can enrollment time be decreased?

PGx Trials Promises to Reduce Sample Size of Clinical Trials



Impact on Clinical Trial Size

Hypothetical PGx clinical trial



PGx test identifies patients with 100% chance of responding

Fewer Screenings Reduces Enrollment Time

Activity	Timeline w/o PGX	Timeline w/ PGx
Discussions with sites, investigators	Sept 2007	Sept 2007
Final protocol	Nov 2007	Nov 2007
FDA feedback	Jan 2008	Jan 2008
First Patient In (FPI)	**Q1 2008**	**Q1 2008**
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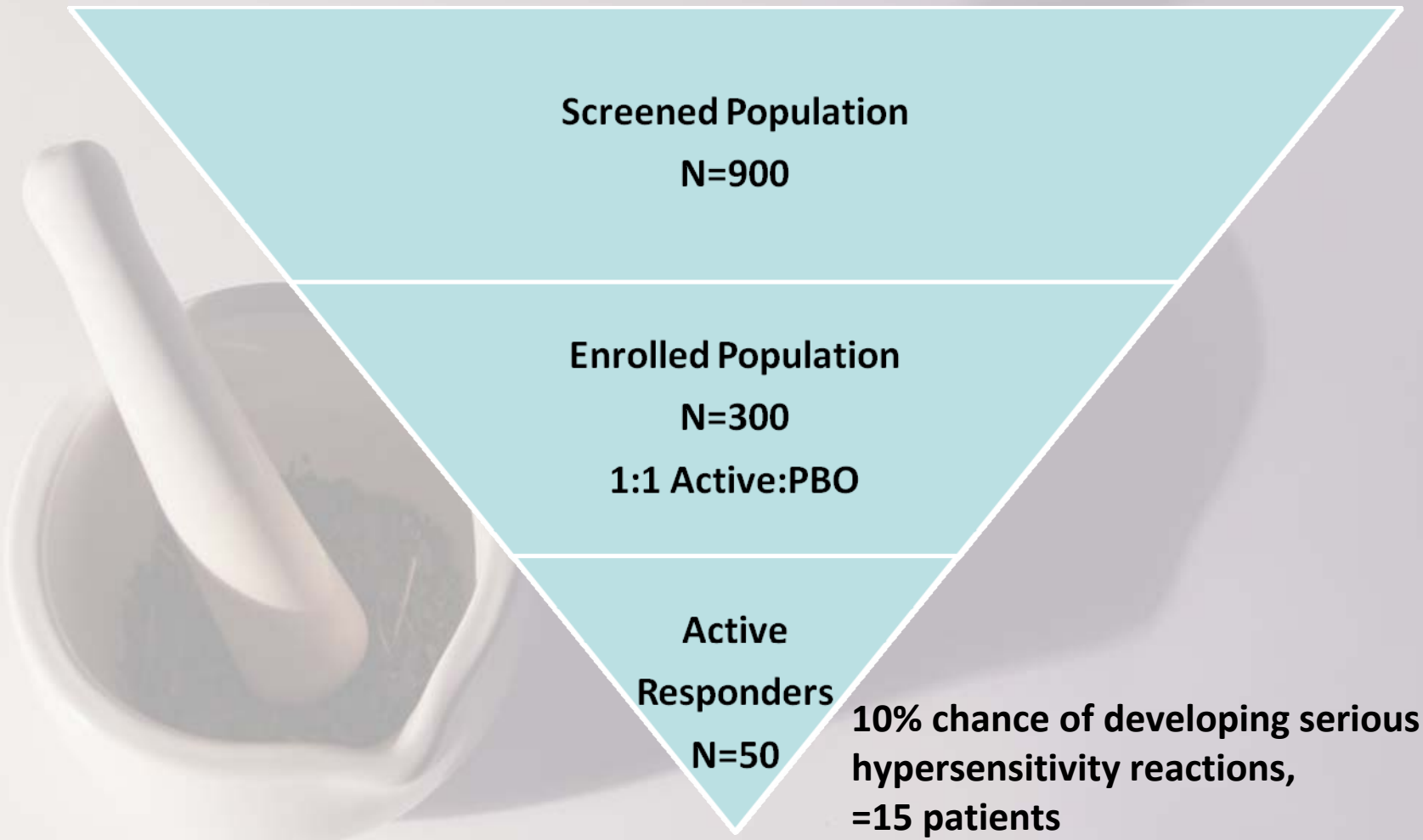
Enriching Study Populations Promises Fewer Failed Studies

- Sample size dependent on “effect size” and variance estimate in power calculation
- If these estimates are incorrect, study may fail even when drug is efficacious
- Possible to:
  - Size study based on traditional effect size, variance
  - Use PGx test to enrich population
  - Improve probability of study success

Traditional Clinical Trials Sometimes Challenged by Benefit Risk Ratio

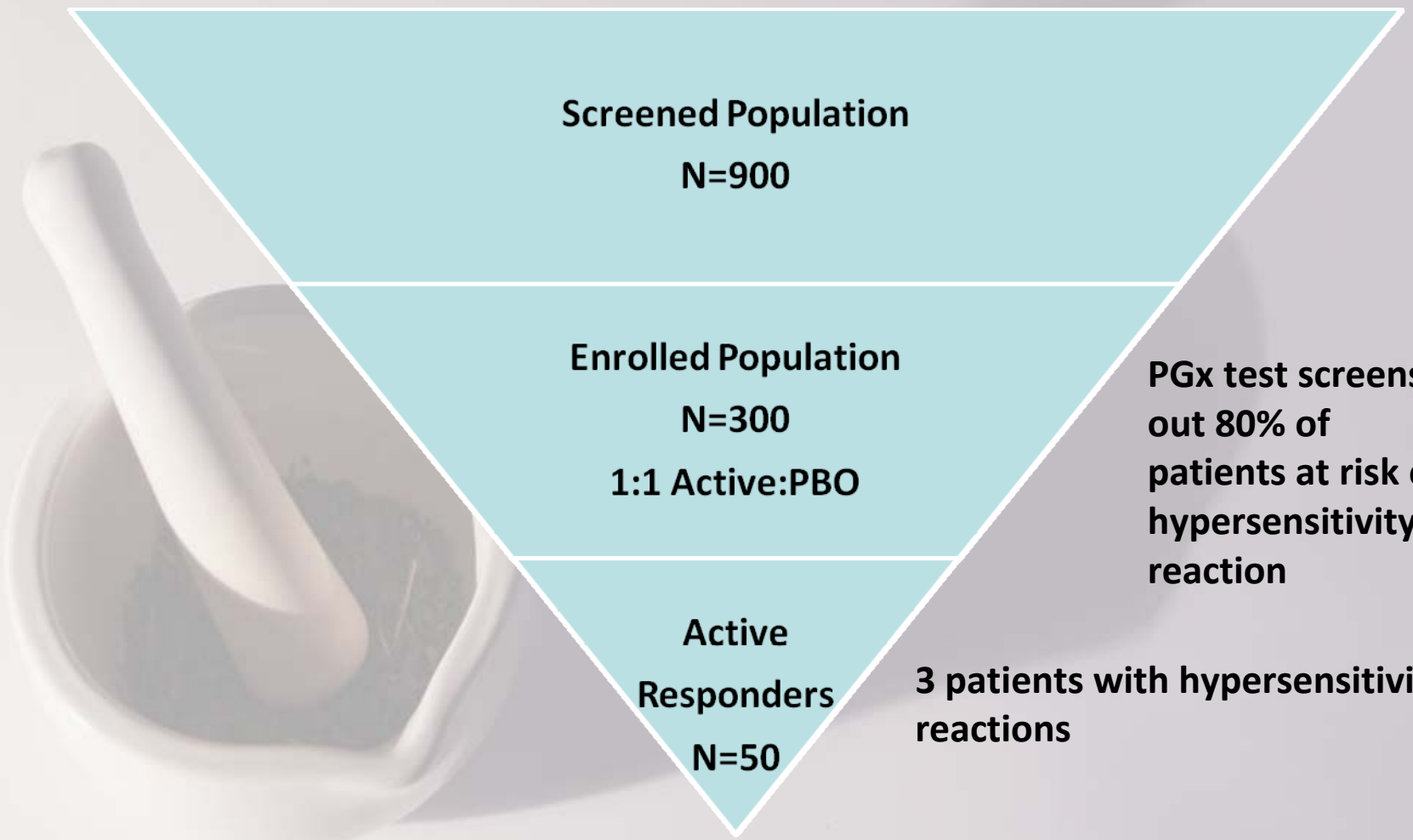
Recent clinical trial



10% chance of developing serious hypersensitivity reactions, =15 patients

PGx May Improve Benefit Risk Ratio by Screening Out Patients with High SAE Risk

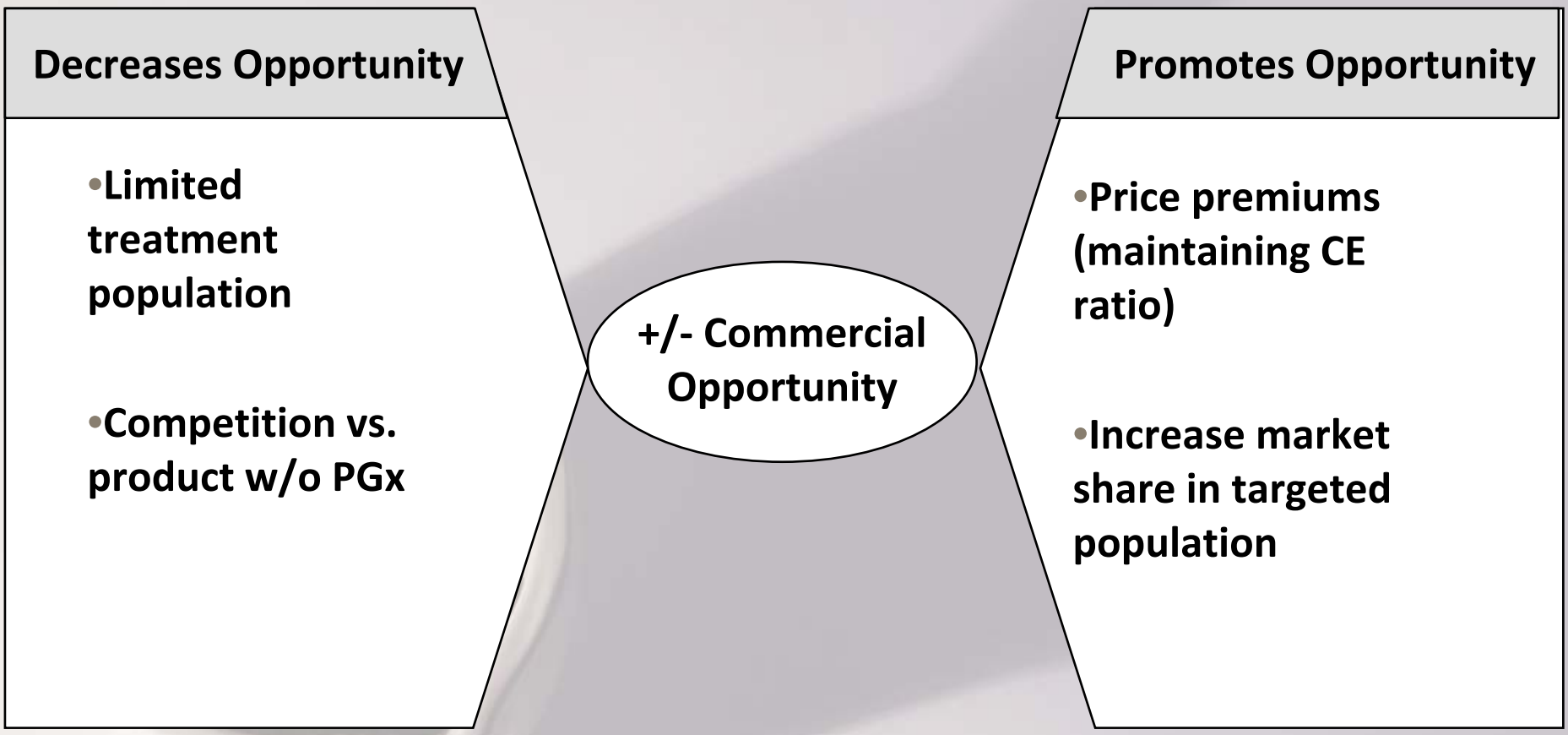
Hypothetical PGx clinical trial



PGx test screens out 80% of patients at risk of hypersensitivity reaction

3 patients with hypersensitivity reactions

PGx Promise on Commercial Opportunity is Variable Across Products



Dependent upon disease, competition, safety issues, efficacy rates, etc.

Despite These Promises, There are Significant Challenges

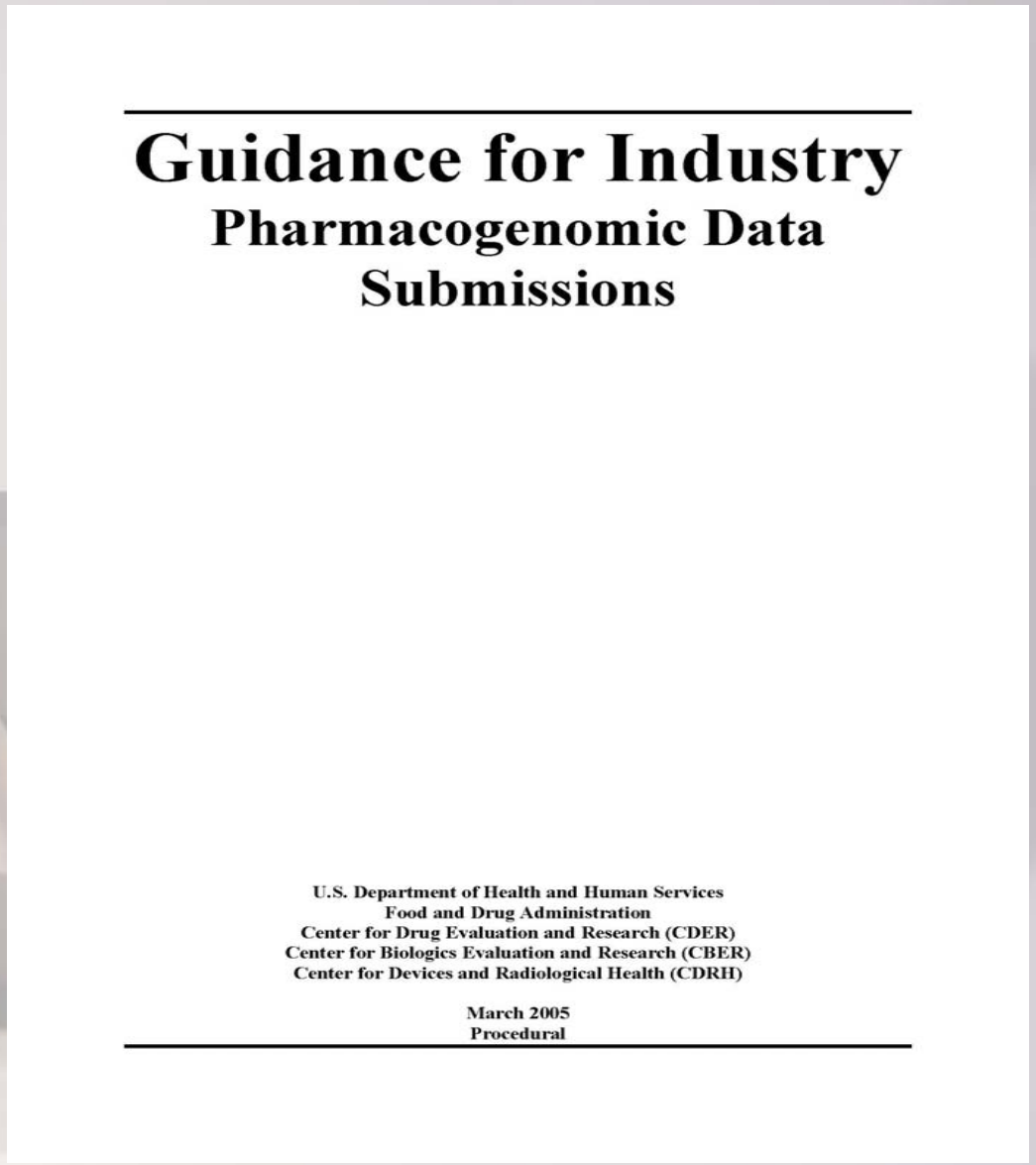
- Development and validation of PGx test may require large clinical and epidemiological studies
  - Net savings from more efficient clinical trials?
  - Quicker regulatory filings?
  - Timing of PGx test development?
- Sponsors may be required to run larger trials, or additional smaller trials, to ensure adequate patient exposures in regulatory filings
  - Net savings?
  - Quicker regulatory filings?
- NPV of commercial opportunity?

Impact on Drug Development Has Been Marginal

What Do Regulators Think?

- General
- Label
- PGx evidentiary requirements

FDA Issued PGx Guidance in 2005



Guidance for Industry

Pharmacogenomic Data Submissions

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
Center for Devices and Radiological Health (CDRH)

March 2005
Procedural

FDA: PGx is "Exploratory" and Recommends Co-Development of New Drugs and PGx Tests

- From the FDA Guidance Document:

"At the current time, most pharmacogenomic data are of an exploratory or research nature, and FDA regulations do not require that these data be submitted to an IND, or that complete reports be submitted to an NDA or BLA."

"…FDA recommends co-development of the drug and the pharmacogenomic tests, if they are not currently available, and submission of complete information on the test/drug combination to the Agency. The FDA plans to issue further guidance on co-development of pharmacogenomic tests and drugs."

Will the FDA Require Inclusion of PGx Test Information in the Product Label?

- FDA regulations state: *"if evidence is available to support the safety and effectiveness of the drug only in selected subgroups of the larger population with a disease, the labeling shall describe the evidence and identify specific tests needed for selection or monitoring of patients who need the drug."*[1]
- Pharmaceutical Science Advisory Committee recommended that information should be included in label if there is:
  - *A polymorphic receptor, drug metabolizing enzyme or transporter involved in the drug kinetics*
  - *A test to detect the genetic variant*
  - *Evidence that is has clinical consequences (efficacy or safety)*[2]

1.Specific requirements on content and format of labeling for human prescription drugs, 21 CFR 201.57.

2. FDAAdvisoryCommittee.com, "Pharmacogenetic data with clinical consequences should be described in labeling," 2003, http://www.fdaadvisorycommittee.com/FDC/AdvisoryCommittee/Committees/Pharmaceutical+Science/042303_pharmacogenetics/042303_PharmacogeneticsR.htm,Accessed on (2/15/2006).

Recent Labels with PGx

- ~60 products with PGx information in US product label
- Herceptin—PGx to identify HER2 overexpression
  - *"HERCEPTIN should only be used in patients whose tumors have HER2 protein overexpression." - Herceptin label*
- Warfarin---PGx recommended for PK, dosage adjustments
  - *"… healthcare professionals are not required to conduct CYP2C9 and VKORC1 testing before initiating warfarin therapy, nor should genetic testing delay the start of warfarin therapy." – FDA website*
- Mercaptopurine, azathioprine—PGx for risk of severe myelosuppression, dosage adjustments
  - *"It is recommended that consideration be given to either genotype or phenotype patients for TPMT" – AZT label*
- Irinotecan—PGx recommended for risk of neutropenia, dosage adjustments
  - *"…a reduction in starting dose by at least one level in Camptosar should be considered for patients known to be homozygous for the UGT1A1 allele…"*

Will the FDA Modify the Evidentiary Standards for Regulatory Approval of PGx Tests?

- Historically, FDA has taken a light regulatory approach with laboratory testing, including PGx
- Testing seen as posing low clinical risk
- Currently, little regulatory requirements to demonstrate impact of PGx test on clinical utility or patient benefit

What's Happening in Europe?

- CHMP about to issue several guidance documents
  - "Guidelines on the use of PGx in PK studies" (3Q 09)
  - "Reflection paper on co-development of PGx biomarkers and test platforms" (3Q 09)
  - "Reflection paper on statistical and methodological issues associated with PGx biomarkers" (4Q 09)
  - "Reflection paper on genomics and personalised medicines" (4Q 09)
- And holding discussions with external stakeholders…
  - EFPIA Efficacy and PGx Working Group, to discuss priority issues in PGx
  - FDA/CDER, to discuss PGx submissions, including PGx biomarkers data requirements

What Do Payers Think?

- Coverage issues
- Information needs

PGx Drug Biomarkers Are Valued by Payers

Decreased size of patient population – Limits payers' volume demand and budget impact

"This is ideal as it means we are dealing with defined patient sub-populations" – UK payer

"Biomarkers reduce costs because of smaller patient population in combination with higher effectiveness" – German KOL

"These are targeted therapies therefore very important" – French KOL

Increased probability of efficacy – Improves payers' confidence that money spent will lead to outcomes

"We're always more willing to spend more money if we know we're going to get the outcome with some certainty" – US Payer

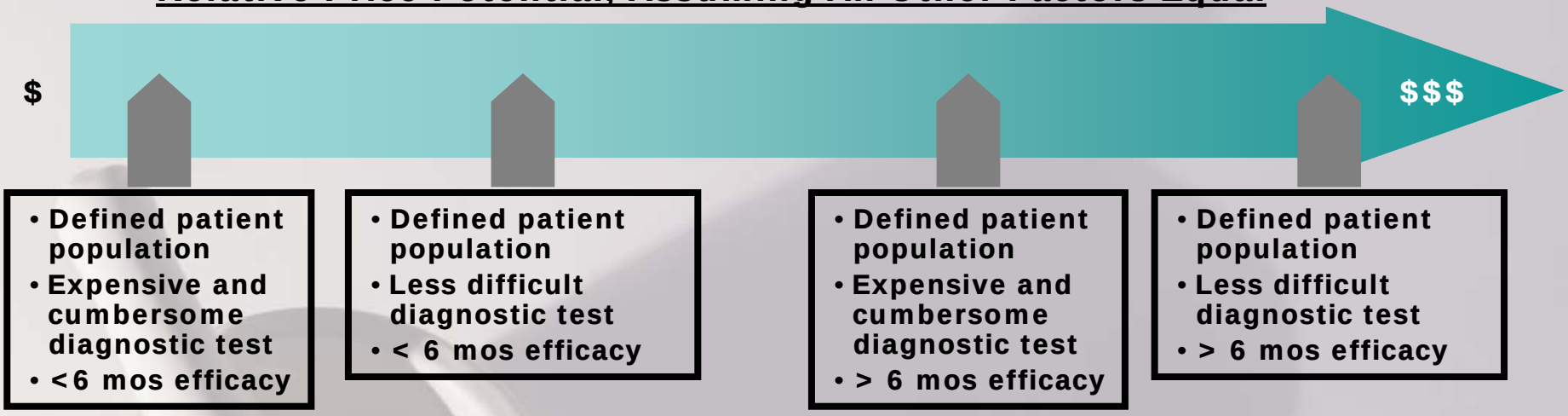
"Herceptin is pricey but the PBS is paying. The drug and the diagnostic get reimbursed, the idea being that it works, and they can prove it" – AUS KOL

Payers value biomarkers if they provide clear guidance on an appropriate, responding population and reduce overall budget impact

Ref.: IMS Research

Payers May Accept a Premium Price for PGx Drugs When There is Extended Survival Benefit in the Patient Population

Relative Price Potential, Assuming All Other Factors Equal



- The cost of a diagnostic test will be included in the decision-making process when evaluating new drugs, but often the tests must be funded separately

"Right now the major challenge is going to be how CMS funds diagnostics. It's just not built into the system." – US CMS Expert

"The diagnostic justifies a higher price since we're guaranteed efficacy in those patients" – US Payer

Ref.: IMS Research

In the UK, NICE Endorsed Herceptin for Use in Metastatic Breast Cancer in Patients with HER2 Overexpression

- Roche's economic model produced cost/quality adjusted life year (QALY) = 37,500 GBP
  - Costs included PGx costs
- Above "threshold" of 30,000 GBP/QALY
- Final Appraisal Dossier (FAD) suggested that Appraisal Committee, despite high cost effectiveness ratio, were comforted by PGx restrictions on access

However, Erbitux for mCRC Demonstrated that PGx Restrictions on Access No Guarantee of NICE Recommendation

- Indicated for EGFR expressing patients
- NICE submission included cost/QALY estimate ~ 80,000 GBP
- Not recommended for use by NICE

Looking Forward

Outstanding Questions

- Will the industry invest in co-development?
- Who owns PGx information collected in a clinical trial?
- In a physician's office?
- What are the regulatory evidentiary standards for co-development?
- What are the HTA evidence standards to support use recommendations?
- What are the ethical issues if patients are denied access to life saving pharmaceutical based on a PGx test?
- What are the private sector's and government's role as a source of R and D funding in PGx?
- ….

Summary

- PGx unlikely to fundamentally change drug development and commercialization
- Regulatory standards are in development
- Payers value PGx tests to restrict populations and improve outcomes
- Payers are likely to include PGx tests in co-developed drugs as a component of treatment costs and use current decision-making framework
- And there are many issues and questions that PGx raises!

Many Thanks!

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- Jan Hirsch, Ph.D., UCSD

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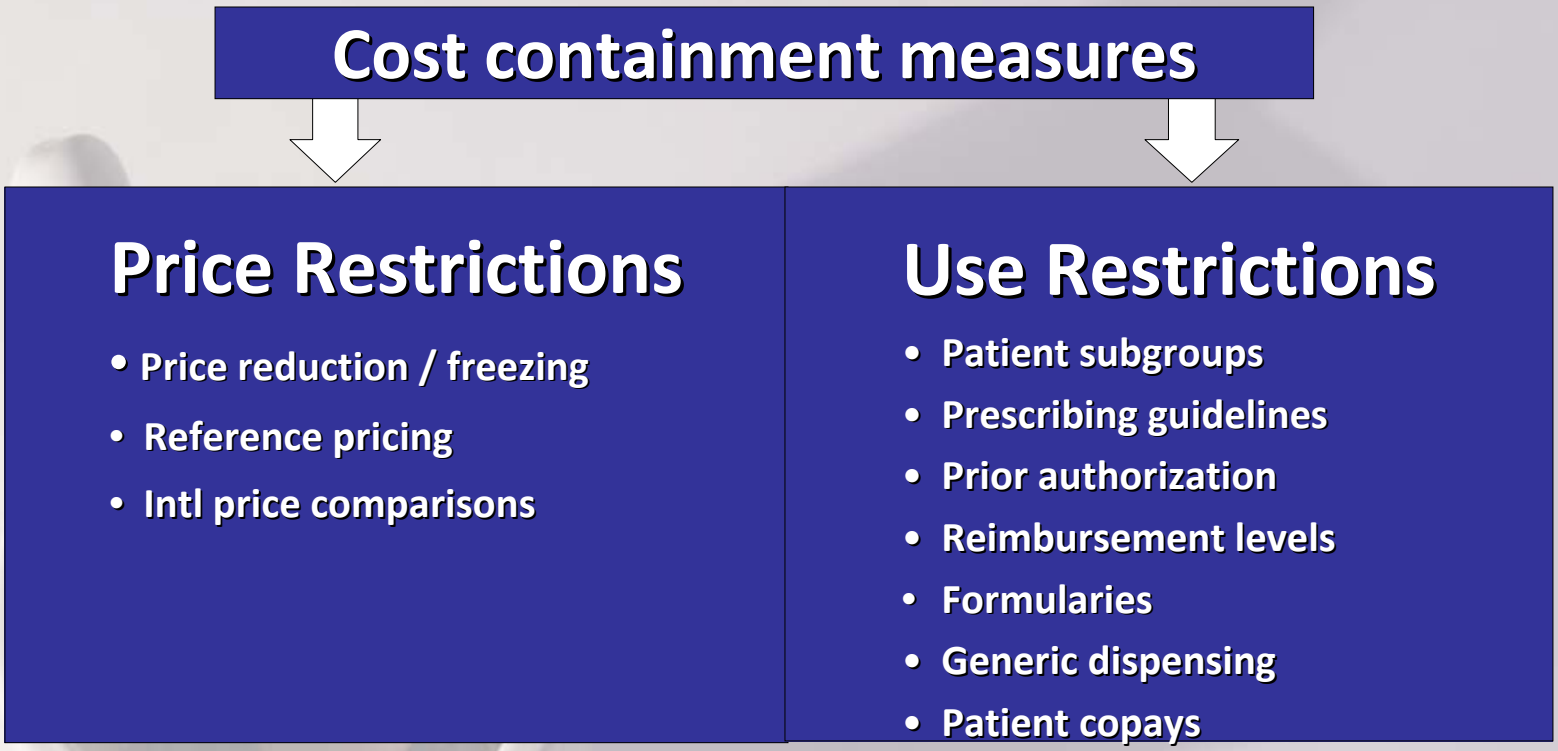
Backup

In Sum, PGx Drugs May Have Considerable Benefits

- ✓ Fewer patients screened
- ✓ Fewer patients enrolled
- ✓ Shorter study times
- ✓ Improved benefit risk ratios
- ✓ Shorter timelines to regulatory submission
- ✓ Upside to commercial opportunity

Public, Private Payers Manage Drug Costs Via Price and/or Volume Measures



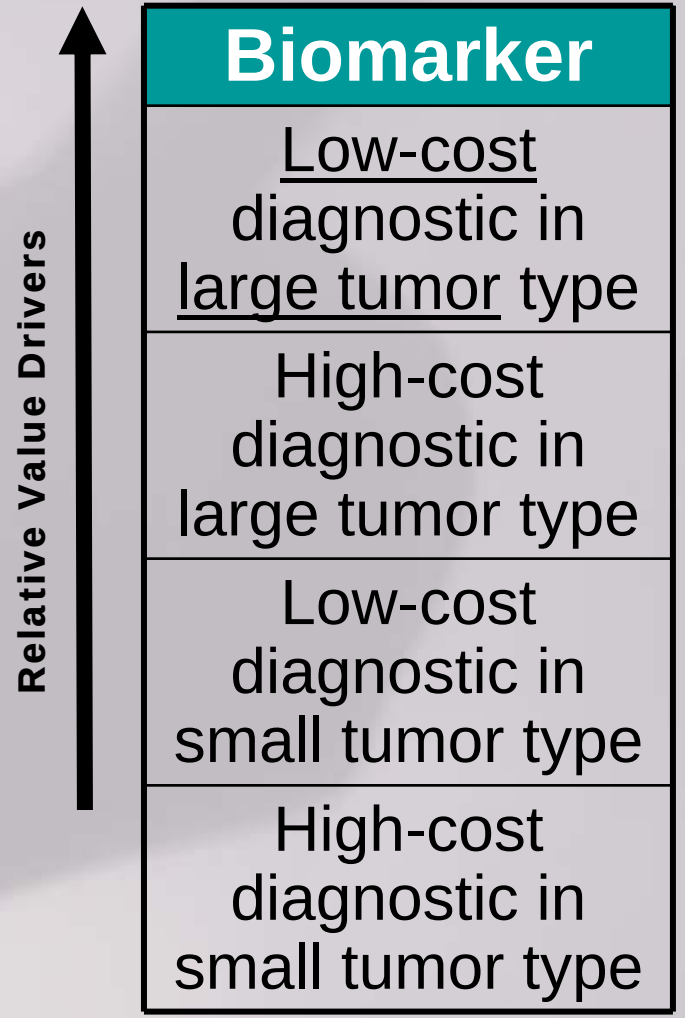
Reimbursement Policies of PGx Drugs Similar to Other Drugs Associated with Diagnostic Tests

- For example, patients require a cholesterol test before receiving cholesterol lowering drug
- Patients may be required to receive a PGx test before receiving a PGx drug
  - Depends on test impact on clinical and patient outcomes
- Restrictions based on PGx test will be dependent on the disease state, additional clinical information, and the clarity of the PGx test result

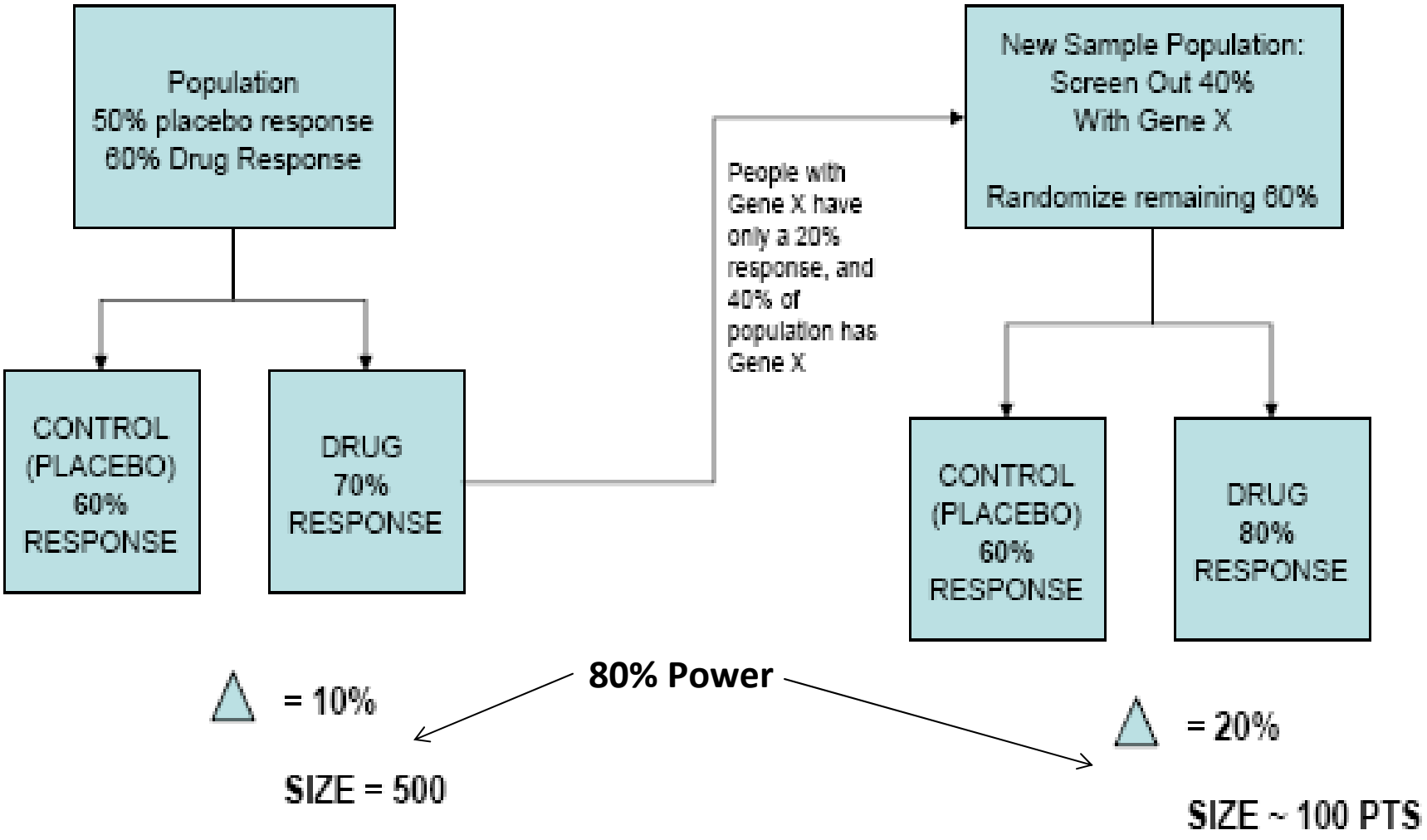
Payers Will Also Consider the Qualities of a Diagnostic When Evaluating Biomarker

Qualities of diagnostic

1. **Expensive and invasive diagnostic screenings**
   - **Concern and skepticism among payers about benefit of the product vs. difficulty & expense of conducting diagnostic**
   - **Additional cost of genetic testing considered as part of the product's cost**
   - **Additional complications of obtaining and completing the genetic test adds difficulty**
2. **Lower cost and less invasive diagnostics**
   - **Greater excitement among payers because less additional cost for diagnostic test and therefore more feasible**



Another Perspective: Decrease in Sample Size Dependent on Difference Being Detected



See http://linus.nci.nih.gov/brb for interactive comparison of traditional vs. PGx trial designs

Restricting Access Based on PGx Biomarkers

- Policy implemented via
  - Reimbursement levels/patient copays
  - Prescribing guidelines
  - Prior authorization

- Many NICE appraisal scopes include this language:
  - *"…If evidence allows, consideration will be given to subgroups in whom the treatments may be particularly appropriate."*
  - However, no recommendations to date on PGx use (non-label) to identify such subgroups

- Increases cost effectiveness by minimizing treated, non-responders

Payers Could Also Restrict Use of PGx Drugs with Safety Issues

- Policy implemented via
  - Reimbursement levels/patient copays
  - Prescribing guidelines
  - Prior authorization

- Delivers patient and payer benefit from minimizing costly SAEs

Information Needs of Payers on Stand-Alone PGx Tests are Similar to Other Technologies[3]

- Well-designed studies demonstrating PGx impact on
  - Clinical outcomes
  - Economic outcomes
- Studies comparing PGx testing to usual care
- Studies conducted in real-world populations
- Studies published in peer-reviewed literature
- Algorithms or guidelines to guide use in clinical practice
- Patient and clinician education

[3] Deverka et al. Clin Pharmacol Ther 2007; 82:427-434.

In General, This Evidence has Not Been Available Making Coverage Decisions Challenging

- Coverage decisions dependent on[4]
  - Strength of evidence
  - Correlation between PGx test and clinical action
  - Incorporation of PGx test into clinical guidelines

- CMS recently ruled against coverage of PGx testing for warfarin
  - Impact on "real world" patient outcomes was not available
  - As a result, CMS recommending Coverage with Evidence Development (CED) for warfarin PGx tests
- Fundamental issue—who pays to develop the evidence base for stand alone PGx tests?

[4] Meckley LM, Neuman PJ. Personalized medicine: factors influencing reimbursement. ISPOR Annual Meeting, Orlando, 2009.

PGx May Impact a Drug's Commercial Opportunity

- Decreases treatment population
- Competition against product w/o PGx test
- Opportunity to capture efficacy improvement in product price
  - Maintain similar cost effectiveness position
- PGx may drive market share in targeted population

In General, European HTA of PGx Drugs Have Included the PGx Test as a Component of the Drug Cost

- The costs include all direct health care costs, including the cost of the PGx test
- The outcomes include the clinical and economic outcomes attributable to the drug
- The role of the PGx test has been to select the appropriate patients for drug treatment
- PGx test costs typically included in a budget impact analysis for payers
- When stand-alone PGx tests are recommended for current treatments (e.g., warfarin), these are viewed and evaluated according to a diagnostic test framework

PGx Test May Have Particular Value to Payers in Tumor Types that Have Larger Patient Populations

Level of Desirability of Biomarker

	Breast Cancer	CRC	NSCLC	Pancre-atic	Melan-oma	RCC	HCC
High	✓	✓					
Med			✓				
Low				✓	✓	✓	✓

High impact in large tumor types

- Narrows eligible population and therefore potential budget impact
- Less unmet need in general treatment, but value in extended efficacy for specific patient population

Lower impact in small tumor types

- Already small patient population therefore payers are less concerned about narrowing it
- Low existing survival makes any additional survival valuable at some level

✓ Acceptable in majority of countries

Ref.: IMS Research