The Role and Economic Impact of Gene Patents in Drug and Diagnostic Development

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Genetic variation is responsible for all inherited aspects of our lives, including variability in drug response

eye color

height

disease

personality

drug response variability

One size fits all isn't working for anyone

Patients

- Drugs are not precise
- Too long to get it right
- Many don't respond at all
- *Patients are suffering*

Drug Companies

- Not enough winners
- Billions lost each year
- Blockbuster model is dying

MANY stalled drugs are better than existing treatments for a subset of patients

It's not working for investors and payers either

Genetic Guided Diagnostic and Drug Development

Why

- Improve patient care by better selection of therapies
- Change healthcare paradigm
- Capture sustainable market value

How

- Identify clinically important questions with genetic variability
- Discover genetic contribution
- Minimize adverse events or exclude non-responders

Impact

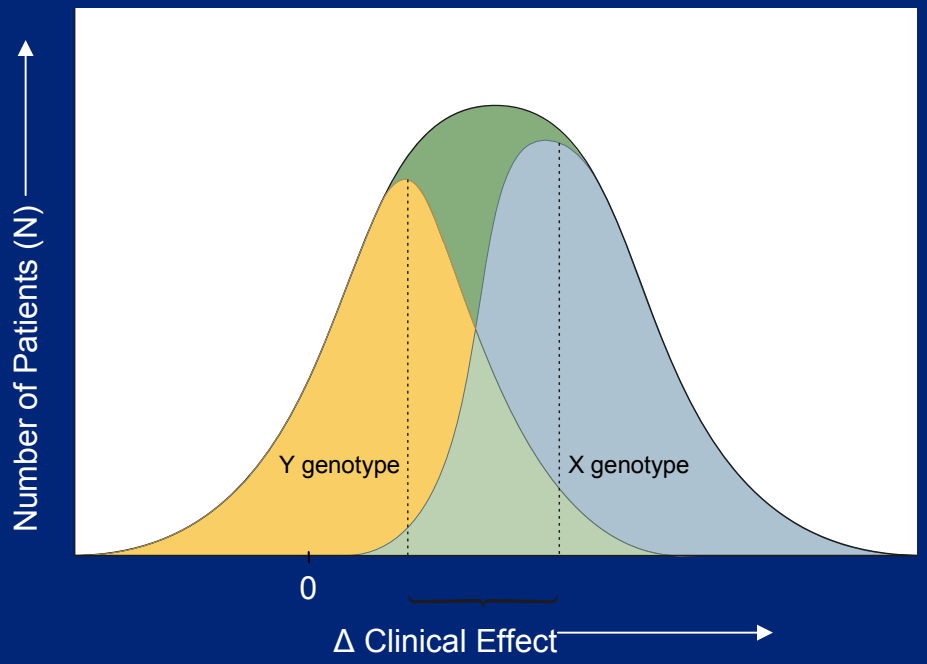
- Add science to the “Art of Medicine”
- Increase appropriate product usage

Use Patents for PGx Diagnostics are Critical but not Sufficient to Create Clinical and Commercial Value

- A PGx “diagnostic” is generally a probability assessment
- Options to care must exist
  - Results from the “diagnostic” should alter patient care
- Clinical Utility of the probability assessment must be valid
- Reimbursement is key
  - single test generates less value
- An approved label is critical
- Incorporation into clinical practice has many barriers

A Genetic Diagnostic will Provide a Probability Assessment: to Add Science to the "Art of Medicine"

Is there a genetic contribution to response and how can it be found?



Current Example of Efficacy Probability: Meridia Label

Approximately 60% of patients that lose at least 4 pounds in the first 4 weeks go on to achieve a placebo-subtracted weight loss of > 5% of their initial body weight by 6 months. Conversely, of those patients on a given dose of Meridia who did not lose at least 4 pounds in the first 4 weeks of therapy, approximately 80% did not go on to achieve a placebo-subtracted weight loss of > 5% of their initial body weight on that dose by month 6.

Can we avoid the wasted 4 week trial of Tx?

Who will order, pay for and interpret the test?

A Pharmacogenomic Application Must Have Clinical Utility

- Wen-Hung Chung, Nature, April 2004: Demonstrated striking association of the allele HLA-B*1502 with the carbamazepine-induced Stevens-Johnson syndrome in China (93.6% PPV and 100% NPV).
- There are only 8 cases of carbamazepine-induced SJS per 1 million person years.
- What is the clinical utility of screening millions of subjects to determine risk of this very rare event?

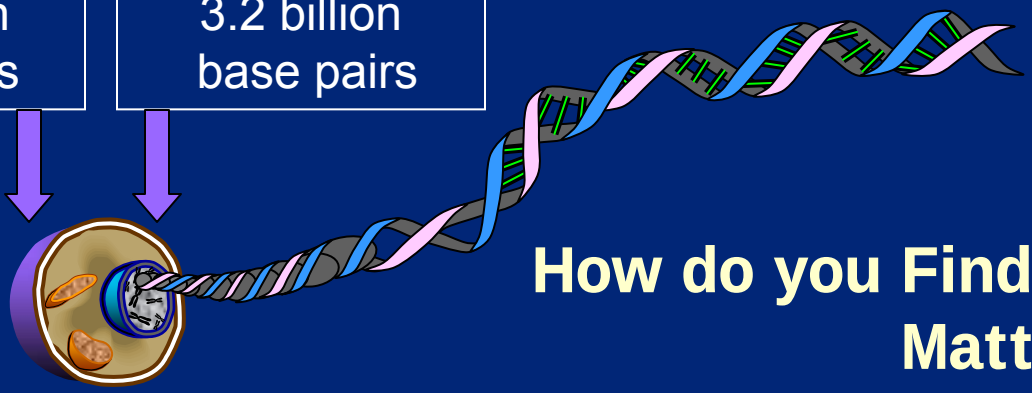
- Daniel Chasman, JAMA, June 2004: Two common and tightly linked SNPs were significantly associated with reduced efficacy of pravastatin therapy.
- Patients with a single copy of the minor allele had a 22% smaller reduction in total cholesterol (only 9.2 mg/dL absolute difference).
- "…the proportion of the variance that can be explained by HMG-CoA reductase SNPs 12 and 29 is small in comparison with the expected influence of clinical determinants such as compliance and diet."

Scientific relevance ≠ clinical relevance

How is a Genetic “Diagnostic” Discovered

Genotyping is one technology that will serve as an example to illustrate importance of patents and exclusivity

From Mother	From Father
3.2 billion base pairs	3.2 billion base pairs



How do you Find the Genes that Matter?
Genetics by the numbers

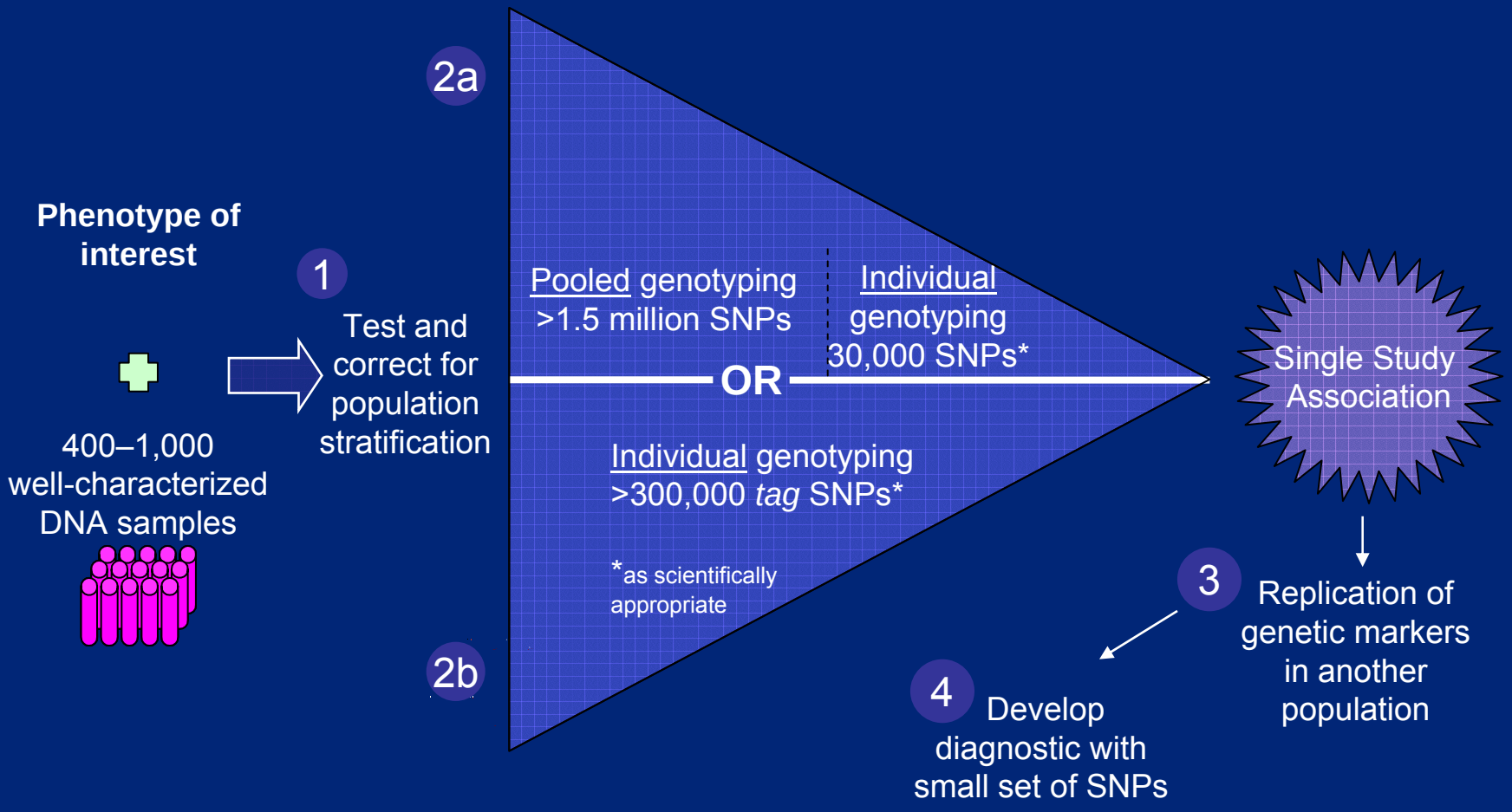
SNPs

Estimated 8-10 million Common SNPs	4 million known SNPs	2.4 million assayable SNPs for flexible use by Perlegen	300,000 – 500,000 “tag SNPs” used for whole genome studies	5,000 – 10,000 used to replicate	2 – 50 SNPs in a diagnostic

Example: Genetic Risk Stratifier of Myocardial Infarction

- Subjects with hypertension, diabetes, and hyperlipidemia are already at risk for MI – which subset is at highest risk?
- Many classes of medications are available for treatment of these diseases: multiple drugs are often required
- Copious evidence exists documenting that optimal control in each area is associated with less events
- Multiple surveys reveal that these diseases are not adequately controlled
- What subset of the population should be optimized with currently available treatments?
- Those at greatest risk for events could receive the most aggressive therapy

Whole Genome Association Study



Controls for MI Critical !

Would Such a Genetic Test Generate Value?

- Value of genetic diagnostics are extremely limited due to one-time use
- Due to this fact most genetic tests are expensive
- Expense may precludes general use for guidance on aggressiveness of treatment - particularly with generic drugs
- Who performs the test?
  - MD
  - Central Lab
  - Pharmacist
- Who reimburses for the genetic test?
- How to market the test once approved?

- Without exclusivity and patent protection, this approach will not be pursued

What about a Drug-Diagnostic Combination Approach: FDA's Concept Paper


Draft
Preliminary Concept Paper — Not for Implementation

Drug-Diagnostic Co-Development
Concept Paper

Draft — Not for Implementation

Department of Health and Human Services (HHS)F
Food and Drug Administration (FDA)
April 2005

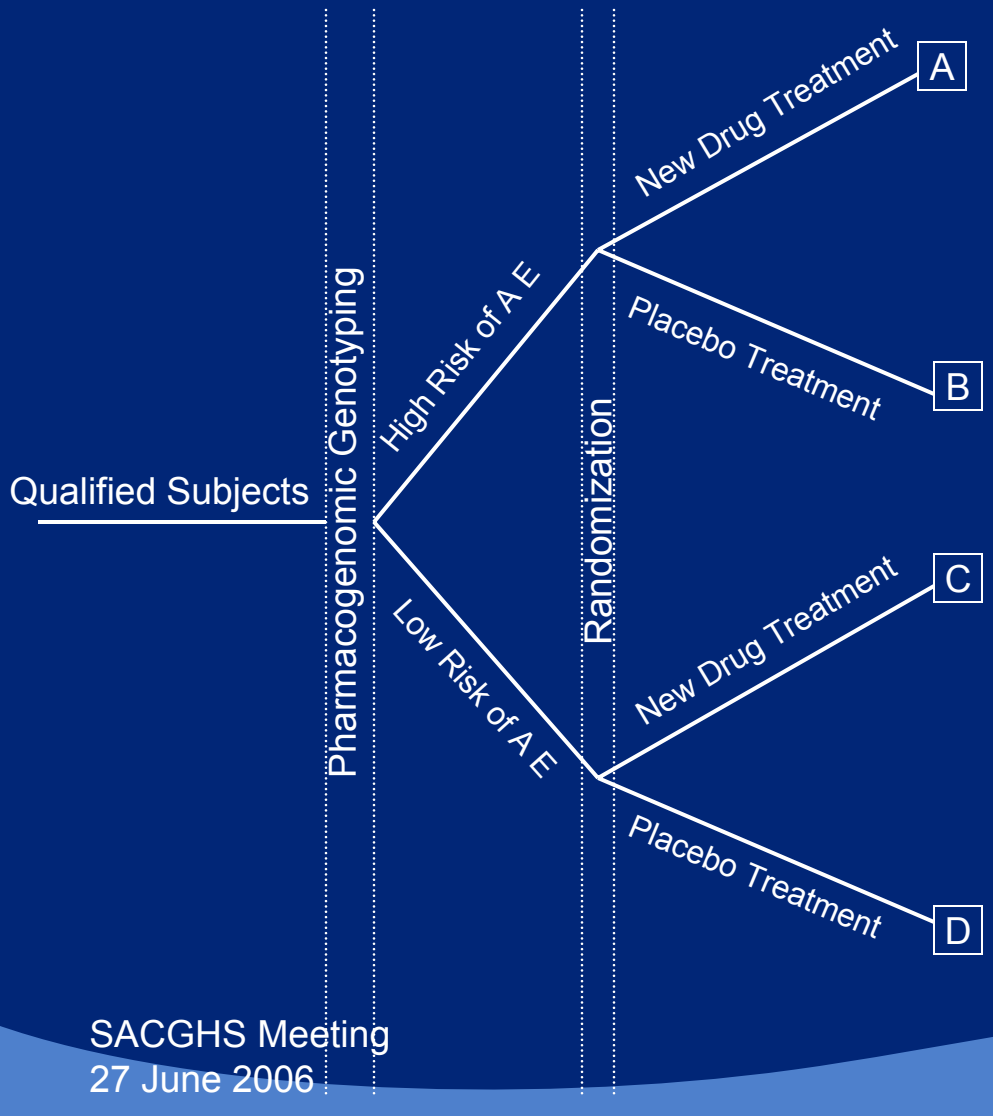
- Draft published in April 2005
- Public comments now in process

- What would this look like?

Example of a Drug-Diagnostic Development Approach to Decrease an Adverse Event

- Assume your goal was to reduce a class effect adverse event by 50% and simultaneous introduce a new drug in that class
- The adverse event was not immediately life threatening but could lead to hospitalization
- Other drug classes are available for the treatment of this disease
- Providing information to the physician about increased risk of the adverse event would allow other options to be explored
- Requires simultaneous development of the diagnostic with the drug
- Requires identification of an acceptable “draft” diagnostic prior to conduct of pivotal trials

Combination Filings for Dx and Drugs: Requires Unique Study Design



Statistical Analyses

- 1° Efficacy Analysis compares Δ from baseline in 1° Endpoint between groups C vs D
- Safety analysis includes all subjects
- 1° Diagnostic clinical utility analysis compares % A E in group A vs C
- Replication generally required

Patent on Association of PGx Diagnostic Critical but not Sufficient

- Clinical utility must be adequate to convince FDA to restrict use of the drug to only those tested and appropriate
  - IP will not protect use of the drug without use of the diagnostic
  - Reimbursement not likely if test is only informative
  - Clinician reticent to adopt technology that is only informative
  - Threat of litigation not an incentive
- Incorporation into clinical practice has many barriers that the label can help overcome

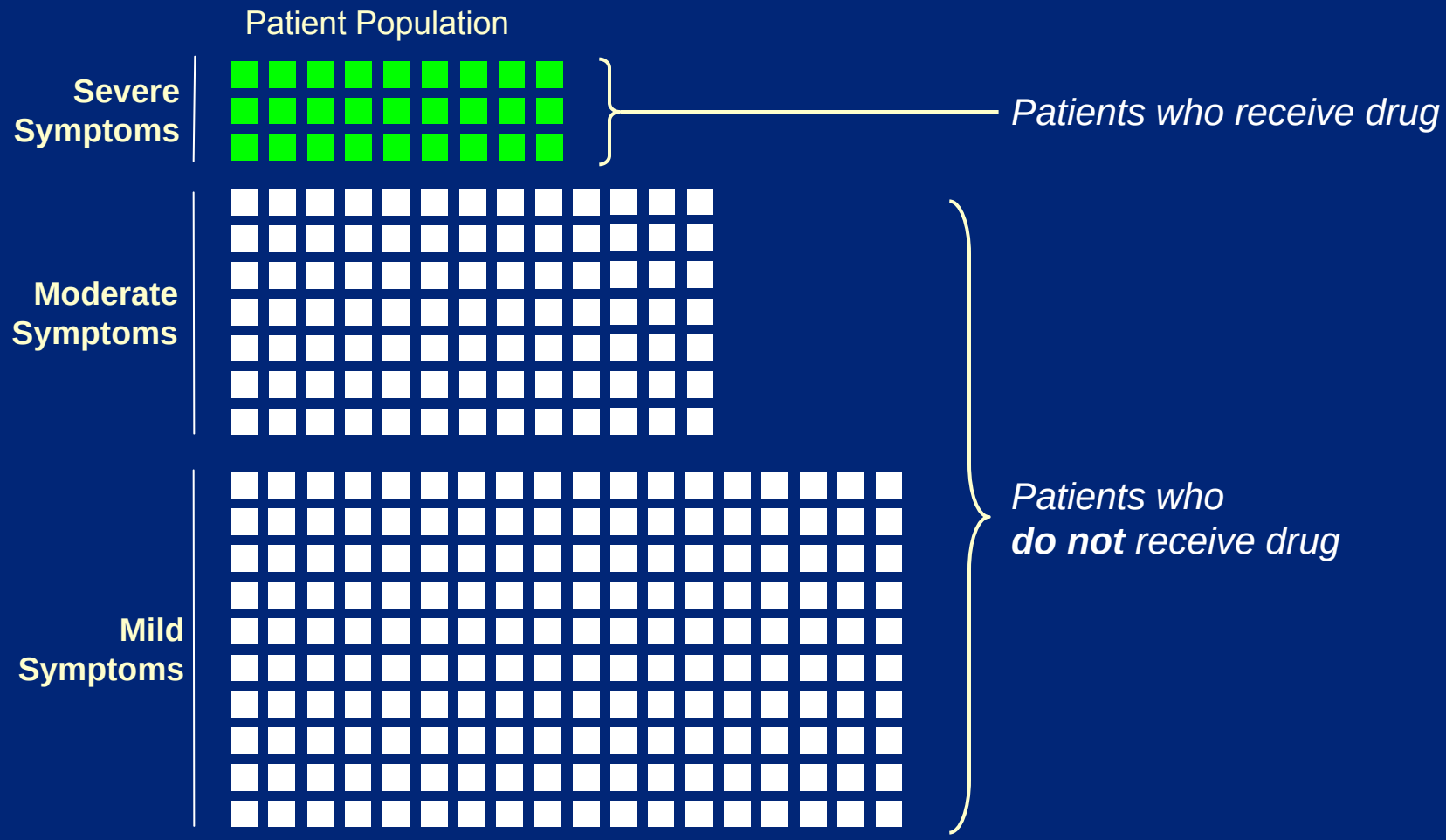
A Genetic Diagnostic Targeting Efficacy Could Also be Useful: Provided Treatment OPTIONS are Available

- Allows subjects to be assigned to beneficial treatments sooner
- Instead of just getting more subjects on the drug, more appropriate subjects are being treated
- Others who would not benefit can be appropriately treated with other therapies

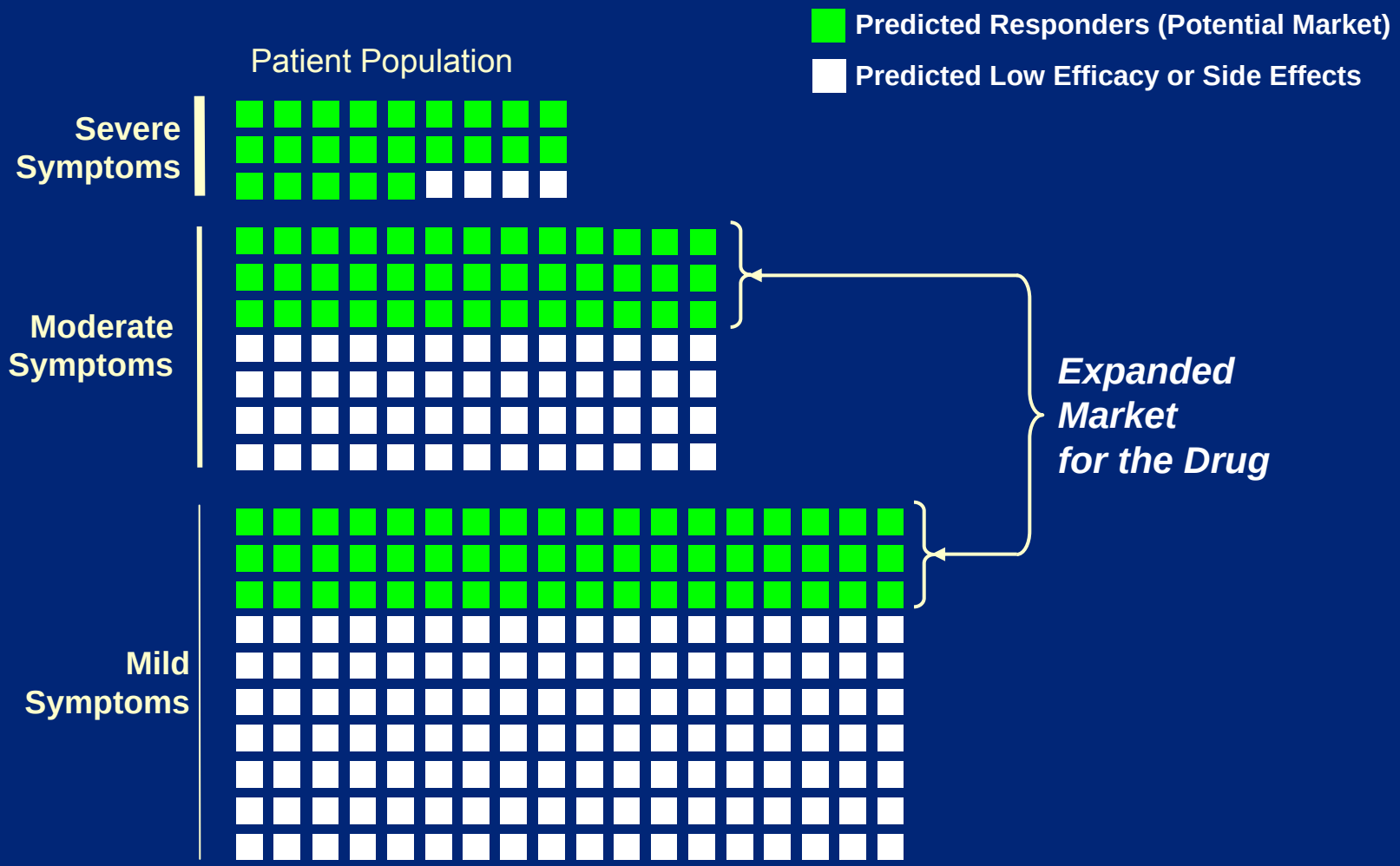
Commercial Acceptance of "Targeted" Drugs:

Some drugs that could benefit many patients are restricted to those with the most severe symptoms…

Treatment Paradigm Without Pharmacogenomics



Predicting drug response based on DNA could mean expanding the market to more patients that could benefit from the drug . . .



Reaping the Benefits of Genomic and Proteomic Research

Recommendations by Committee on IP Rights in Genomic and Protein Research and Innovation

- Excellent, informative overall document
- Concurrence with most recommendations
- Additional Suggestions:
  - Recommendation 7: Add industry scientists developing these technologies to USPTO advisory committee
  - Endorse the utility standard that a patent applicant show “specific benefit in currently available form”
  - Recommendations 10 and 12: Validity, features, properties, inherent characteristics or advantages of the invention (diagnostic) are already under authority of FDA if the diagnostic is approved. If it is not approved it will not be widely used. Do we ask for independent verification of drug efficacy?

How Can We Lower the Barrier to Routine Clinical Use of Appropriate PGx Diagnostics?

- FDA support and Critical Path Initiative
  - Finalization of co-development guidance
- Patent protection of discovery of validated genetic and proteomic associations
- Education of USPTO on immerging science and application
- Continued NIH support of basic and clinical science (Genome Center, Hap-Map, Translational Medicine)
- Support anonymous access to samples for exploratory research
  - "Guidance on Informed Consent for In Vitro Diagnostic Device Studies Using Leftover Human Specimens that are Not Individually Identifiable"
- Commission a group to evaluate reimbursement decisions so that this final barrier can be overcome in appropriate cases

Questions?