Ethical, Legal and Policy (ELP) Implications of Pharmcogenomics

Patricia Deverka, MD
Duke University
Institute for Genome Sciences and Policy's
Center for Genome Ethics, Law and Policy
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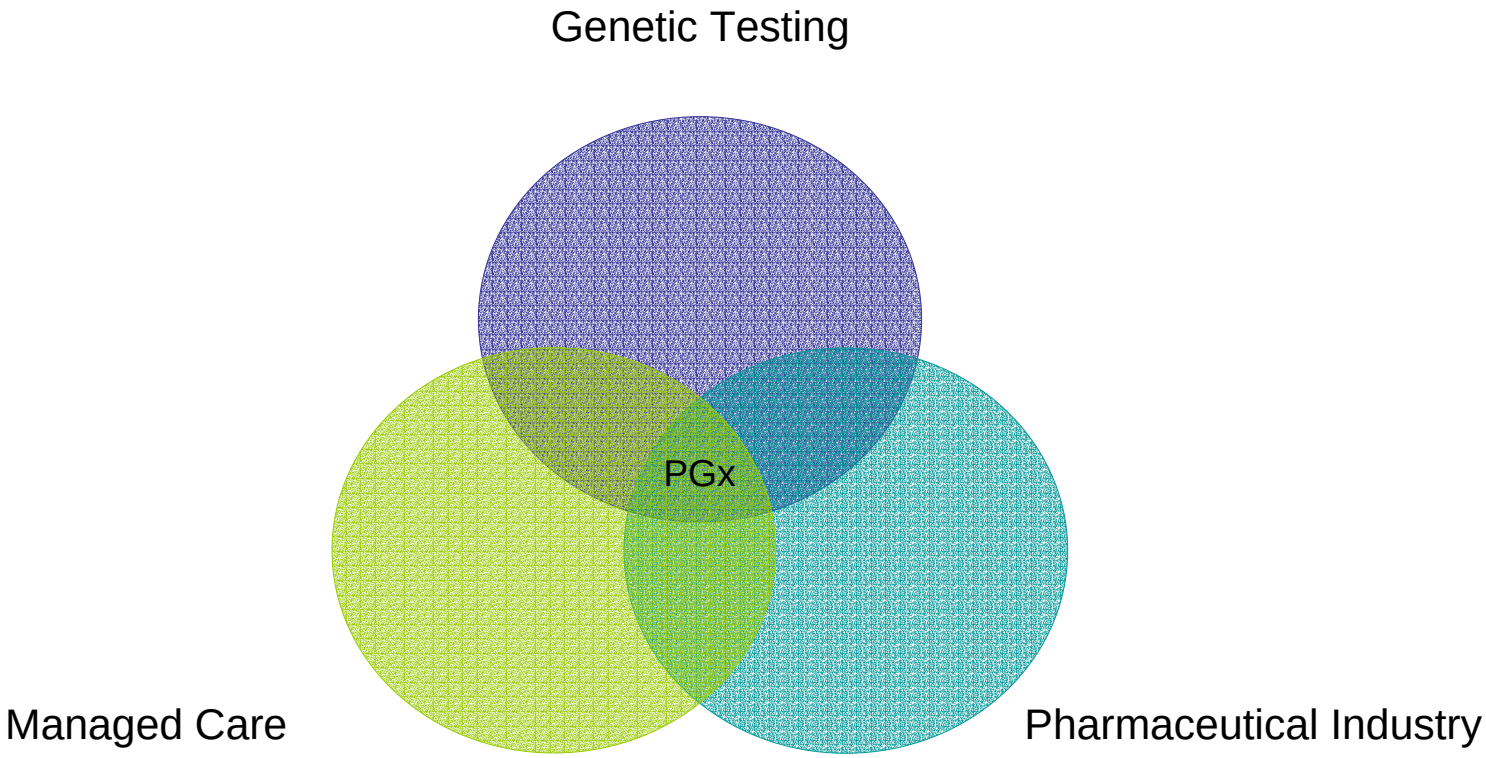
Pharmacogenomics brings 3 controversial areas together



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Current and potential applications for PGx determine the ELP issues

- Research
  - New drugs
  - Existing drugs
- Clinical practice
  - "Right drug, right patient, right time, right dose"
- Post-marketing surveillance
  - PGx tests and drugs
  - Current system would require major redesign and large investments

ELP concerns in clinical research

- Informed consent in the era of DNA banking
- Privacy and confidentiality concerns
  - Degree of anonymization is critical
  - Procedures to limit unauthorized disclosures
  - Potential for discrimination
- Harms to families or groups
  - Collateral information
  - Race-related information
- Stratification
  - Orphan subgroups
  - Genetically homogenous groups resulting in less safety data
- Incentive structure
  - IP issues
  - Focus by pharmaceutical companies on new drugs, rather than marketed drugs (branded and generic)

PGx research requires creation of biorepositories linking genotypic and phenotypic information

- Informed consent framework adapting to unique aspects of biorepositories
- Shift in emphasis from protecting subjects from physical harms to primarily informational harms
- Consent to all unspecified future research studies (blanket consent) may not be considered sufficient to meet the standards of informed consent
  - Difficulties associated with reconsent procedures
- Exclusive focus on the individual research subject is arbitrary from an ethical standpoint
- Recognition of potential for group harms, even with anonymized samples
- Debate over the importance of research participants having some measure of control over the research done with their stored tissue
- Narrow criteria for recontact and disclosure of results
  - Do investigators have a duty to contact participants years after a study is completed?
- Separation of informed consent for collection and storage of tissue samples for PGx testing from participation in clinical trials

PGx and race

- No precise biological or genetic definition for race and ethnicity
- Some PGx variants more common in some ethnic/racial groups than others
- Clinical studies demonstrating important differences in response to conventional pharmacologic therapies across various racial groups
  - Much debate about the scientific validity of these studies
  - BiDil example
    - PGx may actually resolve problems with prescribing drugs based on self-identified race

PGx and race – potential harms

- Reinforce notion that racial differences have a genetic basis
- Statements about efficacy based on evidence in one particular population not valid in genetically different populations (unless controlling for differential distribution of genetic variants)
- Drugs could be marketed to particular racial groups in a misleading manner
  - Give impression that all members of that group would benefit
  - Give impression that the drug is more effective than other non-racially defined medicines
- If certain genotypes linked to poor medication response more common in certain racial minorities, members could be stigmatized by implication they are more difficult or expensive to treat
- Physicians may use race instead of genotype as basis for drug selection

“Orphan” genotypes

- PGx data may reveal a drug is unlikely to be safe or effective for a particular genotypic subgroup of general population or disease group
- PGx data might reveal that a formerly large market for a drug for all with a particular disease is really comprised of genotypic subgroups of those with disease
- Potential adverse result is that drugs will not be developed for these genetically–defined subgroups
- Ethical concerns arise if:
  - No other safe and effective treatment available for the disease
  - Orphan subgroup so small that they never attract investment over the duration of drug patent
  - The drug in question that works well for the larger group must provide substantial benefit for a serious disease

ELP issues in clinical practice

- Marketplace introduction of PGx testing without adequate validation
  - Lack appropriate regulatory framework
  - Failure to define a clinically and economically relevant evidence base for PGx tests and test-drug combinations
- Suboptimal access to and use of PGx testing
  - Professional and payer knowledge gaps about genetics
  - Defining physician obligations to offer a PGx test and obligations to follow PGx test results
- Liability
  - Physicians, pharmacists, pharmaceutical companies
- Testing without adequate consent
- Inappropriate uses of PGx testing as a result of direct marketing (DTC advertising)
- Secondary information conveyed by PGx results that may produce psychosocial harms
  - Likelihood of other diseases; Progression of current disease
  - Unsolicited information about family members
- Discriminatory uses of PGx information by third parties
  - Insurers/Employers - based on belief that disease cannot be adequately treated given currently available therapies or based on knowledge of disease predisposition
- Higher drug costs leading to barriers to access

Rapid and unmanaged introduction of genetic tests into marketplace

- Inappropriately induces demand for services
- Hype
  - Reinforces notion of genetic determinism and essentialism
- Predictive values of PGx tests may be too low to be clinically useful
  - Shift public and private resources away from more effective ways of improving public health
- Lack of information about PGx tests may lead to real harms to patients by physicians and payers
  - Inaccurate test results
  - Poor counseling from physicians (unable to accurately interpret test results)
  - Coverage policies that are not justified by the science

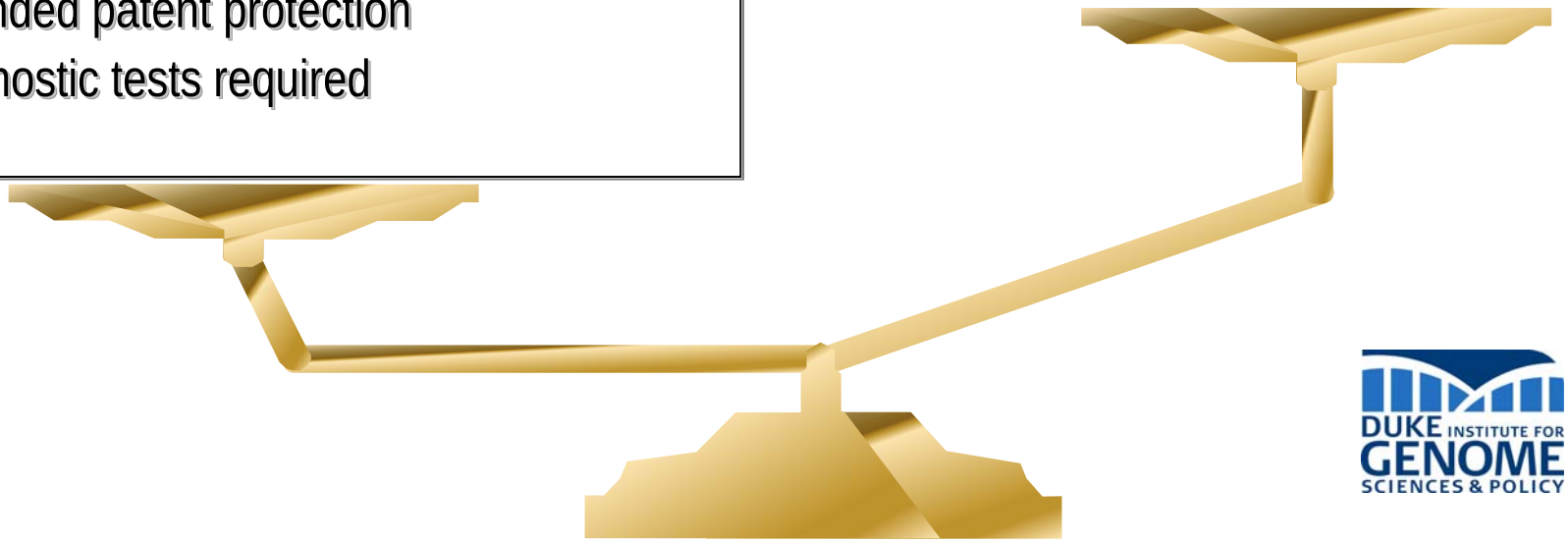
Payer perspective: what will be the impact of pharmacogenomics on total healthcare costs?

Decreased healthcare costs

- Avoid use of expensive drugs in non-responders
- Save patients avoidable adverse effects
- Improved compliance
- Improved health outcomes
- System cost offsets

Increased healthcare costs

- Higher drug prices
- Expanded patient populations for drugs
- Enforcement of privacy safeguards
- Extended patent protection
- Diagnostic tests required



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Use of PGx testing by payers

- Whether PGx becomes an important element of clinical practice depends upon whether (and how) it is reimbursed
- PGx needs to be evaluated in context of current cost-containment practices
- Ethically desirable at individual level not to pay for a drug that is unsafe or ineffective
- Ethically desirable at group level because it fulfills the stewardship obligation for managing collective and scarce resources
- Both rationales are difficult to operationalize given probabilistic, not binary nature of results
- Tension between policy rationality versus individual patient rationality
- Ethical justification is predicated on acceptable level of reliability and predictive value of pharmacogenetic tests and an allowance for appeals process

When might direct consumer access to PGx testing be permissible?

- When tests meet appropriate standards of analytic and clinical validity and results are conveyed in an accurate and understandable manner
- When test contains information about response to over-the-counter drugs, dietary regimens, etc
- When individual has insurance coverage for the drug, but not the corresponding PGx test
- When individuals are concerned about stigmatization or discrimination

Is PGx special or unique relative to other new medical technologies?

YES

- Uniquely identifying
- Permanency of sample
- Breadth of information
- Uniquely predictive ("Future diary")
- Familial implications
- Collateral information
- Complexity of science
- Distribution of genetic variability differs by race/ethnicity

NO

- PGx is just a prescribing tool
- Testing in context of determining best intervention
- PGx results can be separated from disease susceptibility results
- Genetic variation only one factor impacting drug response
- Reinforces notions of genetic determinism, essentialism, exceptionalism
- Will make patients less willing to be tested
- No evidence of discrimination

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PGx highlights need to resolve long-standing problems regarding integration of new technologies into clinical practice

- Lack of information relevant to clinical practice
  - Health technology assessment infrastructure
  - Translational researchers and funding
- Lack of clear regulatory requirements
- Lack of cost-effectiveness data
- Lack of a robust PMS system
  - Underreporting; missing critical data elements
  - Underfunded
- Lack of information technology capabilities across the healthcare system