

Protecting Patients from Invalid and Excessive Claims in Personalized Medicine

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Topic

The Products

- Targeted therapies (drugs and biologics)
- Tests (and testing services) that predict patient response to specific therapies

The Objective

- Protect patients from invalid and over-hyped claims about what these products can do

A Question of Strategy

- How to draw the line between regulation of medical products and regulation of medical practice

Thesis

- Making targeted therapies safe and effective may require significant control over how physicians use products in clinical settings. This is not a traditional focus of FDA oversight.
- Careful sharing of oversight responsibilities, and possible creation of new regulatory institutions, may be required, involving:
 - FDA
 - State medical practice regulators
 - The drug-injury compensation framework
 - Systems for approving health-care reimbursements
 - The medical profession and scientific community

Traditional Line between Product and Practice Regulation

“[FDA-approved product] labeling is not intended either to preclude the physician from using his best judgment in the interest of his patient, or to impose liability if he does not follow the package insert.”

Dep't of Health, Education & Welfare, FDA, Legal Status of Approved Labeling for Prescription Drugs; Prescribing for Uses Unapproved by the Food and Drug Administration, 37 Fed. Reg. 16,503-16,505 (July 30, 1972)

Types of Claims for Tests Used in Personalized Medicine

Analytical Claims	The test detects the presence or absence of a gene or other biomarker with a specified level of accuracy
Clinical Validity	The biomarker is known to affect how the human body works (e.g., whether a person can make a specific liver enzyme that affects drug metabolism)
Clinical Utility	This knowledge can affect clinical outcomes (e.g., the test can be used to screen patients to reduce drug-related injuries)

FDA requires such claims to be substantiated with data, if a test manufacturer is going to make them

SUPPLEMENT: Two Types of Tests

In vitro diagnostic product (IVD product):

- Made by a device manufacturer
- Sold to labs for use in clinical testing
- Regulated by FDA (Federal Food, Drug & Cosmetic Act 21 USC 301 *et seq.*)

Lab-made tests (“home brews”)

- Made by labs for own use in testing patients
- Regulated by HHS/CMS/CDC under Clinical Laboratory Improvement Amendments of 1988 (*42 USC 263a et seq.*; *42 CFR 493*)
- FDA has statutory authority to regulate them, but has not done so in an exercise of enforcement discretion
- Claims are internally validated at the lab but are not reviewed by an external regulator

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Traditional FDA Review of Genetic Tests

Intensity of Review →

Scope of Coverage ↓

	Analytical Claims	Claims of Clinical Validity	Claims of Clinical Utility
IVD Products	✓	✓	✓
Home-brew Tests			

NIH-DOE and SACGT Proposed Policy

Intensity of Review →

Scope of Coverage ↓

	Analytical Claims	Claims of Clinical Validity	Claims of Clinical Utility
IVD Products	✓	✓	✓
Home-brew Tests	✓	✓	✓

NIH-Dep't of Energy Joint Task Force (1997)
Secretary's Advisory Committee on Genetic Testing (2000)

The Traditional Product Regulatory Paradigm

- Prior regulatory review of claims made by product manufacturers
- Product labeling to communicate indicated uses and warnings to clinicians
- Limited or no federal regulatory oversight of:
 - Physician compliance with labeling
 - Product-related claims made by physicians

*Can this paradigm do the job
in personalized medicine?*

Variable Labeling of Targeted Therapies

Labeling Scenario	Description	Example
Cross-labeling	Drug and test cross-reference each other and give instructions for joint use	Trastuzumab (Herceptin™)
Non-specific reference	Disclosure that drug response varies with a particular gene, but no test product or instructions specified	Atomoxetine (Strattera™)
Nondisclosure	Drug with known or suspected variability that is undisclosed in labeling	Many

Limits to Cross-labeling as a Solution (even if all tests were FDA-regulated)

- Unclear statutory authority for FDA to require cross-labeling of drugs and tests made by different manufacturers
- Rapid evolution of targeting strategies and tests
 - Can labeling keep pace with rapid evolution of targeting strategies and new tests?
 - Can labeling be specific enough to guide clinicians in day-to-day prescribing decisions?
- Limited impact of labeling revisions on physician prescribing practice

Other Problems Protecting Patients via the product-regulatory framework

- Clinical validity and utility of a targeting strategy depend as much on the claims physicians make about tests, as on the claims manufacturers make.
 - Safety and effectiveness may entail much tighter restrictions on off-label use than FDA traditionally has exerted.
- Off-label use is unusually complex for these therapies, due to joint use of two products, either or both of which can be used off-label.

Different Off-label Use Scenarios Raise Different Concerns about Safety & Efficacy, Ethics, and Economic Waste

Off-label Use of Drug and Test

- Use of an unsubstantiated targeting strategy to direct the use of a drug to treat a condition for which the drug is not approved.

On-label Use of Drug

Off-label Use of Test/Targeting Strategy

- The drug is being used to treat the health condition for which it is intended.
- Individual patient response is predicted, based on unsubstantiated beliefs about the impact of a particular gene on drug response.

Off-label Use of Drug On-label Use of Test/Targeting Strategy

- The drug is approved for use in one illness and is known to be metabolized by a particular enzyme. Now it will be used to treat another illness, but patients will still be checked to see whether they have the enzyme they need for proper metabolism of the drug.

Use Directly Counter to Indicated Targeting

- Use of a targeted therapy in a population subgroup other than the one for which it has been approved (e.g., giving a therapy that is for HER-2 positive tumors to a patient whose tumor was tested and shown to be HER-2 negative).

Options for Addressing Off-label Use

- Continue a permissive, “one-size-fits-all” policy on off-label use of FDA-approved products
 - Rely primarily on the tort framework to control off-label uses that are particularly wasteful or dangerous
- Nuanced policy on off-label use of products in personalized medicine
 - Distinguish the various scenarios of off-label use and take steps to manage the “bad” ones

Nuancing Alternatives

- **Ban or discourage the “bad” off-label uses**
 - Expand FDA’s authority to impose restrictions on clinical use of targeted therapies and tests
 - Enhance state requirements for physician compliance with product labeling for these products
 - Require involvement of licensed PGx counselors in certain types of prescribing decisions
 - Deny insurance reimbursement for “bad” uses
 - Refine tort liability standards to single-out “bad” uses of targeted therapeutic products
- **Allow off-label use subject to informed consent**
 - Leave off-label use within physician discretion, but require informed consent for uses that have a particularly dubious risk/benefit profile

Who will decide what is bad?

Integrative Product and Practice Regulation

