

Pharmacogenomic Testing (PGT) and Cancer Therapy

Summary of Medicare Evidence Development
and Coverage Advisory Committee (MEDCAC)
January 27, 2010

Centers for Medicare and Medicaid Services
Office of Clinical Standards and Quality
Coverage and Analysis Group

1/27/2010 MEDCAC Meeting: Purpose

- “CMS seeks guidance from the panel to inform future coverage determinations. We want to ensure that Medicare beneficiaries have access to any demonstrated improved health outcomes of PGT, and are protected from inaccurate or inappropriate pharmacogenomic testing that could compromise therapy or increase the risks of adverse events during therapy.”

— *Source: CMS, November 2009*

Why PGT?

- Anticancer agents are generally toxic, and are given at doses near those that produce adverse effects.
- Individuals vary widely in how they respond to anticancer agents.
- Ideally, treatment with anticancer agents should be guided toward optimizing net benefit (benefits net harmful effects) to patient.

Sheok MH, Evans WE. ALL – a model for pharmacogenomics in cancer therapy. Nature Rev Cancer (2006):6, 117-29

'Classic' Assessment Tools to Individualize Anticancer Therapy

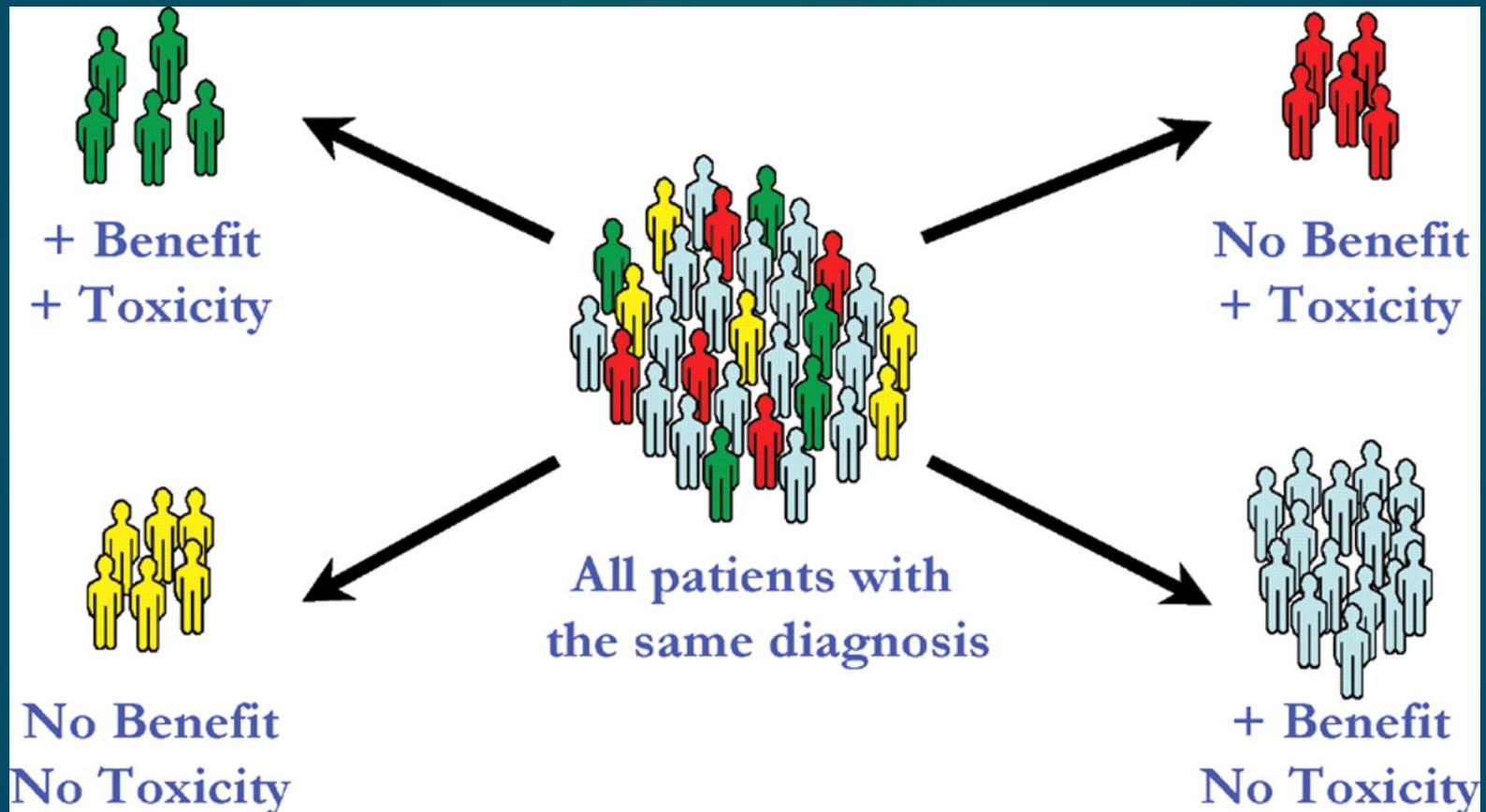
- Height, Weight (→ BSA)
- Age
- Tumor Burden (Residual Disease)
- Other markers of drug absorption / distribution / metabolism / excretion:
 - Hepatic, renal function
 - Plasma protein levels
- Other factors: diet, medications, co-morbidities, etc.

Undevia SD, et al. Pharmacokinetic variability of anticancer agents. Nature Rev Cancer 2005 June; 5: 447-58.

Potential PGT Roles

- Select patients likely (or unlikely) to benefit from a given agent or class of agents (*KRAS* , EGFR antagonists)
- Modify dosage to improve efficacy if genotype data indicates variation in drug metabolism (*CYP2D6* , tamoxifen)
- Indicate patients more likely to experience treatment-limiting adverse events (*UGT1A1* *28 , neutropenia)

Ideal: PGT → [↑ Benefit, ↓ Risk]



*S. Marsh, H. McLeod. Pharmacogenomics: from bedside to clinical practice.
Hum Mol Gen (2006):15, R89-93*

Examples Selected for MEDCAC Discussion

PGT for:	Cancer:	Agent(s):
<i>CYP2D6</i>	Breast	Tamoxifen
<i>UGT1A1</i>	Colon	Irinotecan
<i>HER2/neu</i>	Breast	Trastuzumab
<i>BCR/ABL</i>	CML	Imatinib
<i>KRAS</i>	Colon	Cetuximab or panitumumab

Invited Presentations

Invited Guest Speakers

- **Dr. Andrew Freedman**
Clinical and Translational Epidemiology Branch
Division of Cancer Control and Population Sciences, NIH/NCI

“Cancer Pharmacogenomics: Research Frontiers”
- **Dr. Thomas A. Trikalinos**
Assistant Director, Tufts-New England Medical Center EPC
Assistant Professor of Medicine, Tufts University

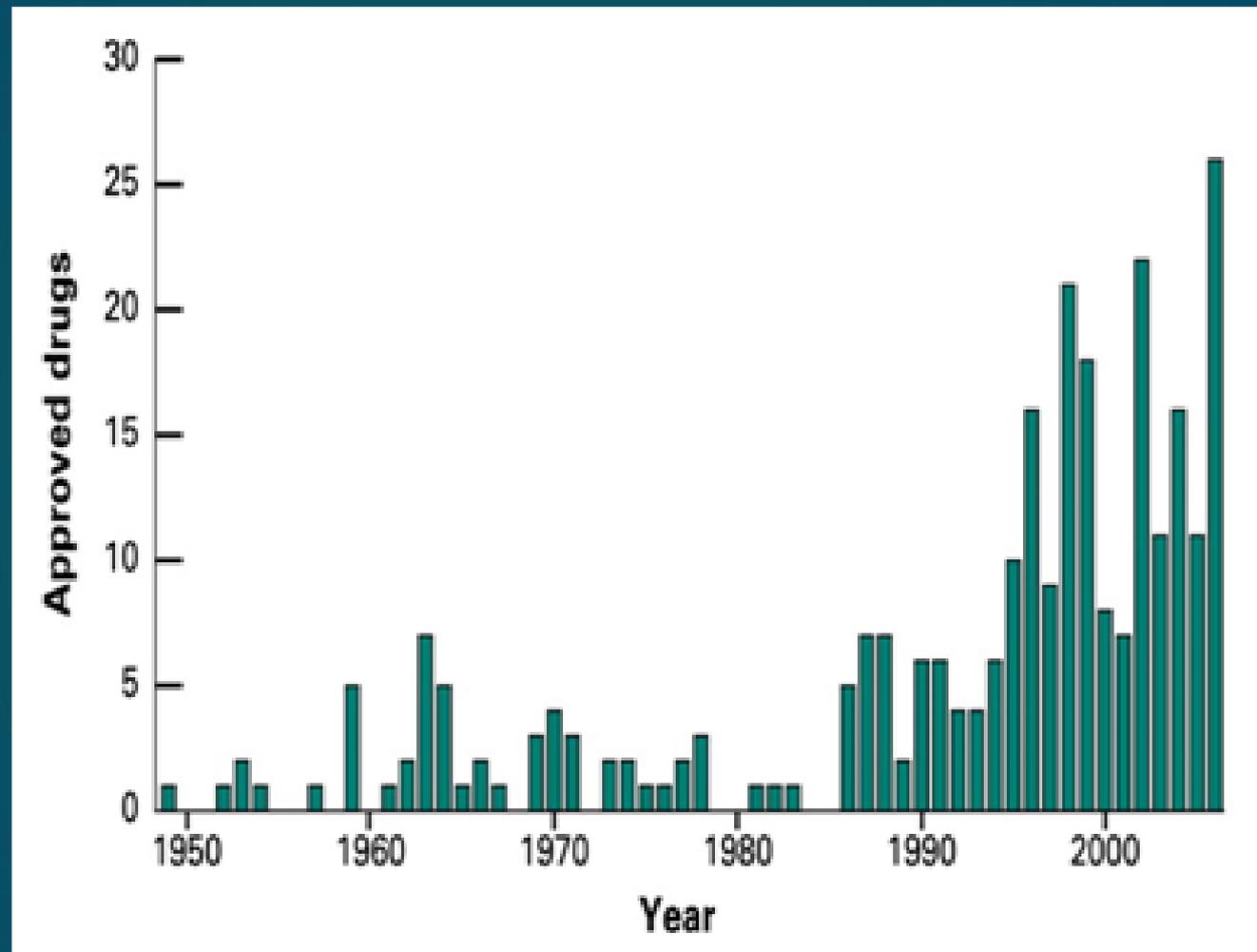
“Reviews of Selected Examples of Pharmacogenetic Testing”
[Sponsor: Agency for Healthcare Research and Quality (AHRQ)]

Advancing Personalized Cancer Therapies: The Role of Pharmacogenomic Testing

Andrew N. Freedman, PhD

Clinical and Translational Epidemiology Branch
Division of Cancer Control and Population Sciences
National Cancer Institute

Currently Approved Oncology Drugs

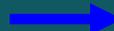
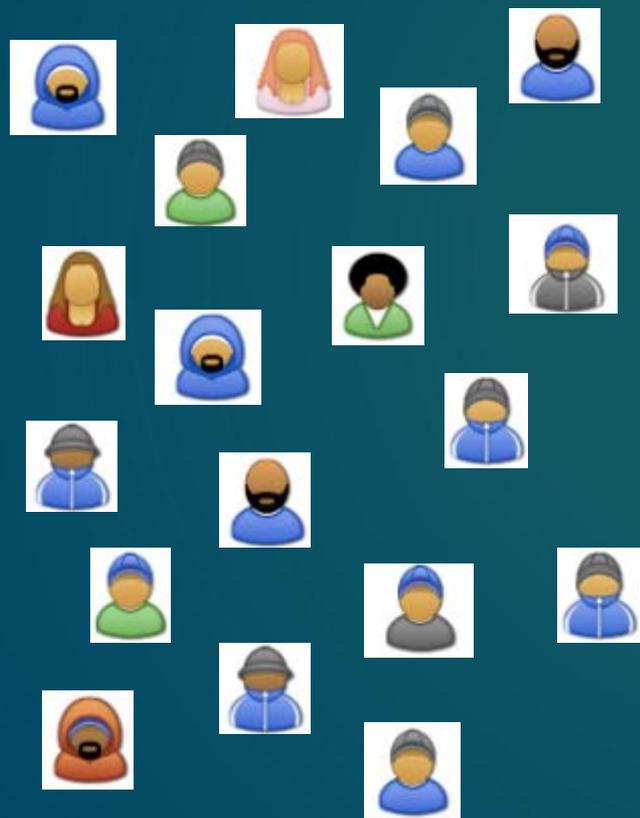


Citation: Listing of approved oncology drugs with approved indications, <http://www.fda.gov/cder/cancer/druglistframe.htm>, and approval statistics, <http://www.accessdata.fda.gov/scripts/cder/onctools/statistics.cfm>. Center for Drug Evaluation and Research, Food and Drug Administration.

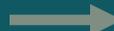
© Oxford University Press 2007. DOI: 10.1093/jnci/djk105

Personalized or Predictive Medicine

Patients with same diagnosis



Respond to treatment



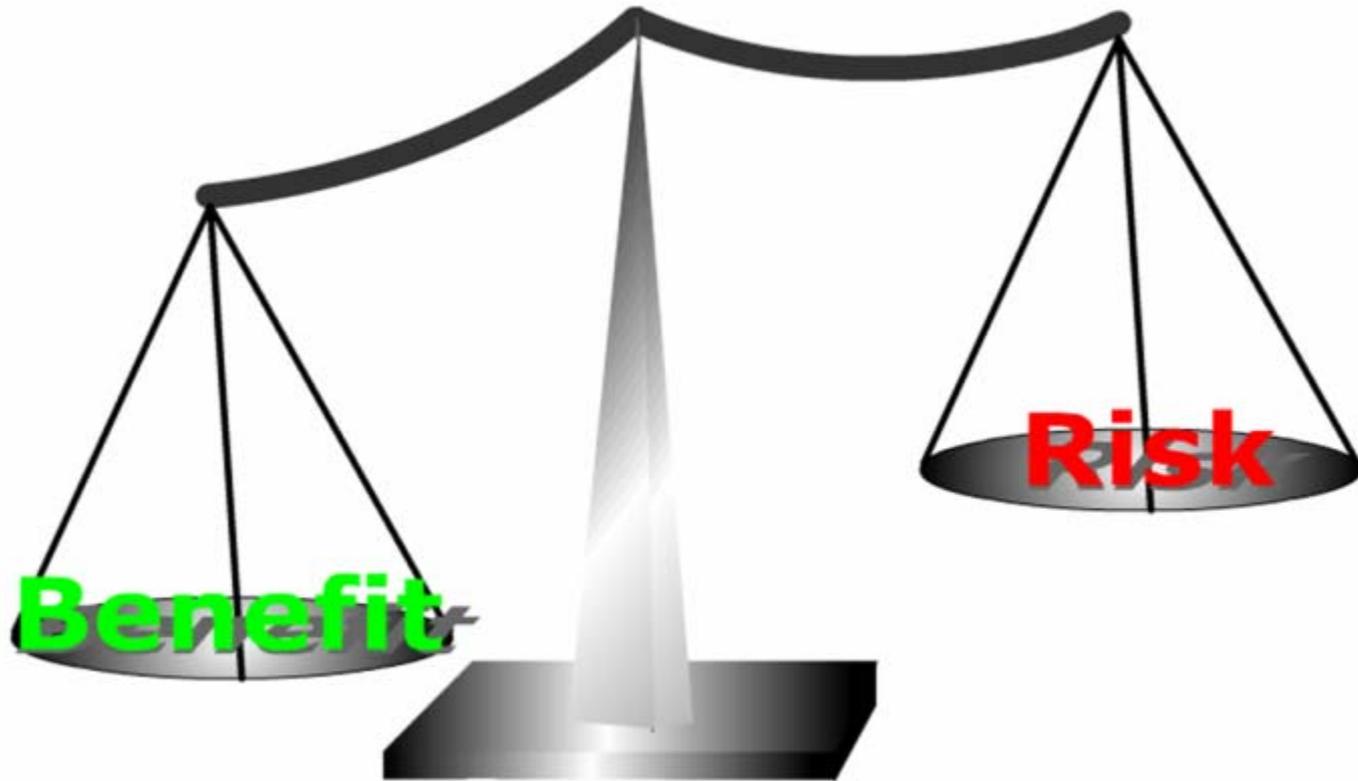
No response to treatment



Experience adverse events



Goal of Genomic Pharmacoepidemiology

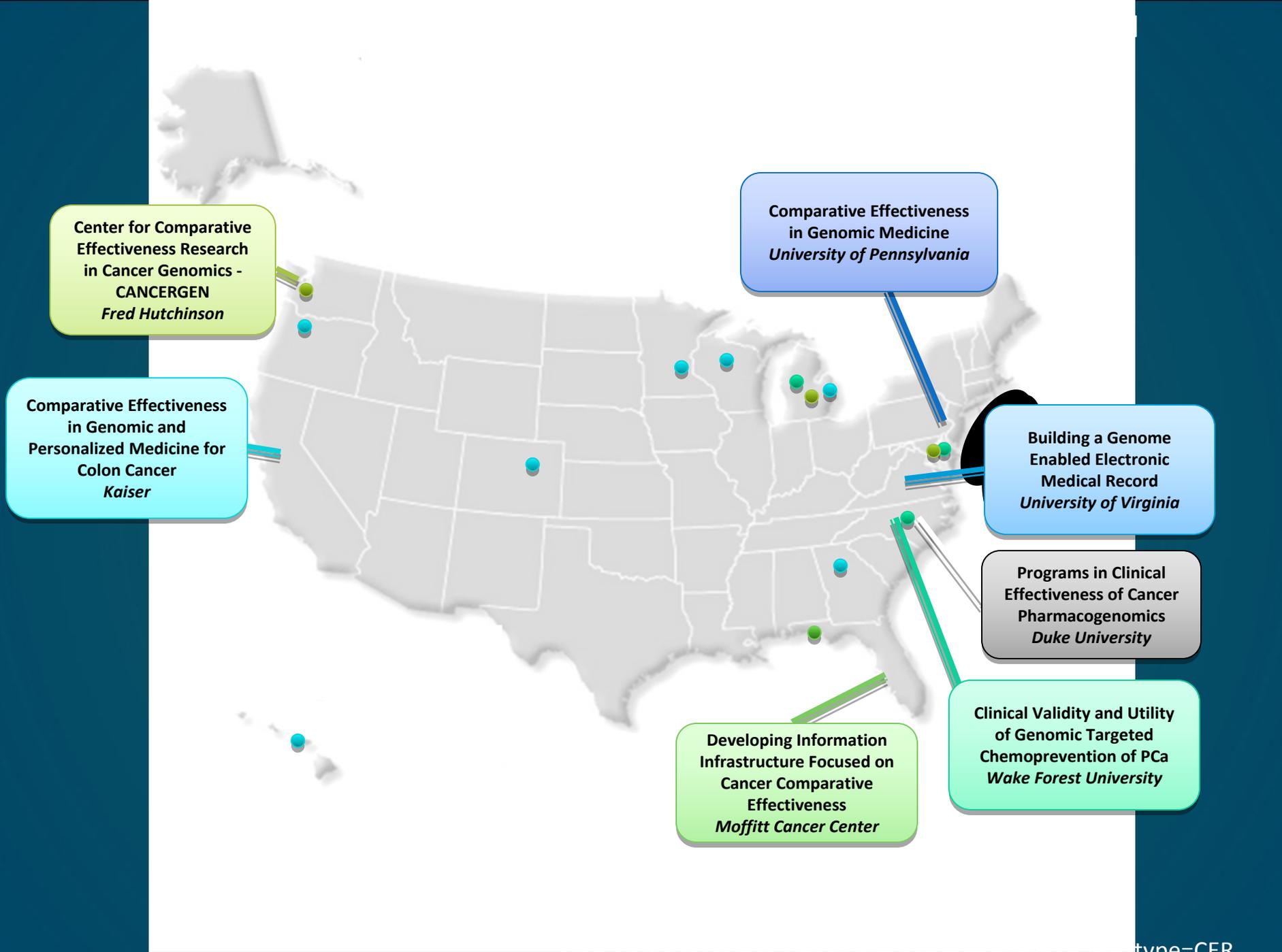


Optimize Therapy So Benefits Outweigh the Risks



"Here's my
sequence..."

New Yorker





“Personalized medicine represents a revolutionary and exciting change in the fundamental approach and practice of medicine and holds unparalleled promise for public health.”

Senator Barack Obama, March 23, 2007

Technology Assessment: Selected Pharmacogenetic Tests for Cancer Treatment:

CYP2D6 for Tamoxifen in Breast Cancer

KRAS for anti-EGFR antibodies in Colorectal Cancer

BCR-ABL1 for Tyrosine Kinase Inhibitors in CML

T Terasawa, I Dahabreh, P Castaldi, T Trikalinos

Tufts Evidence-based Practice Center

Agency for Healthcare Research and Quality

Key Questions for the TA

1. Does the genetic test result predict response to therapy?
2. What patient- and disease-related factors affect the test results, their interpretation or their predictive response to therapy?
3. How does the gene testing impact the therapeutic choice?
4. What are the benefits and harms or adverse effects for patients when managed with gene testing?

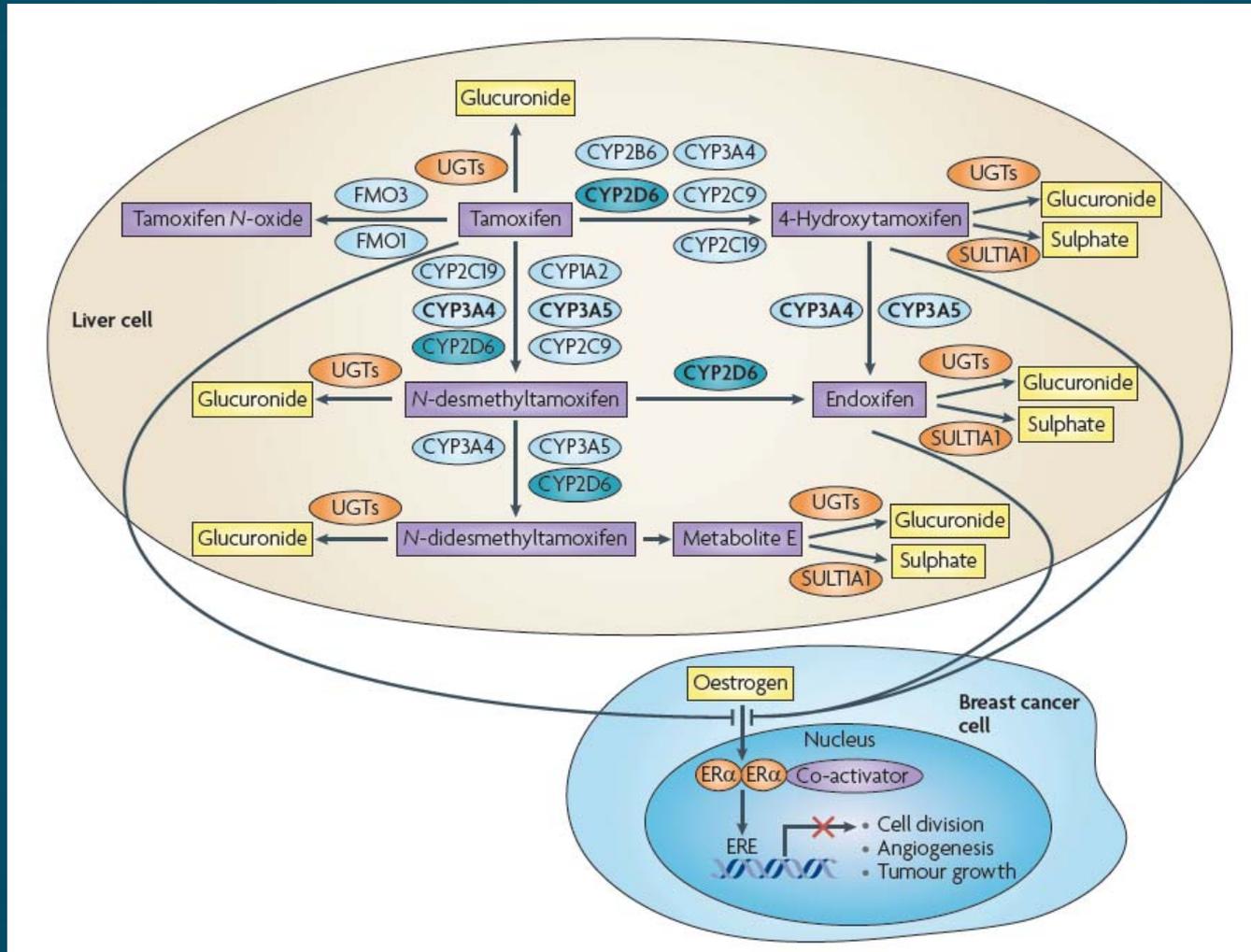
TA's pharmacogenetic test trio

Gene	Drug	Disease
<i>CYP2D6</i>	Tamoxifen	Breast cancer
<i>KRAS</i>	Anti-EGFR antibodies*	Colorectal cancer
<i>BCR-ABL1</i>	Tyrosine kinase inhibitors**	Chronic myeloid leukemia (CML)

*Cetuximab and panitumumab

**Imatinib, dasatinib, nilotinib

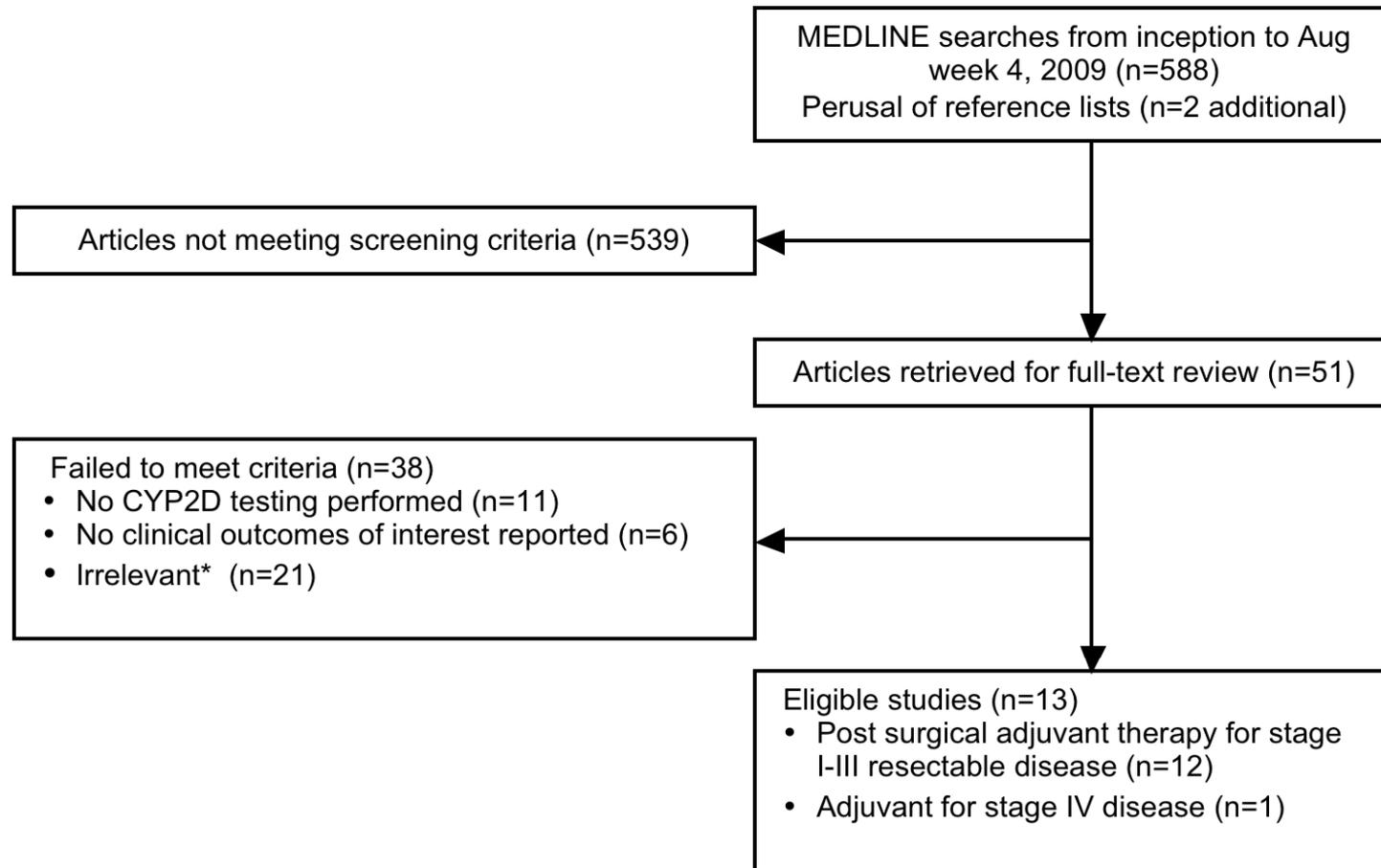
CYP2D6 and tamoxifen for breast cancer



Heterogeneity of *CYP2D6* Genotypes and Enzyme Activity

<i>CYP2D6</i> alleles	Allele designation	Enzyme activity	Allele abbreviation
*1, *2, *33, *35	Normal or wild type	Normal	EM
*3, *4, *5-8, *11-16, *18-21, *36, *38, *40, *42, *44, *56, *62	Null	No protein, inactive or negligible	PM
*9, *10, *17, *29, *41, *59	Reduced activity	Decreased	IM
*22-28, *30-32, *34, *37, *39, *43, *45-55	Unknown activity	Unknown	Not applicable
<i>Duplicated alleles</i>			
*1×N, *2×N, *35×N	Multiplication of normal alleles	Increased	UM
*10×N, *17×N, *29×N, *41×N	Multiplication of reduced activity alleles	Decreased	IM
*4×N, *6×N, *36×N	Multiplication of null alleles	Inactive or negligible	PM
*43×N, *45×N	Multiplication of alleles of unknown activity	Unknown	Not applicable

Literature flow



13
studies

* Irrelevant includes publications with no primary data, studies on healthy population, and studies on medications that inhibit CYP2D6.

Example: TA Conclusions, *CYP2D6*

Inconsistent association between *CYP2D6* status and outcomes

- Studies differed in the direction and statistical significance of findings
- Unclear whether *CYP2D6* status can predict differential response to treatment in the adjuvant setting
- Evidence is very limited in the metastatic setting
- In agreement with 2009 ASCO practice guideline update

Cross-cutting methodological issues

Role of “repurposed” RCTs

- Cannot *measure* effects of testing on patient outcomes or treatment decisions (need comparative studies for that)
- Later genetic analysis of archived but prospectively collected samples is generally accurate
- However, such analyses should be corrected for multiple comparisons to control for inflation of type I error and spurious findings.
- In general, independent validation in a different set of patients is a way to control for false positive findings.

Other

Multiple studies on each topic frequently originated from a limited number of specialized centers

- Identifying non-overlapping populations becomes problematic (See diagram, next slide)
- Threat to the generalizability of study findings

Remarks from Public Commenters

Remarks from Public Commenters

- Clarification needed: “clinical utility”
- Barriers (cost, time) to clinical utility studies cited
- Importance of monitoring *BCR-ABL* for CML
- Importance of context in evaluating clinical utility of genetic testing
- Support for further testing; Current projects underway by pharmacy benefit management firm to introduce PGT to MDs

CAP – AMP member poll

- Based on PT* testing participation,
 - *HER2/neu* : 1200 labs
 - *KRAS* (new): 133 labs (expected)
 - *BCR-ABL*: 86 labs
 - *CYP2D6* or *UGT1A1* testing: ~ 30-40 each
- Based on CAP – AMP member poll,
 - Labs providing *HER2*, *BCR-ABL*, *KRAS*: majority
 - Labs providing *CYP2D6* or *UGT1A1*: minority

* - 'PT' is proficiency testing (to confirm external validity of test process)

MEDCAC Panel Votes

MEDCAC Voting Scale

1 Low Confidence	2	3 Intermediate Confidence	4	5 High Confidence
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Questions, January 2010 (I)

Q1: “How confident are you that there is sufficient evidence to determine whether pharmacogenomic testing **affects health outcomes** (including benefits and harms) for patients with cancer whose anticancer treatment strategy is guided by the results of testing as described in situations a) - e) below?”

- a) *CYP2D6* / breast cancer / tamoxifen
- b) *UGT1A1* / colorectal cancer / irinotecan
- c) *HER2/neu* / breast cancer / trastuzumab
- d) *BCR-ABL* / chronic myelogenous leukemia / imatinib
- e) *KRAS* / colorectal cancer / cetuximab, panitumumab

MedCAC Panel Votes, 1/2010: Q1

Gene	Drug	Disease	Panel Voted
<i>CYP2D6</i>	Tamoxifen	Breast cancer	2.07
<i>UGT1A1</i>	Irinotecan	Colorectal cancer	1.93
<i>HER2/neu</i>	Trastuzumab	Breast cancer	4.33
<i>BCR-ABL1</i>	Imatinib, other TKIs	Chronic myeloid leukemia (CML)	a) 4.47 b) 2.47
<i>KRAS</i>	Cetuximab, panitumumab	Colorectal cancer	4.40

Notes for *BCR-ABL1*: a) For diagnosis and monitoring b) To detect treatment failure

Questions, January 2010 (II)

Q2: “For those items where the answer to Question 1 is at least in the Intermediate range (mean score ≥ 2.5), how confident are you that pharmacogenomic testing improves health outcomes for patients with cancer whose anticancer treatment strategy is guided by the results of testing as described in situations a) - e) below?”

- a) *CYP2D6* / breast cancer / tamoxifen
- b) *UGT1A1* / colorectal cancer / irinotecan
- c) *HER2/neu* / breast cancer / trastuzumab
- d) *BCR-ABL* / chronic myelogenous leukemia / imatinib
- e) *KRAS* / colorectal cancer / cetuximab, panitumumab

MedCAC Panel Votes, 1/2010: Q2

Gene	Drug	Disease	Panel Voted
<i>CYP2D6</i>	Tamoxifen	Breast cancer	N/A
<i>UGT1A1</i>	Irinotecan	Colorectal cancer	N/A
<i>HER2/neu</i>	Trastuzumab	Breast cancer	4.67
<i>BCR-ABL1</i>	Imatinib, other TKIs	CML	a) 4.33 b) N/A
<i>KRAS</i>	Cetuximab, panitumumab	Colorectal cancer	4.33

Notes for *BCR-ABL1*: a) For diagnosis and monitoring b) To detect treatment failure

Questions, January 2010 (III)

Q3: “How confident are you that these conclusions are generalizable to

a. community based settings?

b. the Medicare beneficiary population?”

Q4. “Please discuss any important evidence gaps and recommend how they should be addressed.”

MedCAC Panel Votes, 1/2010: Q3

Are findings based on current evidence generalizable to:	Panel vote:
a) Patients in community settings ?	4.20
b) Medicare patients?	4.27

Questions, January 2010 (IV)

Q3: “How confident are you that these conclusions are generalizable to

a. community based settings?

b. the Medicare beneficiary population?”

Q4. “Please discuss any important evidence gaps and recommend how they should be addressed.”

MEDCAC Panel: Evidence Gaps

- Additional research concerning co-morbidities (including nutritional status) and concurrent medications in elderly, and effects of these on diagnostic value of PGT
- Standardize genotype-phenotype assignment (e.g., *CYP2D6* alleles and EM-IM-PM)
- Importance of tissue/DNA source banks
- Studies representing more diverse patient groups
- Lack of current evidence of clinical utility; better data needed on function outcomes (QOL)

Contact Information

- Division of Items and Devices
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