SESSION 2: CURRENT LANDSCAPE CLINICAL CONSIDERATIONS AND EVIDENCE

U.S. FOOD & DRUG ADMINISTRATION

AACR American Association for Cancer Research®

MODERATOR

Jennifer Gao, MD
U.S. Food and Drug Administration

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College of Pharmacy

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Department of Veterans Affairs

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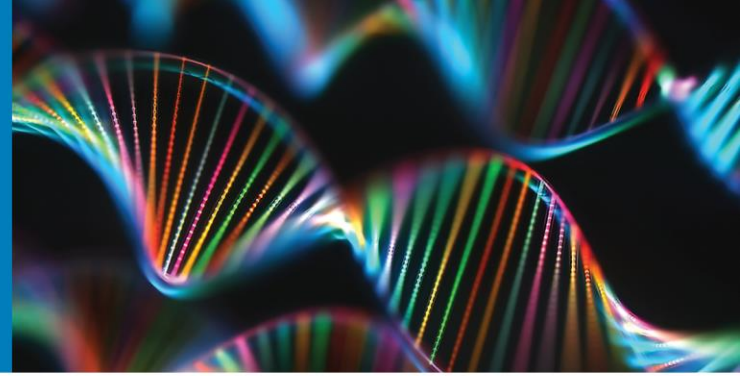
Maryland Oncology Hematology

FDA-AACR Workshop on

TO TEST OR NOT TO TEST – THAT IS THE QUESTION:
DPD DEFICIENCY AND WEIGHING POTENTIAL HARMS

January 16, 2025 I Bethesda, MD



Tumor Biomarker Validation: When Should a Tumor Biomarker be Applied in the Clinic? Applied to Dihydropyrimidine Dehydrogenase (DPD) Testing

Daniel F. Hayes, MD, FASCO, FACP

Stuart B. Padnos Professor of Breast Cancer Research at the University of Michigan Rogel Cancer Center

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Disclosure Information

Speaker Name

I have the following relevant financial relationships to disclose:

Grant/Research support from: Angle, Pfizer, AstraZeneca

Stockholder in: InBiomotion, CellWorks, Xilis

Consultant/Board Member for: Arvinas, Artera AI, BioTheranostics, BioVeca, CellWorks, Centrix, Cepheid, Curetaq, Delphi Diagnostics, EPIC Sciences, EXACT Sciences, Freenome, Guardant, Lexent Bio, Predictus, Salutogenic Innovations, L-Nutra, Macrogenics, Microbiologics, OncoCyte,, Strata, Stratipath, Turnstone, Tempus, Xilis

My additional financial relationship disclosures are:

CellSearch (Immunicon/Veridex/Janssen Diagnostics/Menarini Silicon BioSystems)

- Laboratory and Clinical research funding from MSB
- Patent regarding circulating tumor cells licensed to MSB/I receive annual royalties

Novel CTC capture devices – patent pending

Tumor Biomarker Test (TBT) Semantics

- **Analytical Validity**
  - **Is the assay accurate and reproducible?**
    - **Pre-analytic issues (Moore HM, Kelly A, McShane LM, et al: Biospecimen reporting for improved study quality (BRISQ). Clin Chim Acta 413:1305, 2012)**
    - **Analytics themselves**
- **Clinical Validity**
  - **Does the TBT split one population into 2 or more with different outcomes?**
- **Clinical Utility**
  - **Does use of the TBT improve clinical outcomes?**

Clinical Utility unlikely without Clinical Validity,
but
Clinical Validity does NOT = Clinical Utility.

Teutsch SM, et al. 2009. *Genet Med 11:3-14*

Categories of Each Factor to Determine Clinical Utility of a TBT

Analytical Validity
- Excellent
- Good
- Moderate
- Poor

Context
- Which malignancy?

DPD: mostly GI and Breast Cancers
- Which setting?
  - Screening
  - New primary
  - Met
  - Monitoring
    - MRD
    - Established metastases

DPD: Adjuvant or Metastatic
- Which use?
  - Prognosis
  - Prediction

DPD: Predict Toxicity

Endpoint
- Overall Survival, Quality of Life
- Disease-Free, Progression-Free Survival
- Event-Free Survival
- Response

DPD: Toxicity

Magnitude/MCID
- Enormous
- Large
- Moderate
- Small

DPD: Life-Taking or –Threatening Toxicity

Levels of Evidence
- 1
- 2
- 3
- 4-5

CLINICAL UTILITY

(Drs. Hertz, Venook, and Wu will address Context, Magnitude and Level of Evidence)

Hayes DF. 2021. *J Clin Oncol* 39:238-48

How Do We Use TBTs?

- Understand the Intended Use
- Understand how it will be used for that Intended Use
  - What is the Standard of Care (SOC) Paradigm?
  - Do you use it to Opt-In, Opt-Out, or Opt-Alt?
  - What are the Positive and Negative Predictive Values?

Hayes DF. *J Clin Oncol* 2021;39:238-48

Tumor Biomarker Tests: Generation of High Levels of Evidence

- **Clinical Research: Various Strategies to *"Test the Test"***
  - ***Prospective Clinical Trials: Marker is Primary Objective!***
    - ***Sargent D.J., et al. J Clin Oncol. 23:2020-7, 2005***
    - ***Freidlin B., et al. J Natl Cancer Inst. 102:152-60,* 2010**
  - ***Is a Prospective Trial Always Necessary?***
    - ***NO! But use of archived specimens must be done with rigor***
    - ***Simon R.M., Paik S, Hayes DF. J Natl Cancer Inst. 101:1446-52, 2009***
      - **Use specimens collected and archived from previously performed clinical trials that address the specific issue of interest**
      - **Need at least two separate studies with similar/identical results to claim victory**

FOR Germline Pharmacogenomic Markers of Toxicity: *Hertz, DL, McShane, LM, Hayes, DF. Defining Clinical Utility of Germline Indicators of Toxicity Risk: A Perspective. J Clin Oncol 40:1721-1731, 2022*

FOR DPD: *Hertz, DL. Assessment of the Clinical Utility of Pretreatment DPYD Testing for Patients Receiving Fluoropyrimidine Chemotherapy. J Clin Oncol 40:3882-3892, 2022*

Defining Clinical Utility of Germline Indicators of Toxicity Risk: A Perspective

Daniel L. Hertz, PharmD, PhD[1]; Lisa M. McShane, PhD[2]; and Daniel F. Hayes, MD[3]

Journal of Clinical Oncology® 2022

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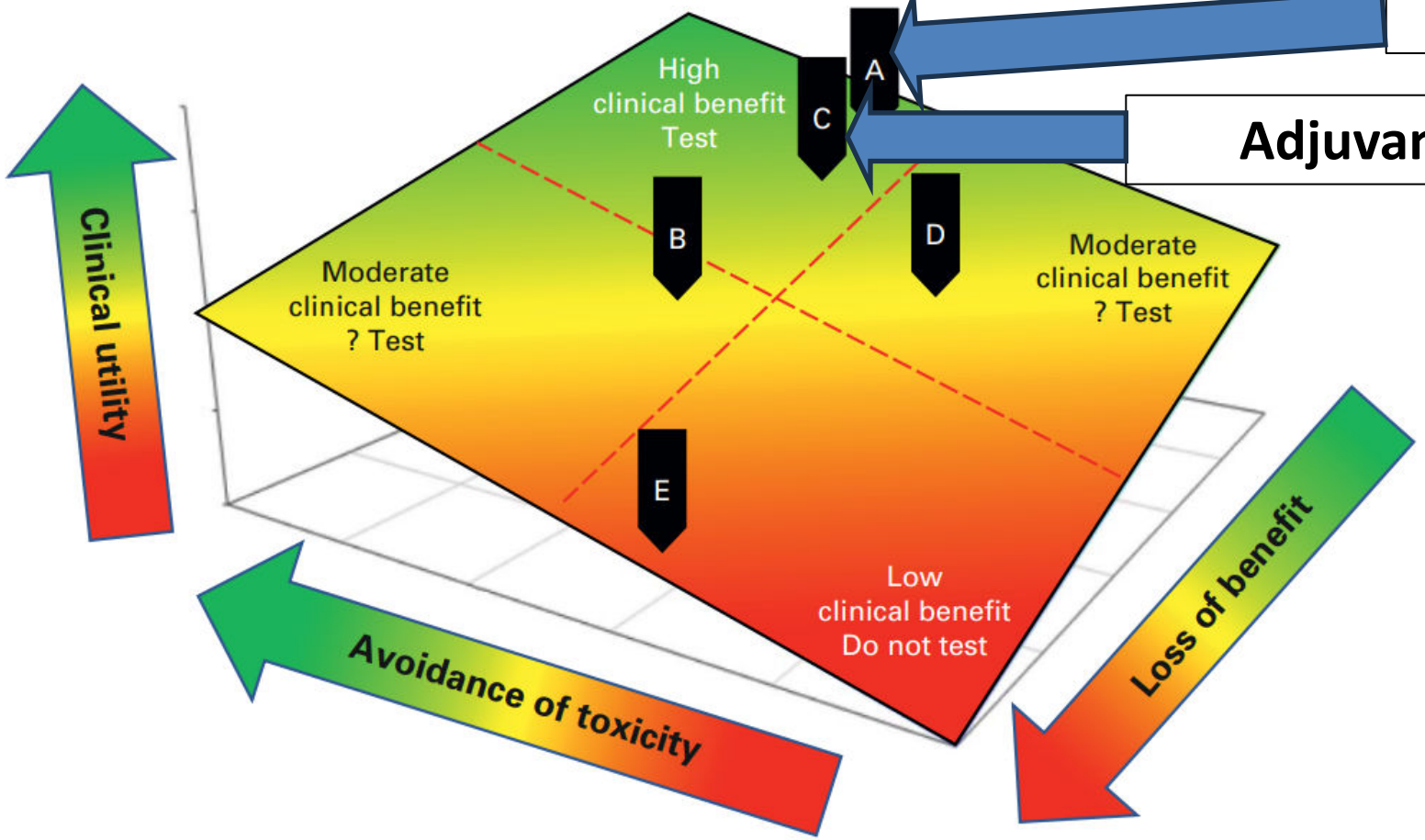
DPD Testing

Metastatic Breast CA

Adjuvant Colon CA



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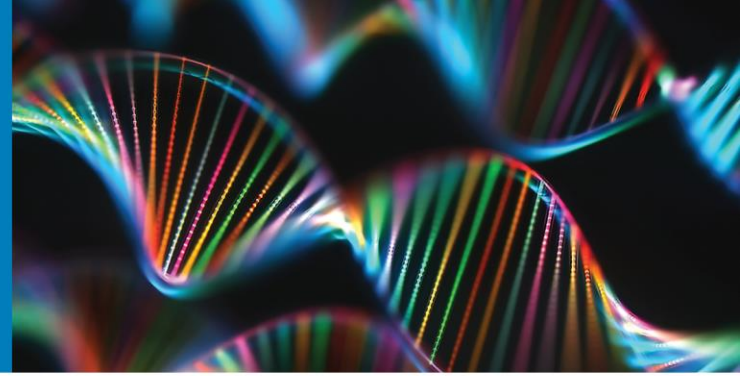

Clinical Utility of Pre-treatment *DPYD* Testing

Daniel L. Hertz, PharmD, PhD

Associate Professor at University of Michigan College of Pharmacy, Ann Arbor, MI

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Disclosure Information

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Daniel Hertz

I have the following relevant financial relationships to disclose:

Related Grant/Research support from: UM Office for Vice Provost of Research, American Cancer Society, LaCar MDx

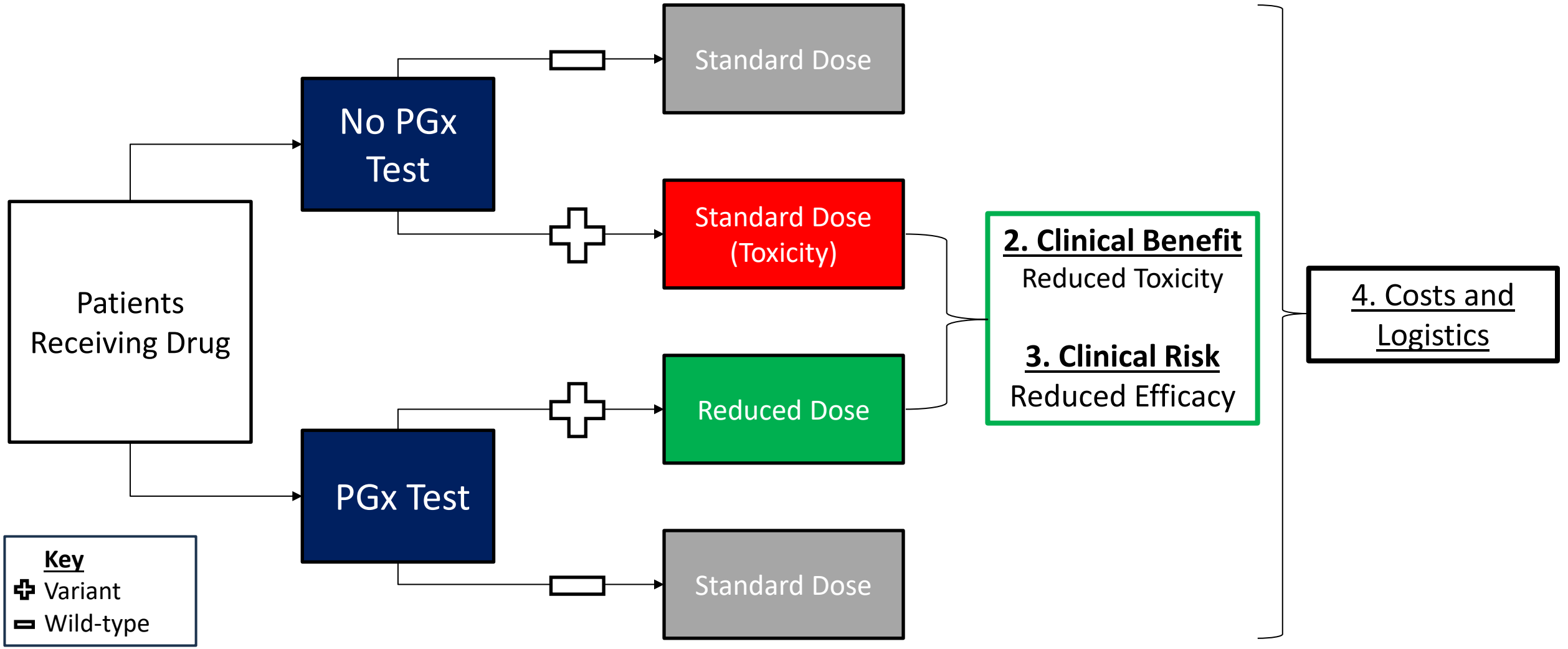
Unrelated Grant/Research support from: UM MICHR, UM Rogel Cancer Center, SWOG Hope Foundation, ACCP, ACS, NCI

I am an unpaid medical advisor to Advocates for Universal DPD/*DPYD* Testing (AUDT)

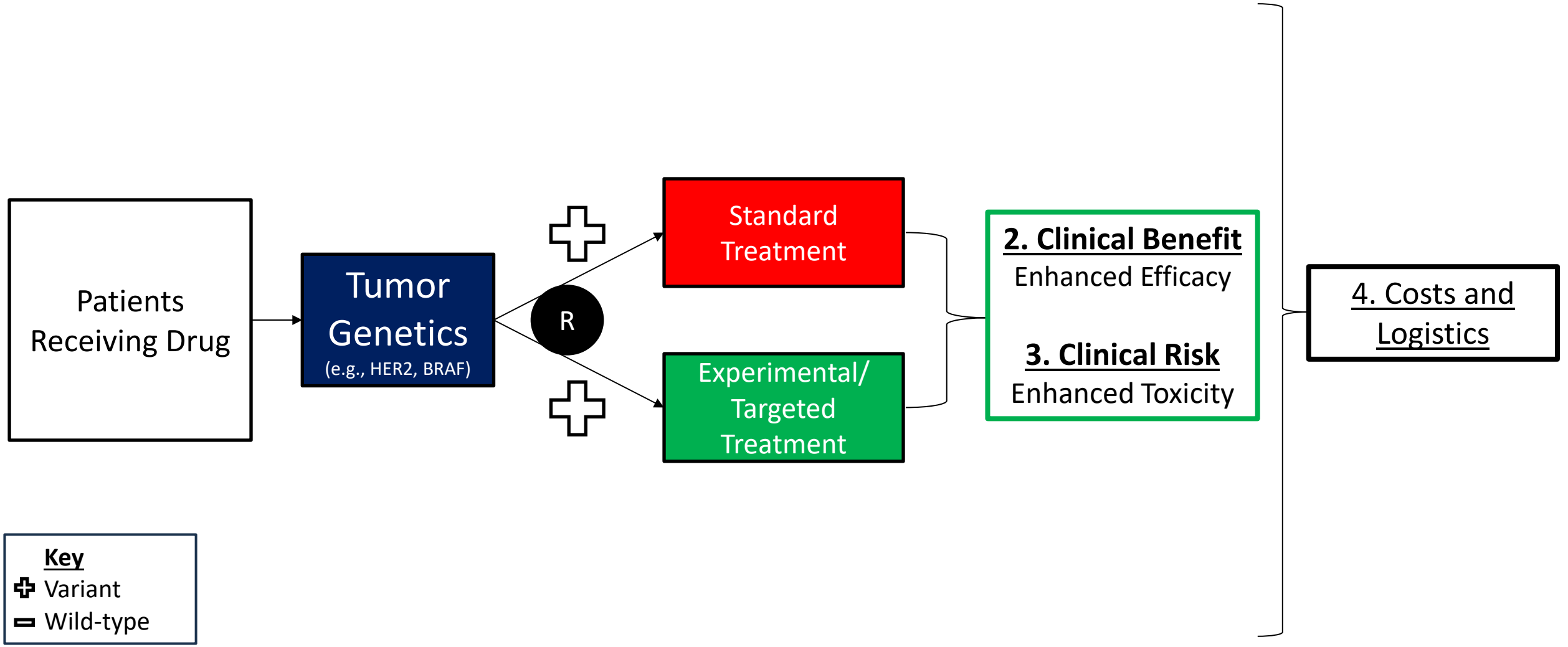
Outline

1. Framework for Clinical Utility of Toxicity PGx
2. Clinical **Benefit** of *DPYD* Testing
3. Clinical **Risk** of *DPYD* Testing
4. Costs and Logistics of *DPYD* Testing

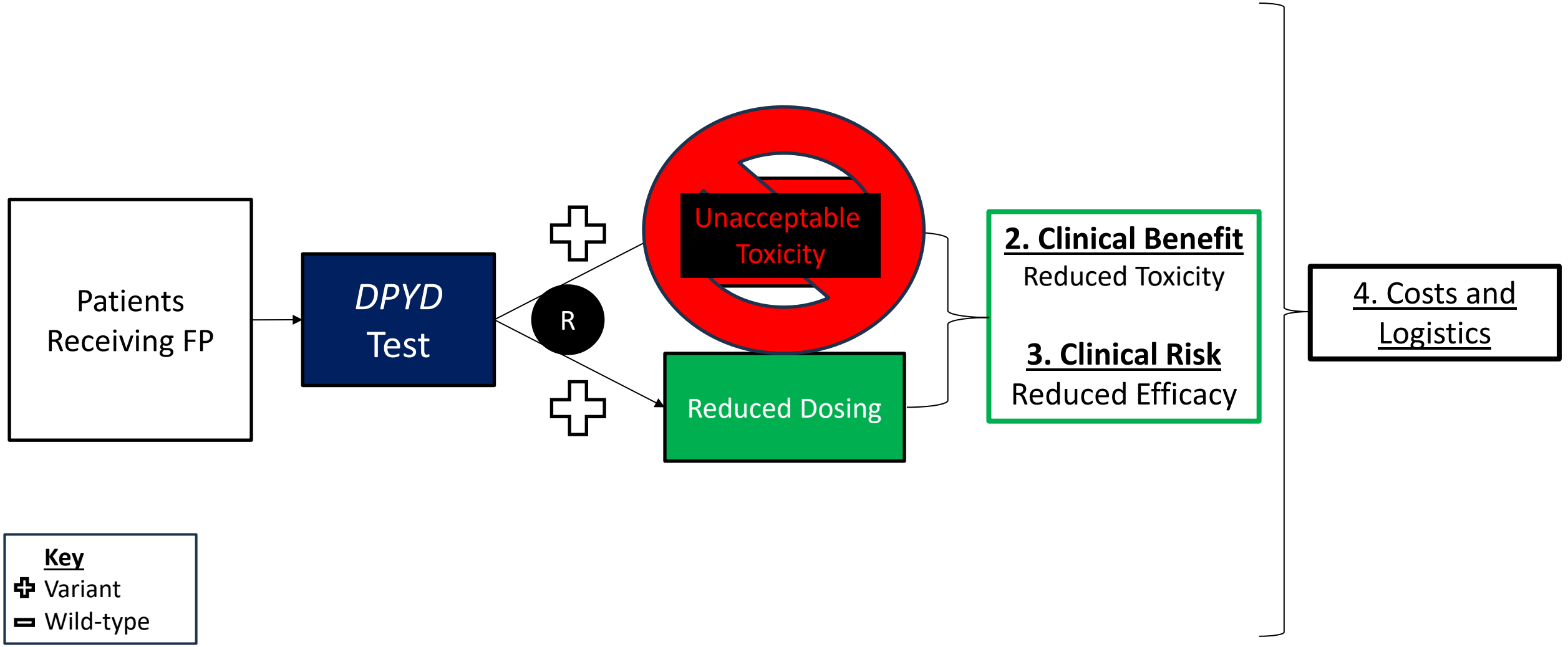
1. Clinical Utility of Toxicity PGx



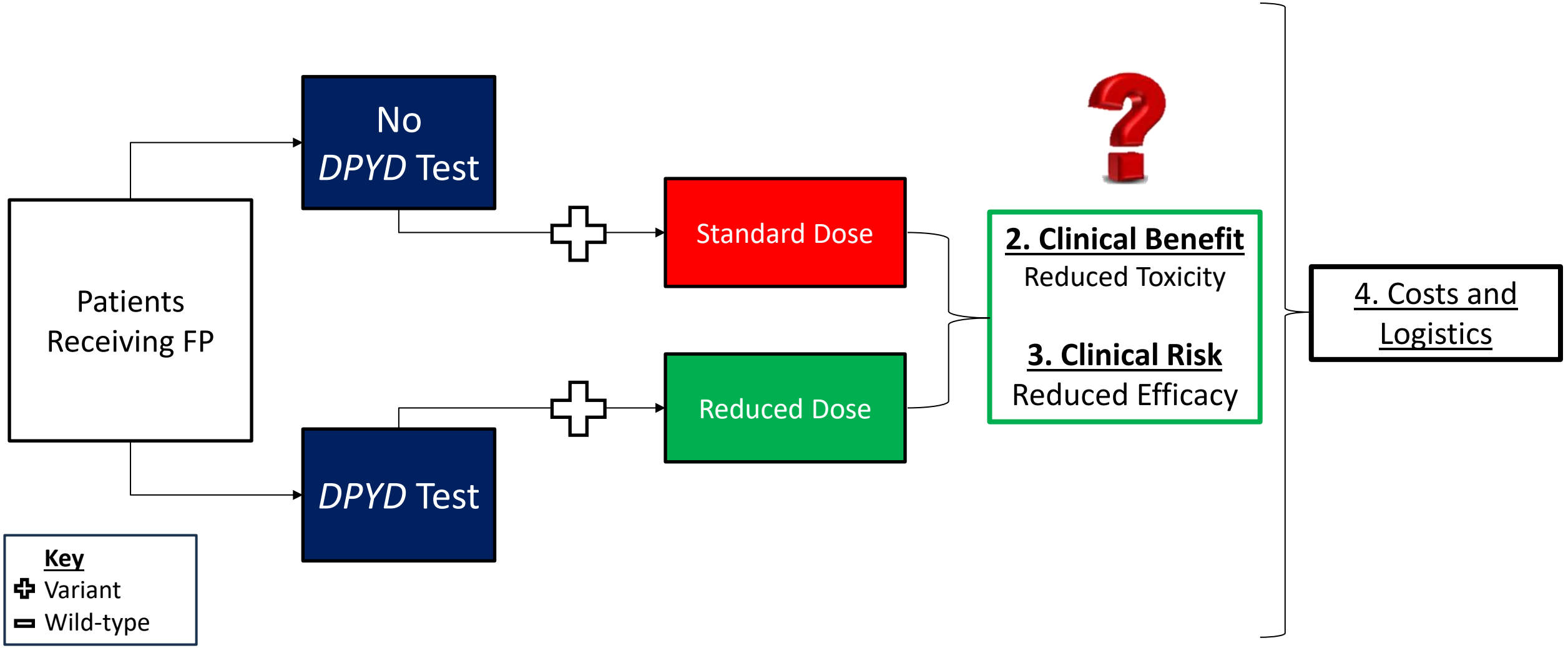
1. Clinical Utility of TBT (Hayes Talk)



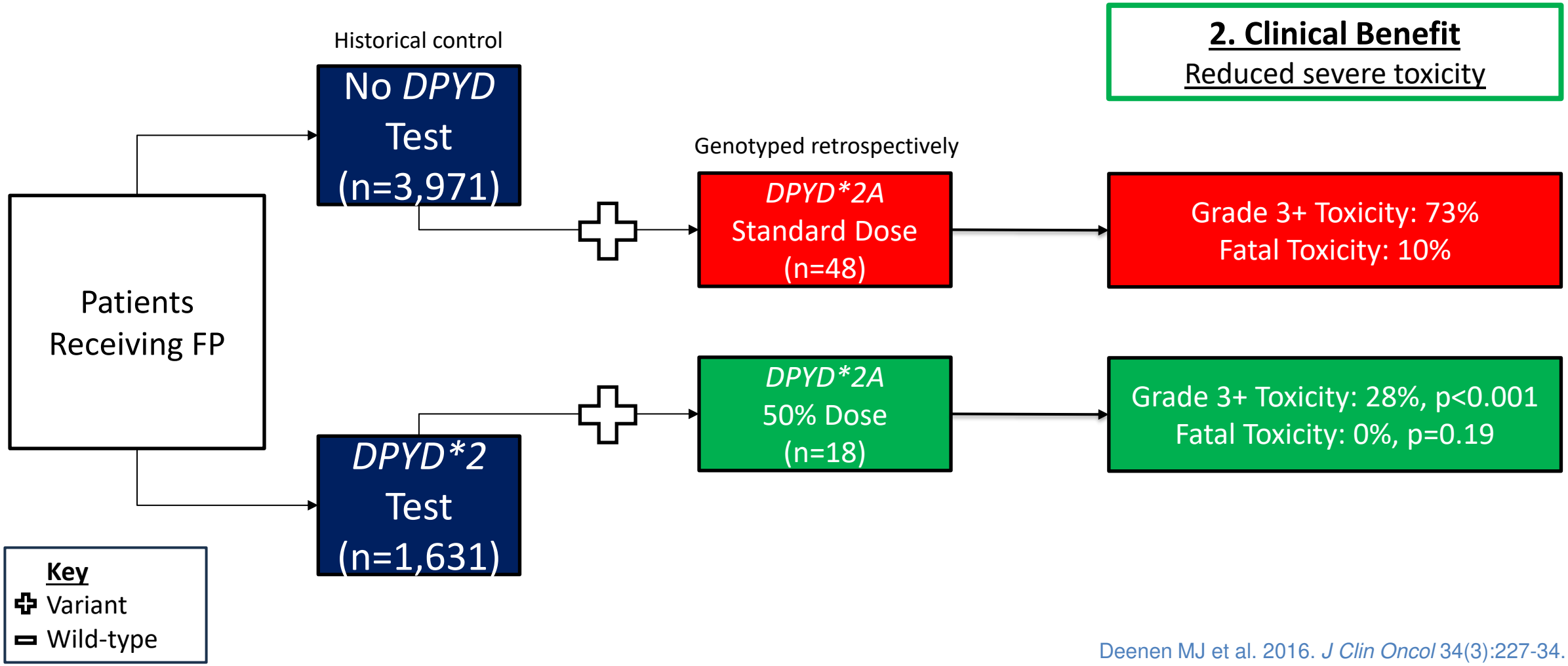
1. Clinical Utility of *DPYD* Testing



1. Clinical Utility of *DPYD* Testing

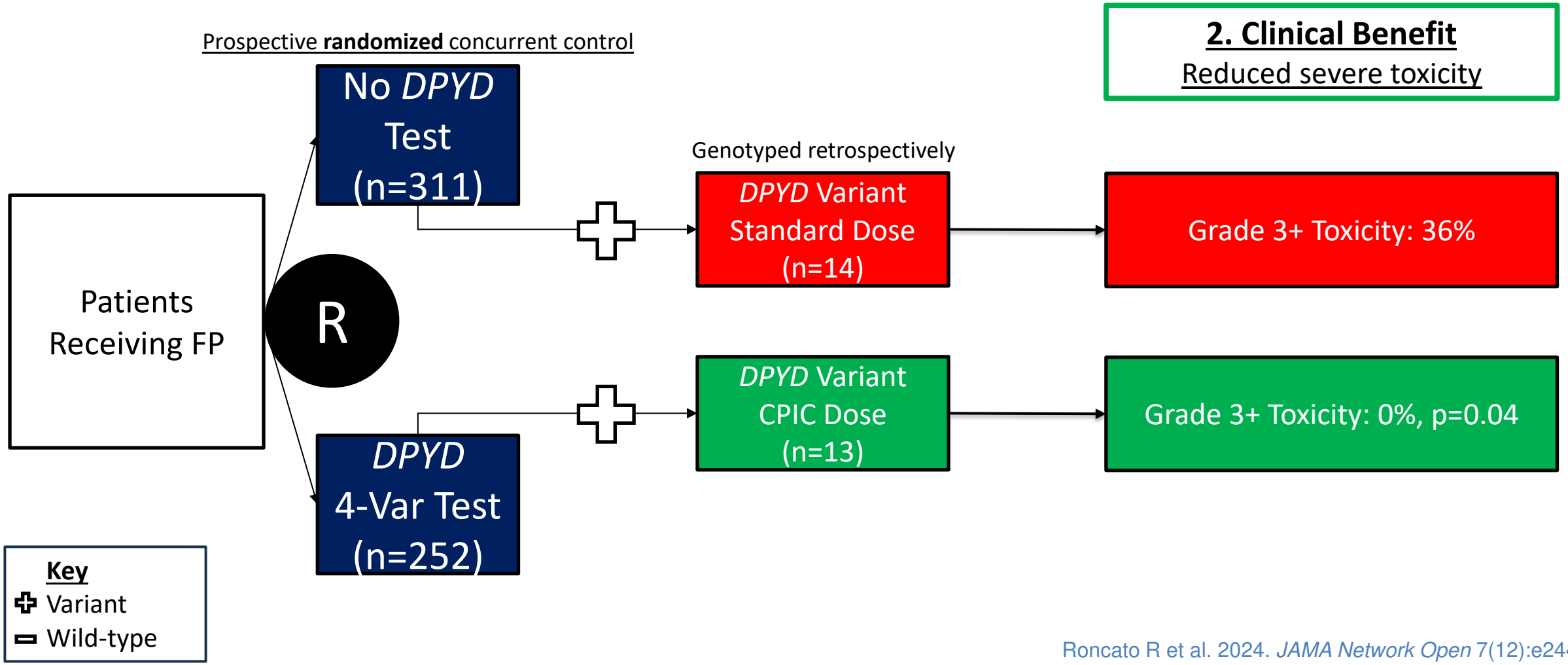


2. Clinical **Benefit** of *DPYD*2A* Testing



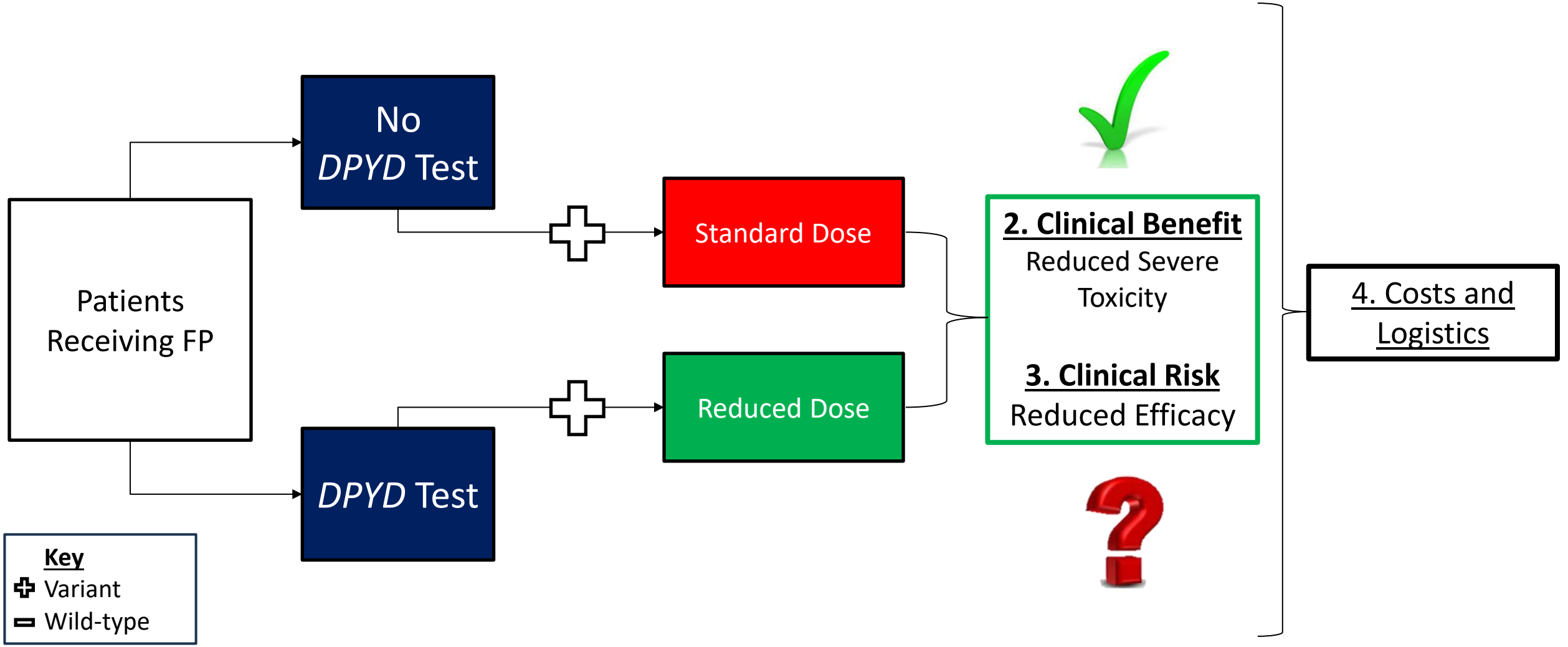
Deenen MJ et al. 2016. *J Clin Oncol* 34(3):227-34.

2. Clinical **Benefit** of *DPYD* 4-Var Testing

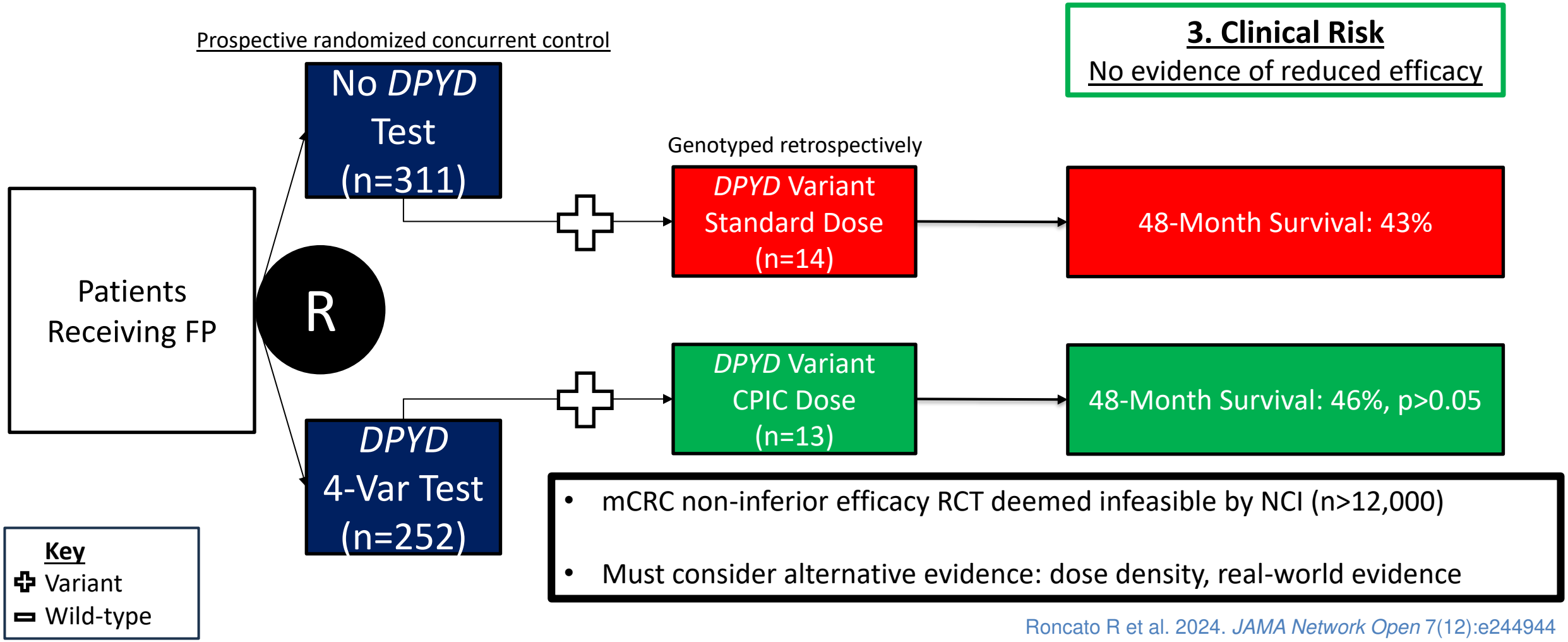


Roncato R et al. 2024. *JAMA Network Open* 7(12):e244944

1. Clinical Utility of *DPYD* Testing



3. Clinical **Risk** of *DPYD* 4-Var Testing



- mCRC non-inferior efficacy RCT deemed infeasible by NCI (n>12,000)
- Must consider alternative evidence: dose density, real-world evidence

Roncato R et al. 2024. *JAMA Network Open* 7(12):e244944

3. Clinical **Risk** of *DPYD* 4-Var Testing

Prospective randomized concurrent control

Patients Receiving FP

R

No *DPYD* Test (n=311)

DPYD 4-Var Test (n=252)

Genotyped retrospectively

DPYD Variant Standard Dose (n=8)

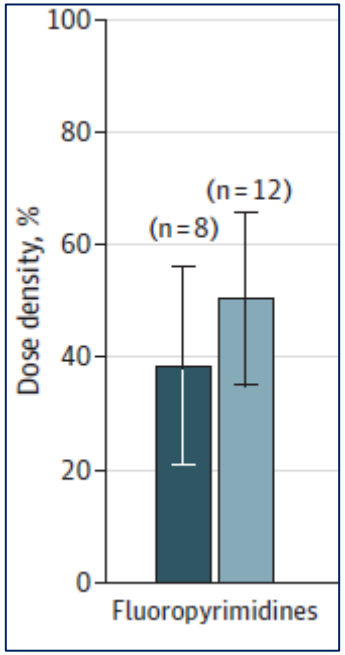
DPYD Variant CPIC Dose (n=12)

FP Dose Density: 38% (↓ due to toxicity)

FP Dose Density: 51% (↓ to avoid toxicity)

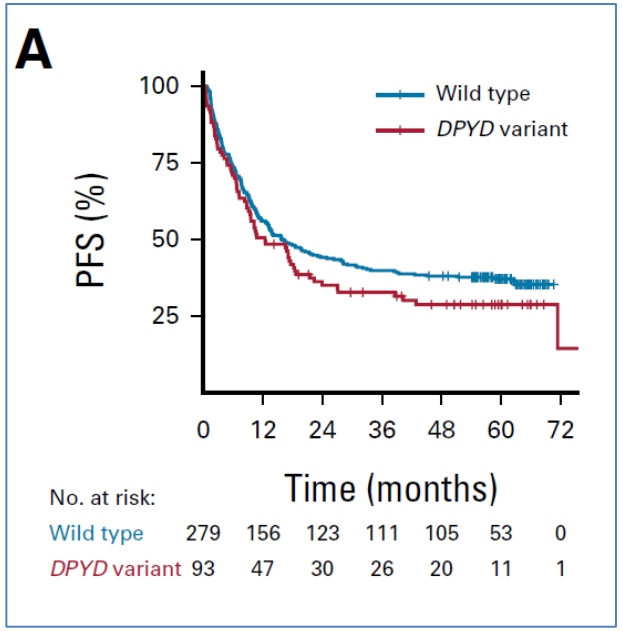
Key
- ✚ Variant
- ▬ Wild-type

3. Clinical Risk
HIGHER FP Dose Density



Roncato R et al. 2024. *JAMA Network Open* 7(12):e244944

3. Clinical **Risk** of *DPYD* 4-Var Testing



Patients Receiving FP

DPYD 4-Var Test (n= 1,103)

DPYD Variant CPIC Dose (n=93)

Wild-Type Standard Dose (n=279)

Key
- Variant
- Wild-type

3. Clinical Risk

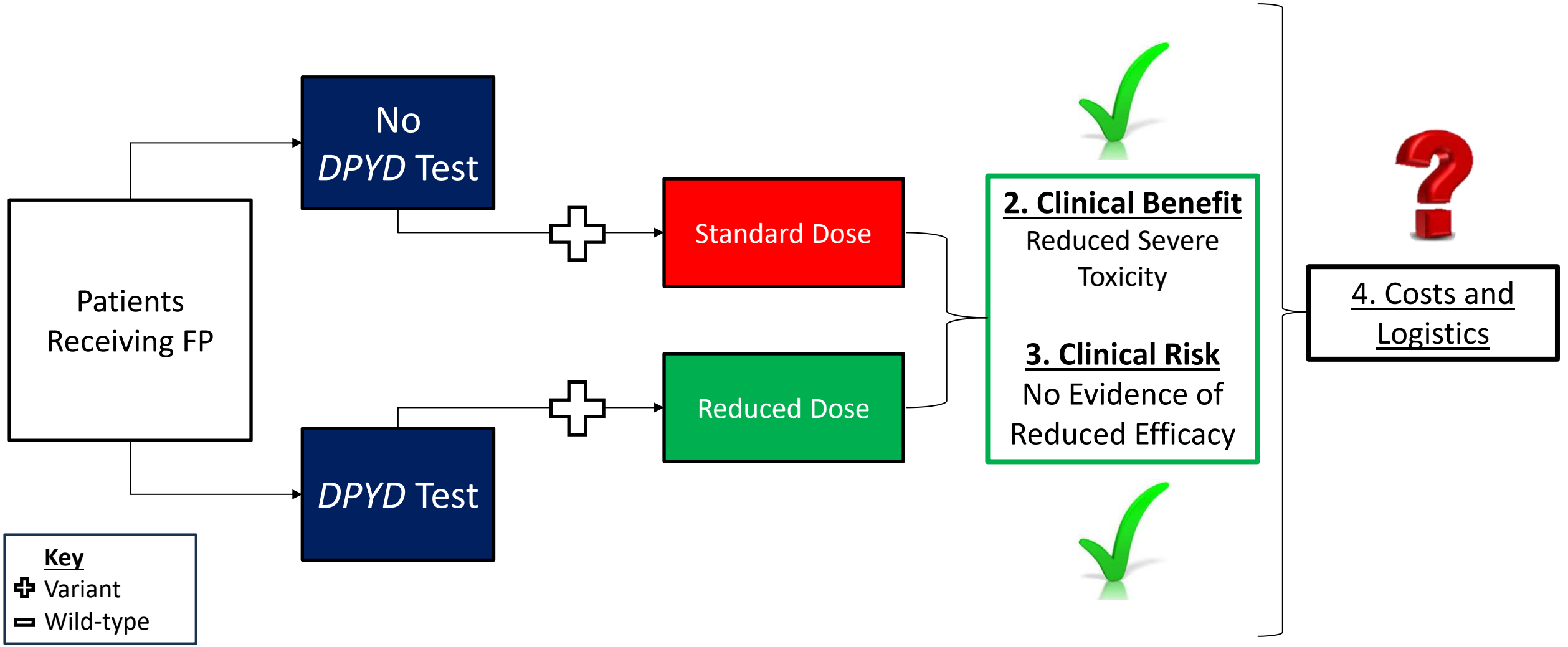
- No reduction in PFS
  - HR=1.23 (95% CI: 0.92-1.63), p=0.16

Note: Improper/Irrelevant Comparator

Knikman JK et al. 2023. *J Clin Oncol* 41:5411-5421

Prospective concurrent control, 3:1 matched by disease, treatment, etc.

1. Clinical Utility of *DPYD* Testing



D Testing

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All You Need to Know About *DPYD* Genetic Testing for Patients Treated With Fluorouracil and Capecitabine: A Practitioner-Friendly G

Federico Innocenti, MD, PhD[1]; Sarah C. Mills, BS[1]; Hanna Sanoff, MD, MPH[2]; Joseph Ciccolini PharmD, PhD[3]; Heinz-Josef Lenz, MD[4]; and Gerard Milano, MD[5]

Fluoropyrimidines (fluorouracil, capecitabine, and other analogs) are highly used anticancer drugs w
However, patients with cancer treated with these drugs might experience severe, life-threatening to
cause of germline genetic variation in the *DPYD* gene. This is a genetic predisposition with an es
mechanistic basis that links genetic variation in the *DPYD* gene to an increase in systemic drug
resulting in an increased risk of toxicity. Pharmacology guidelines provide recommendations on
treatment with fluoropyrimidines or reducing their dose in patients carrying *DPYD* genetic variants con
increased risk of toxicity. However, oncology societies in the United States do not recommend systema
Instead, on April 30, 2020, the European Society for Medical Oncology issued a document recon
genetic testing. In this scenario of contradicting information, practicing oncologists struggle with rea
informed decision on whether genetic testing should be applied before treatment. This is mostly d
certainty about the clinical relevance of genetic testing from the perspective of a practicing oncologist. To
informed decision, practicing oncologists need access to concise information on the genetic variants to
and a practitioner-friendly interpretation of the test results. We believe this information is currently lacki
knowledge, for the first time, we provide a single guide for health care professionals to make an evider
decision about *DPYD* testing for patients with cancer. This article provides the essential knowledge
oncologists to have an informed discussion with their patients about the genetic testing for *DPYD*. This
assists practitioners in quickly evaluating whether, when, where, and how to order a *DPYD* genetic t

JCO Oncol Pract 16:793-798. © 2020 by American Society of Clinical Oncology

- Implementation Guidance

CLINICAL PHARMACOLOGY & THERAPEUTICS | VOLUME 0 NUMBER 0 | Month 2024 (In Press)

ARTICLE

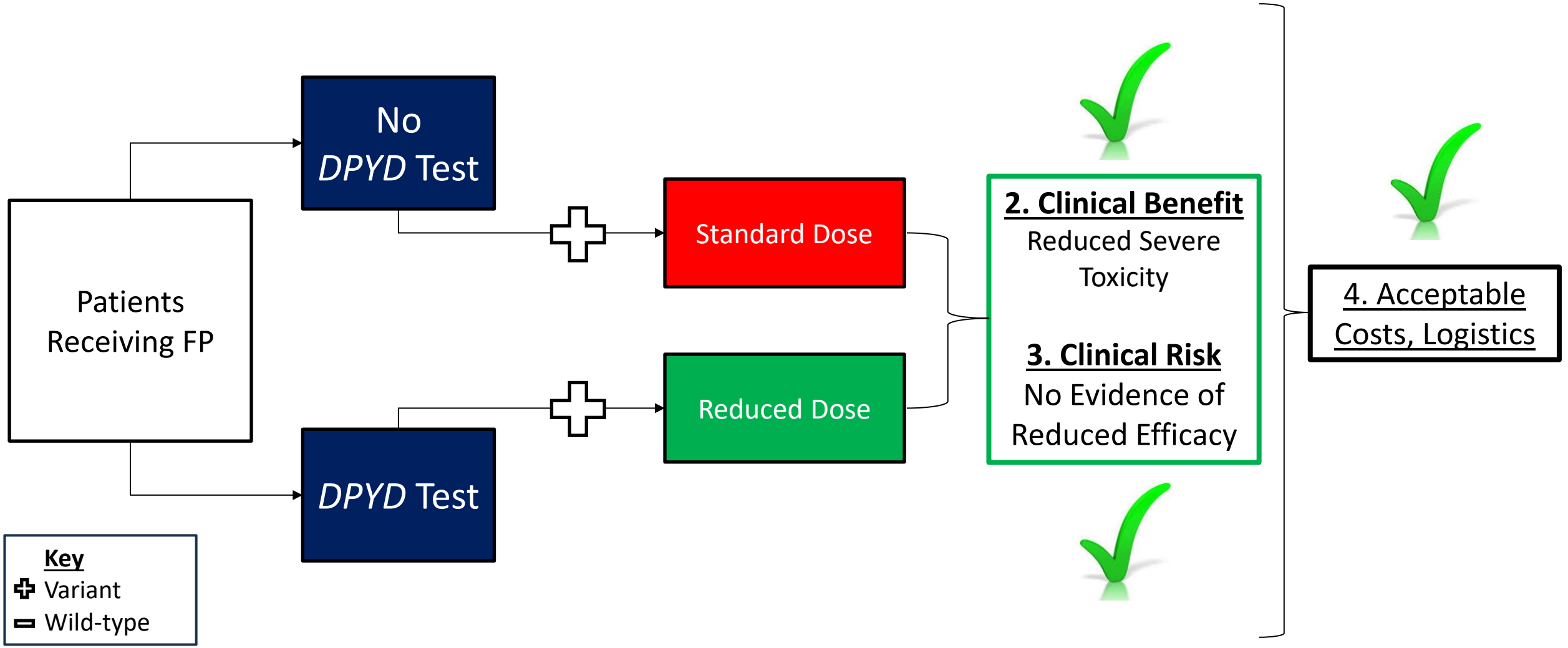
A Guide for Implementing *DPYD* Genotyping for Systemic Fluoropyrimidines into Clinical Practice

Teresa T Ho[#,1], D Max Smith[#,,2,3], Christina L. Aquilante[4,5], Emily J. Cicali [6], Nihal El Rouby[7,8], Daniel L. Hertz[9], Iman Imanirad[10], Jai N. Patel[11,12], Stuart A. Scott[13], Sandra M. Swain [3,14], Sony Tuteja[15], J. Kevin Hicks*[1], on behalf of the Pharmacogenomics Global Research Network Publication Committee

The safety of systemic fluoropyrimidines (e.g., 5-fluorouracil, capecitabine) is impacted by germline genetic variants in *DPYD,* which encodes the dihydropyrimidine dehydrogenase (DPD) enzyme that functions as the rate-limiting step in the catabolism of this drug class. Genetic testing to identify those with DPD deficiency can help mitigate the risk of severe and life-threatening fluoropyrimidine-induced toxicities. Globally, the integration of *DPYD* genetic testing into patient care has varied greatly, ranging from being required as standard of care in some countries to limited clinical use in others. Thus, implementation strategies have evolved differently across health systems and countries. The primary objective of this tutorial is to provide practical considerations and best practice recommendations for the implementation of *DPYD*-guided systemic fluoropyrimidine dosing. We adapted the Exploration, Preparation, Implementation, and Sustainment (EPIS) framework to cover topics including the clinical evidence supporting *DPYD* genotyping to guide fluoropyrimidine therapy, regulatory guidance for *DPYD* genotyping, key stakeholder engagement, logistics for *DPYD* genotyping, development of point-of-care clinical decision support tools, and considerations for the creation of sustainable and scalable *DPYD* genotype-integrated workflows. This guide also describes approaches to counseling patients about *DPYD* testing and result disclosure, along with examples of patient and provider educational resources. Together, *DPYD* testing and clinical practice integration aims to promote safe prescribing of fluoropyrimidine therapy and decrease the risk of severe and life-threatening fluoropyrimidine toxicities.

1. Hertz DL. In Prep. 2. Deenen JCO 2016. 3. Henricks Lancet Oncol 2018. 4. Brooks Clin Colorect Can 2022. 5. Onta

1. Clinical Utility of *DPYD* Testing



Take-Home Points

- Demonstrated clinical utility of genotyping for 4 (or more) *DPYD* variants
  - Benefits (↓ **severe/fatal toxicity**) >>>>> Risks (↔ efficacy loss, costs, logistics)

- Suggested wording for drug labels and clinical guidelines:
  - *"DPYD* testing that includes at least the 4 validated variants (i.e., *2A, *13, p.D949V, HapB3) is recommended in all patients newly initiating systemic FP chemotherapy."

- Testing can always improve, and will rapidly upon widespread adoption
  - Faster, Cheaper, More variants/diversity → Sequencing, Phenotyping
  - More precise dosing (CPIC) for individual *DPYD* variants, FP agents, tumors

- **Don't let perfect be the enemy of good**

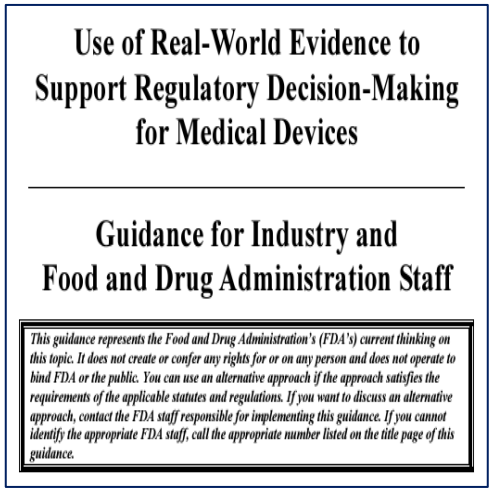
Contribute Your Real-World Data

Oncology Pharmacogenetics Real-world Evidence Consortium (OPREC)

Collect de-identified data of patients receiving *DPYD*-guided treatment →

Precisely estimate clinical benefits and risks of *DPYD* testing

Adobe Express Image Generator



Use of Real-World Evidence to Support Regulatory Decision-Making for Medical Devices

Guidance for Industry and Food and Drug Administration Staff

This guidance represents the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the FDA staff responsible for implementing this guidance. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.

FDA Guidance on Real-world Data

If your site tests for *DPYD* and has data to contribute

Scan the QR code or email DLHertz@UMich.edu

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Guidelines and Diagnostics: Details Matter

Alan P. Venook, MD

Madden Family Distinguished Professor of Medical Oncology and Translational Research at UCSF

Shorenstein Associate Director for Program Development at the Helen Diller Family Comprehensive Cancer Center at UCSF

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Disclosure Information

Alan Venook, MD

I have no financial relationships to disclose

NCCN Board of Directors, UCSF Representative
NCCN Colon/Rectal/Anal Guideline Panel, Vice-Chair
NCCN Hepatocellular and Biliary Guideline Panels, Member

Ramping Up the Rhetoric

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DPYD Testing: Time to Put Patient Safety First

Journal of Clinical Oncology® 2023

Sharyn D. Baker, PharmD, PhD[1]; Susan E. Bates, MD[2]; Gabriel A. Brooks, MD[3]; William L. Dahut, MD[4]; Robert B. Diasio, MD[5]; Wafik S. El-Deiry, MD, PhD[6]; William E. Evans, PharmD[7]; William D. Figg, PharmD, MBA[8]; Dan L. Hertz, PharmD, PhD[9]; J. Kevin Hicks, PharmD, PhD[10]; Suneel Kamath, MD[11]; Pashtoon Murtaza Kasi, MD[12]; Todd C. Knepper, PharmD[10]; Howard L. McLeod, PharmD[13]; Peter H. O'Donnell, MD[14]; Mary V. Relling, PharmD[7]; Michelle A. Rudek, PharmD, PhD[15]; Tristan M. Sissung, PhD[8]; D. Max Smith, PharmD[16]; Alex Sparreboom, PhD[1]; Sandra M. Swain, MD[16]; and Christine M. Walko, PharmD[10]

Although the NCCN stance against routine *DPYD* genotyping may have been acceptable in the past, accumulating data regarding the strong association of *DPYD* gene variants with severe toxicity make that stance increasingly untenable and possibly leaves cancer centers vulnerable to claims of malpractice in cases of fatal toxicity.

Why Focus on the NCCN Guidelines?

- 15 million downloads in 2023 alone
- Consensus of panelists representing 33 NCI-Designated Cancer Centers
- Rigorous COI, sponsor firewall, all volunteerism
- Updated in real time
- Evidence-based where possible
- Submissions accepted from interest groups
- Establishes coverage by Medicare and insurers
  - For details: http://www.nccn.org

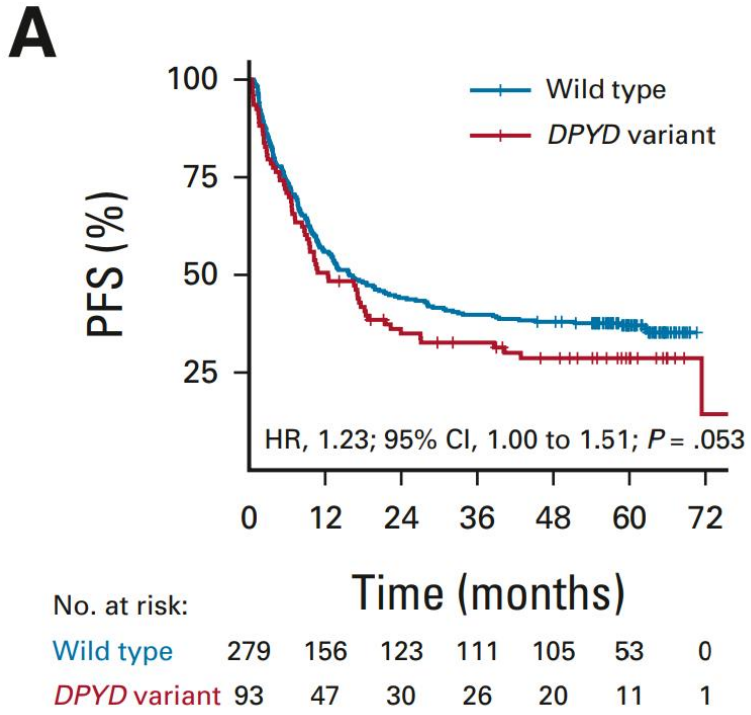
Some Differences of Opinion

1) Reduced Fluoropyrimidine (FP) dose in patients with certain DPYD variants reduces toxicity and risk of major complications.
2) Evidence cited in support of maintained efficacy with dose-reduced FP is not convincing. Studies include patients with a range of cancers, receiving a variety of combination therapies, mostly in advanced cancer. These studies are vastly underpowered to address efficacy.
3) A pre-emptive 50% dose reduction of FP in patients receiving adjuvant treatment could adversely impact survival.
4) CPIC does not distinguish between 5FU and capecitabine in the dosing recommendations.
5) The panel is not nitpicking.

Same Data, Different Interpretation

Survival of Patients With *DPYD* Variant Alleles and Dose-Individualized Fluoropyrimidine Therapy—A Matched-Pair Analysis

Knikman JK et al. 2023. *J Clin Oncol* 41:5411-5421



genotype has been shown to diminish toxicity, it is not certain that dose reductions do not result in inferior efficacy."

MS-50, NCCN Guidelines Colon Cancer 3.2024

has been shown to diminish toxicity, and recent data finds no clear evidence for shorter PFS or OS. ([add Reference for Knikman JCO 2023])"

Proposed language, submitted by Hertz + Surprenant, 4/30/24

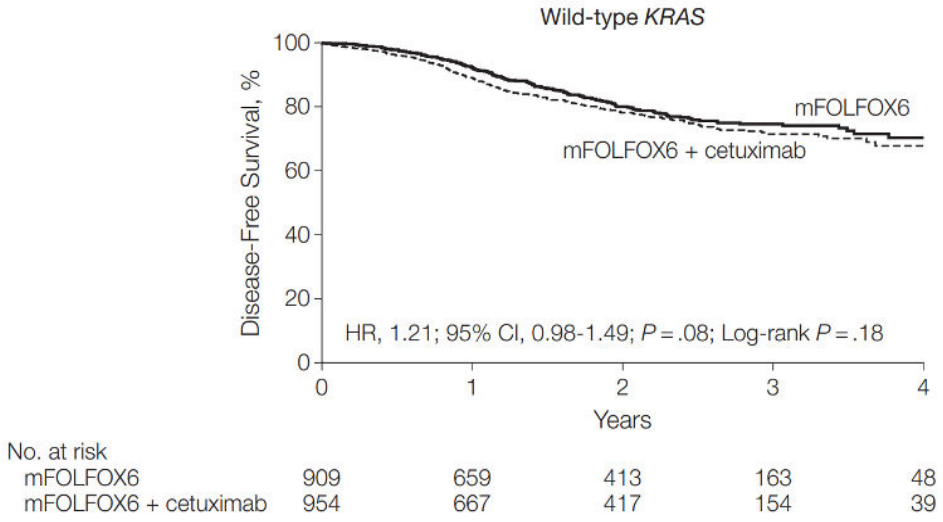
Principles of Adjuvant Therapy: Colon Cancer

- Initiate therapy as soon as is reasonable
- Movement towards "neoadjuvant" treatment
- Majority of benefit derives from early cycles
- Fluoropyrimidines are necessary

Colon Cancer Stage III Adjuvant: N0147

Effect of Oxaliplatin, Fluorouracil, and Leucovorin With or Without Cetuximab on Survival Among Patients With Resected Stage III Colon Cancer

A Randomized Trial



Treatment-related deaths = 20 (N = 2544)

	No. (%) of Patients				
	mFOLFOX6 (n = 894)			mFOLFOX6 + Cetuximab (n = 931)	
Grade 3	Grade 4	Grade 5	Grade 3	Grade 4	Grade 5
321 (35.9)	132 (14.8)	4 (0.4)	504 (54.1)	168 (18.0)	10 (1.1)

	No. (%) of Patients				
	mFOLFOX6 (n = 367)			mFOLFOX6 + Cetuximab (n = 342)	
Grade 3	Grade 4	Grade 5	Grade 3	Grade 4	Grade 5
139 (37.9)	64 (17.4)	1 (0.3)	164 (48.0)	78 (22.8)	5 (1.5)

Alberts SR et al. 2012.
JAMA 307(13):1383-93

DPYD Variants as Predictors of 5-fluorouracil Toxicity in Adjuvant Colon Cancer Treatment (NCCTG N0147)

Adam M. Lee, Qian Shi, Emily Pavey, Steven R. Alberts, Daniel J. Sargent, Frank A. Sinicrope, Jeffrey L. Berenberg, Richard M. Goldberg, Robert B. Diasio

J Natl Cancer Inst, 2014

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Table 2. Grade≥3 5FU-Adverse events and incidence of *DYPD*2A* and D949V variants

	*DYPD*2A* (rs3918290)			D949V (rs67376798)		
Adverse events (grade≥3)	**Carrier, no. (%) (n = 25)**	**Wild-type, no. (%) (n = 2564)**	***P****	**Carrier, no. (%) (n = 27)**	**Wild-type, no. (%) (n = 2562)**	***P****
Overall AEs	22 (88.0%)	1581 (61.7%)	.007	24 (88.9%)	1582 (61.8%)	.004
5FU-AEs	22 (88.0%)	834 (32.5%)	<.001	22 (81.5%)	835 (32.6%)	<.001

compound heterozygote DPYD*2A/D949V = 1 toxic death

TRADE-OFF?

Preemptive testing:

55 pts start w/ 50% dose reduction

Dose adjustment

DPYD*2A

< 12 cycles = 11/25

dose mod = 20/25

D949V

<12 cycles = 8/27

Dose mod = 20/27

I590S *13

< 12 cycles = 1/4

Dose mod = 3/4

no FU adjustments. = 9/56

Patients who require multiple dose red[illegible]s during a cycle for grade 2 toxicity may, at the physician's discretion, be[illegible]e following cycle at one dose level higher than the final dose level during [illegible]ycle. If dose reduction beyond –3 for any agent is required, that agent sho[illegible]ontinued. Dose reductions beyond –2 are not allowed for cetuximab.

Agent*	**Initial Dose**	**Level –1**	**Level –2**	**Level –3**
Oxaliplatin	85 mg/m²	65 mg/m²	50 mg/m²	40 mg/m²
5-FU Bolus	400 mg/m²	320 mg/m²	270 mg/m²	230 mg/m²
5-FU Infusion	2400 mg/m² per 46-48 hrs	1920 mg/m² per 46-48 hrs	1600 mg/m² per 46-48 hrs	1360 mg/m² per 46-48 hrs

Principles of Adjuvant Therapy: Colon Cancer

- Evidence that starting with a 50% dose reduction of FP does not impact survival in adjuvant colon cancer setting

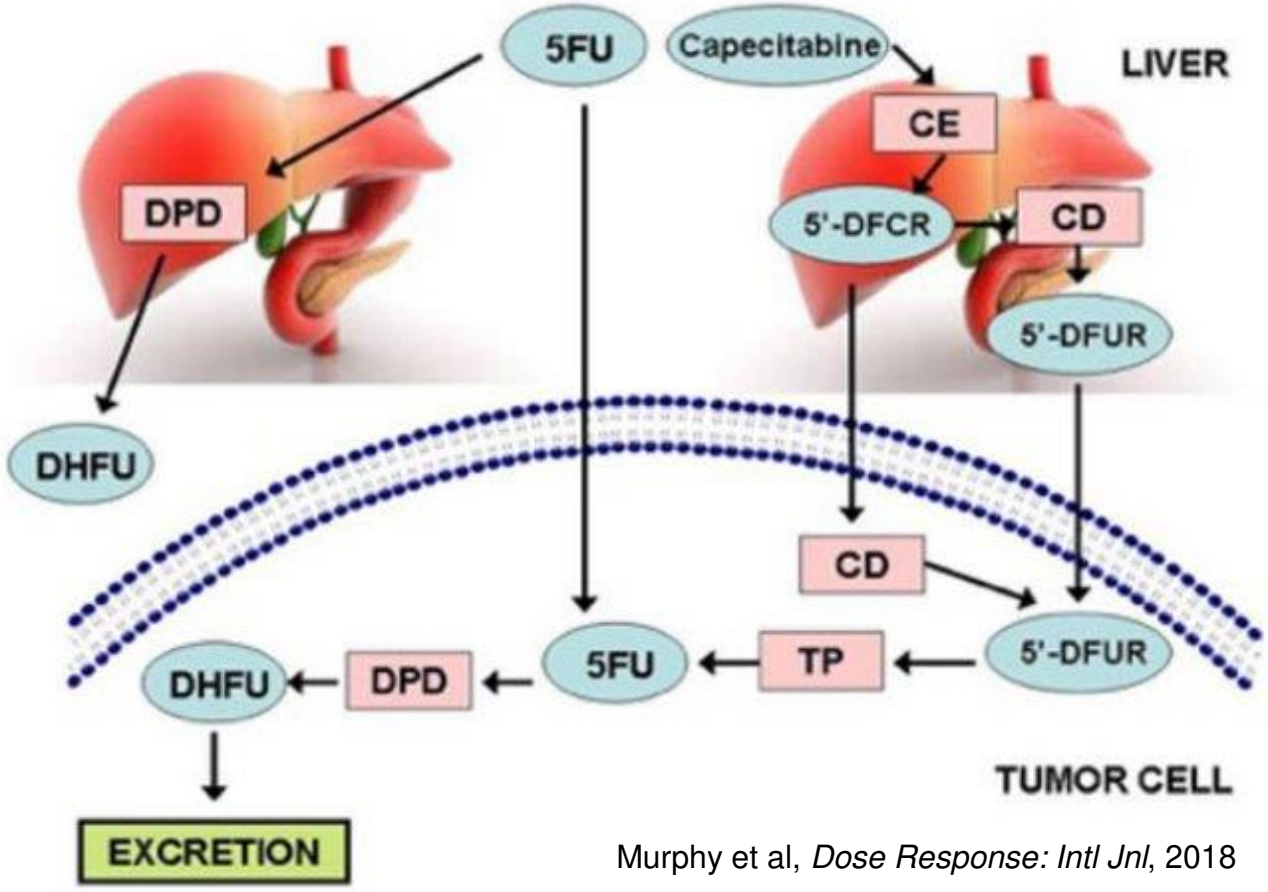
Moving Forward

Personalizing cancer treatment is not just about identifying variant genes of relevance, it is also about addressing such variants in the context of the circumstances of that patient

ISSUES:

- 5FU and capecitabine should not be considered the same drug
- Different diseases and settings may incorporate testing in different ways
- CPIC needs to contextualize its dosing recommendations
- Metabolizing activity of uncommon variants of DPYD can be better characterized
- Simplify the nomenclature

Capecitabine ≠ 5-Fluorouracil



Murphy et al, *Dose Response: Intl Jnl*, 2018

VARIABLES:

- GI transit time
- Absorption
  - Stomach pH
  - Stomach contents
- Drug-drug interactions
- Pro-drug activation
- Clearance
- Microbiome

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