Demonstrating Clinical Effectiveness of a Follow-On Companion Diagnostic Test When a New Clinical Trial is Unfeasible

cobas® *KRAS mutation test*

Abha Sharma, Roche Molecular Systems, Nov 2015

Overview of the Presentation

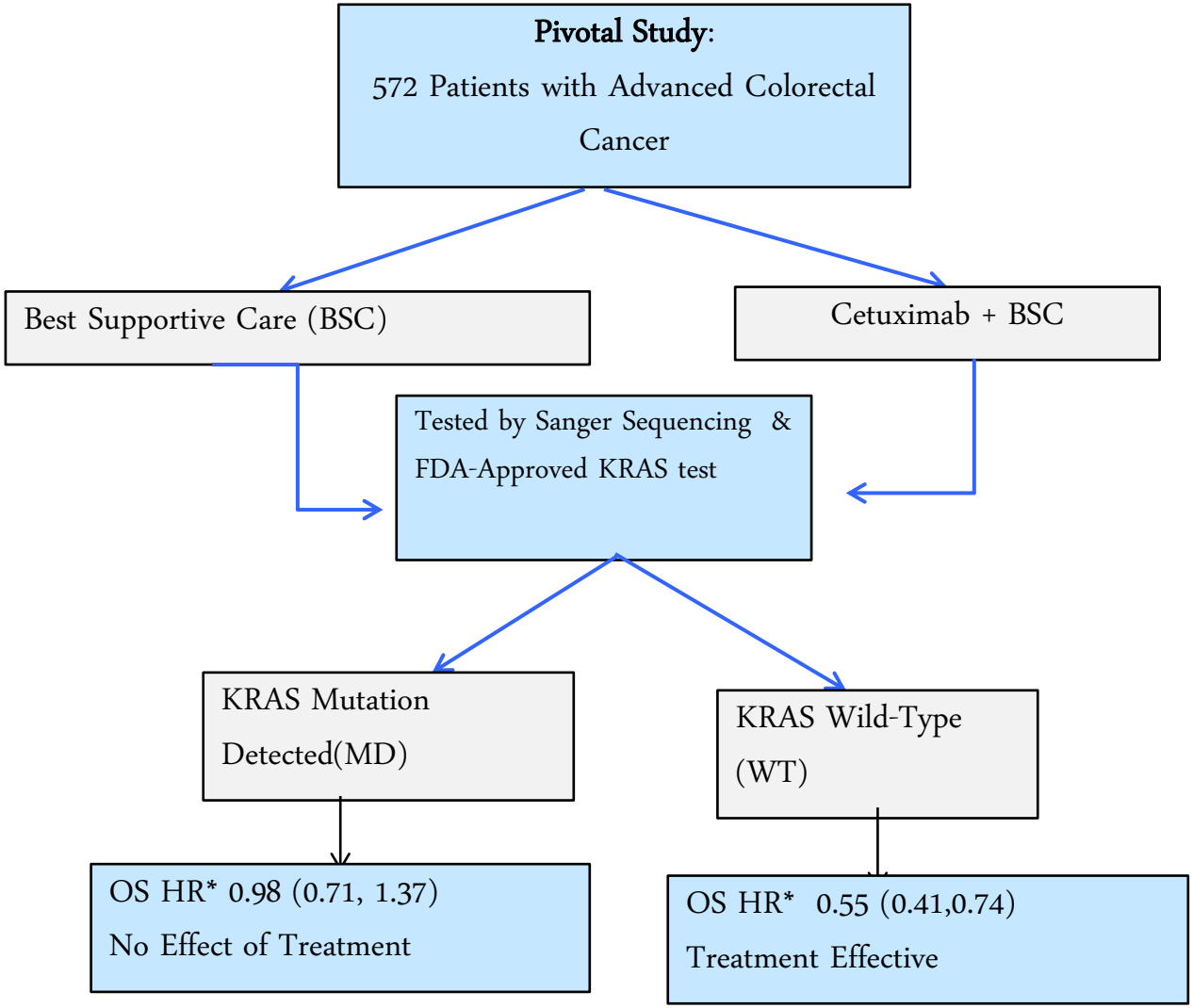
- Background of companion diagnostic test
- Challenge and Approach for follow-on Diagnostic Test
- Demonstrate how to establish drug efficacy for cobas® KRAS Mutation Test as a follow on Companion Diagnostic Test

Background: Companion Diagnostics Test

- **Companion Diagnostics:** A companion diagnostic is an *in vitro* diagnostic (IVD) test, which provides information that is essential for the safe and effective use of a corresponding drug or biological product.

- Study design(s) to demonstrate clinical validity of the ***first companion diagnostic test***
  - Using the final In-Vitro Diagnostic (IVD) version of the test to select patients
  - Bridging from Clinical Trial Assay (CTA) or Lab Developed Test (LDT) to the final IVD Test

Background: Cetuximab Study and FDA-Approved KRAS Test



*Christos S. Karapetis. 2008. NEJM

Challenges for Follow on Companion Diagnostic Test

- unethical to conduct a new prospective trial with the same drug and a placebo arm while an effective approved drug/treatment is available

- Samples may not be available to re-test from a previously conducted trials
  - for first companion Diagnostic Test (**pivotal trial**)
  - involving the same drug/treatment

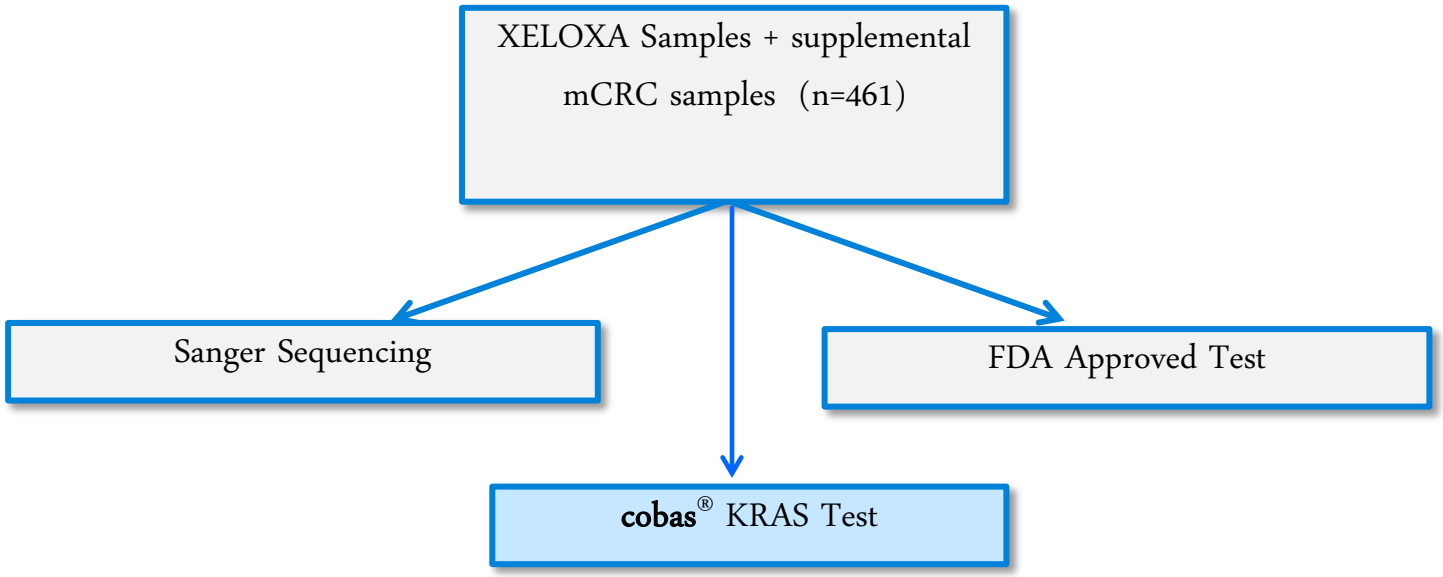
Approach for Follow on Diagnostic Test

1. Test Samples from another clinical study cohort (similar patients population) by
    - The First Companion Diagnostic Test
    - the follow on companion diagnostic test, and
    - the reference method (A sequencing method)

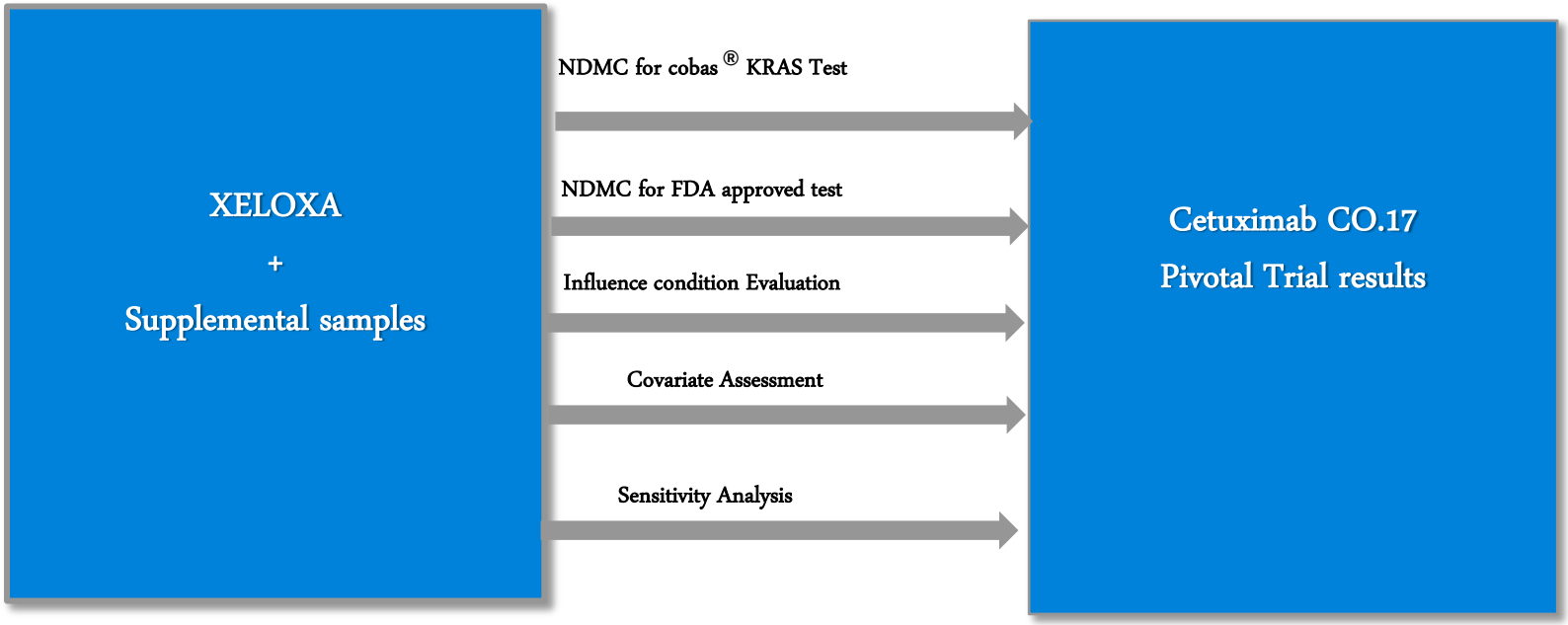
2. Calculate agreement between ***follow on companion diagnostic*** test and the other two tests.

3. "Transport" drug efficacy from the **pivotal study** for the **first** ***companion diagnostic test*** to the ***follow on companion diagnostic test***
    - assuming Non-Differential Misclassification (NDMC): given the comparator method, clinical efficacy is assumed **not** depend on the follow on companion test result
    - The covariate distribution in follow on study cohort is similar to the pivotal cohort or the difference in covariates do not alter the drug efficacy conclusions

Clinical Study Design for cobas KRAS Mutation Test



Five Criteria to Establish Clinical Utility of cobas® KRAS Test



Comparison of the cobas® KRAS Mutation Test with Comparator Methods for Detection of KRAS Mutations in Codon 12/13

cobas® KRAS Mutation Test	Comparator Method							
	Sanger Sequencing				FDA-approved IVD test			
	MD	NMD	Invalid	Total	MD	NMD	Invalid	Total
MD	124	34	5	163	139	9	15	163
NMD	4	268	2	274	10	248	16	274
Invalid	0	19	5	24	0	5	19	24
Total	128	321	12	461	149	262	50	461
PPA (95% CI)	96.9% (92.2%, 98.8%)				93.3% (88.1%, 96.3%)			
NPA (95% CI)	88.7% (84.7%, 91.8%)				96.5% (93.5%, 98.1%)			

NDMC Evaluation by Attenuation Factor (PPV+NPV-1) (Criteria 1 & 2)

Comparator	PPV (95% CI)	NPV (95% CI)	Attenuation Factor (95% CI)
cobas® KRAS Mutation test with respect to Sanger Sequencing	0.858 (0.811, 0.902)	0.975 (0.946, 0.994)	83.3% (77.7, 88.3)
FDA Approved test with respect to Sanger Sequencing	0.840 (0.790, 0.888)	0.956 (0.918, 0.986)	79.5% (73.4, 85.2)
cobas® KRAS Mutation test with respect to FDA Approved test	0.957 (0.927, 0.981)	0.945 (0.909, 0.978)	90.2% (85.6, 94.4)

*Under NDMC: $E(h|R=0) - E(h|R=1) = [E(h|S=0) - E(h|S=1)(\ NPV+PPV-1)$

- Difference in log-hazard ratio for cobas test = difference in log-hazard ratio for reference/first diagnostic test × (PPV+NPV-1)
- The larger (PPV +NPV-1), the better preserving the fraction of the difference in log hazard ratio observed from pivotal study with reference method

*Gene Pennello, etc. 2013. JSM Montreal

Influence Condition Evaluation: (3)

Influence Condition: To enable overall population intended use labeling, the beneficial effect of the drug must not be limited to only the predefined subpopulation

- Our Objective is to show beneficial effect of the drug is limited to KRAS mutation negative subpopulation.
- i.e. 95% CI for the hazard ratio in
  - the Mutation positive subset **includes** 1 (no treatment effect),
  - the Mutation Negative subset **excludes** 1 (significant treatment effect).

Brian A. Millen, 2012, Drug Information Journal

Influence Condition Evaluation Results

Drug Efficacy	cobas® KRAS Mutation Test Status	Samples Tested (N)	Hazard Ratio (HR)	
			Estimate	95% CI
Overall Survival (OS)	No Mutation Detected	272	0.558	(0.422, 0.752)
	Mutation Detected	158	0.908	(0.670, 1.209)
Progression Free Survival (PFS)	No Mutation Detected	272	0.413	(0.304, 0.550)
	Mutation Detected	158	0.869	(0.670, 1.138)

Comparison of Covariates between Two Study Cohorts (4)

- Covariate Distributions were compared between two studies.
- Some covariates distribution were different between the two cohorts, such as age, sex, ECOG score, etc;
- The KRAS mutation types are similar

KRAS Mutation Type	Study Cohort	Pivotal cohort	
N	149	208	
12ALA	12 (8.1%)	14 (6.7%)	P_1=0.317
12ARG	2 (1.3%)	2 (0.9%)	
12ASP	42 (28.2%)	71 (34.1%)	
12CYS	15 (10.1%)	16 (7.7%)	
12SER	13 (8.7%)	11 (5.3%)	
12VAL	35 (23.5%)	54 (25.9%)	
13ASP	30 (20.1%)	40 (19.2%)	

- Drug efficacy (estimated by hazard ratio) was recalculated based on the covariate distribution observed in the pivotal study.
- Demonstrated that **adjusted** treatment effect was
  - significant in cobas KRAS wild type population; and
  - non significant in cobas KRAS mutation positive population.

Covariate differences between the two cohorts do not affect the drug efficacy.

Sensitivity Analysis* (5)

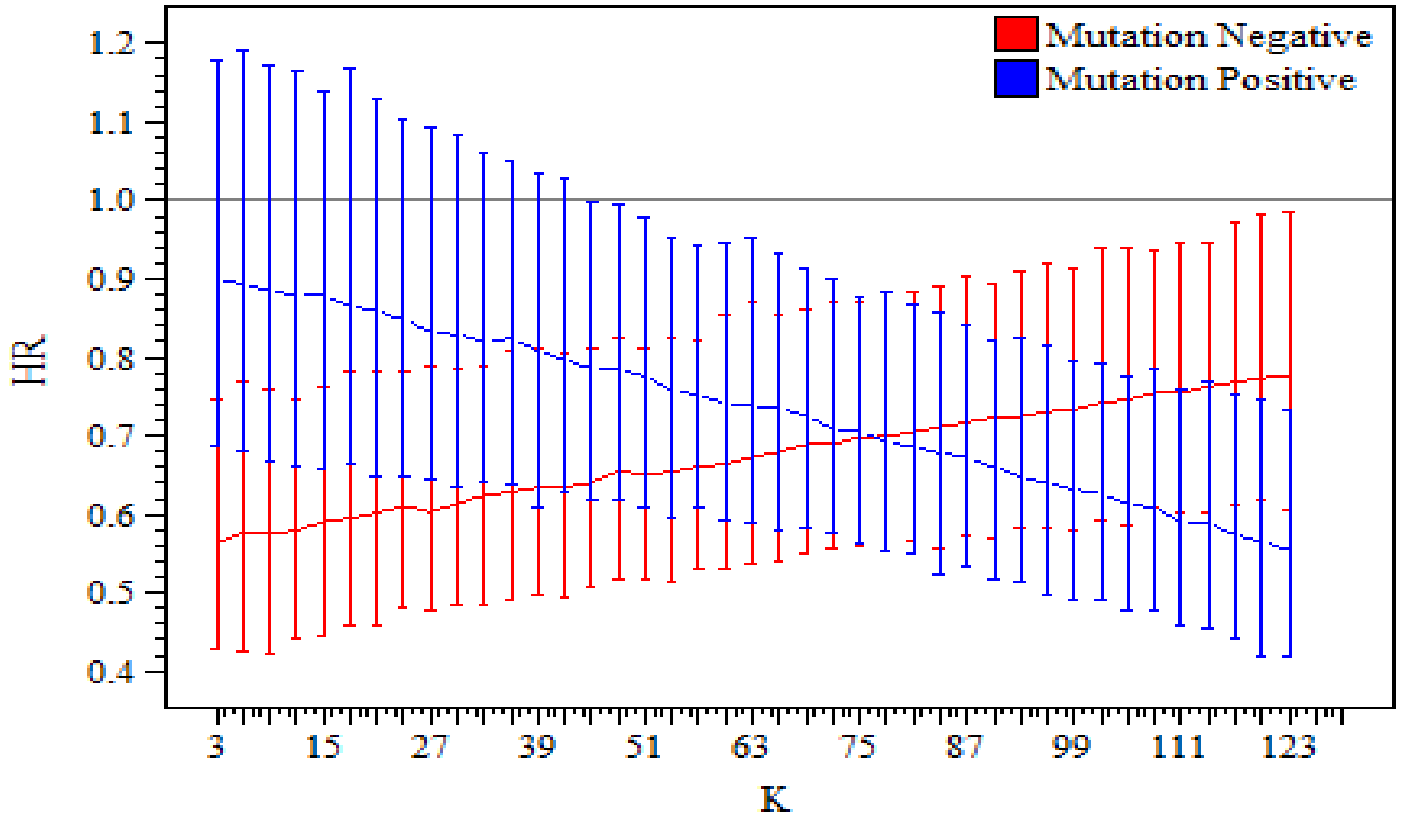
- Sensitivity analysis was conducted to consider the robustness of the study results to the assumptions by simulating how many agreements between **cobas**® test and Sanger sequencing would have to be changed to disagreements before the study fails to show clinical effectiveness.

		Sanger Sequencing	
cobas® KRAS Mutation Test		Pos	Neg
	Pos	a (k)	b (k)
	Neg	c	d

- 'k' patients were moved from positive agreement cell 'a' cell to disagreement cell 'c ' (sanger Pos & **cobas** Neg), and at the same time k' patients were moved from negative agreement cell 'd' to disagreement cell 'b' (Sanger Neg & **cobas** Pos).
- Log Hazard ratios were calculated for each value of 'k'.
- The highest value of k at which the hazard ratio is still statistically significant for cobas negative or still not significant for cobas positive will be determined.

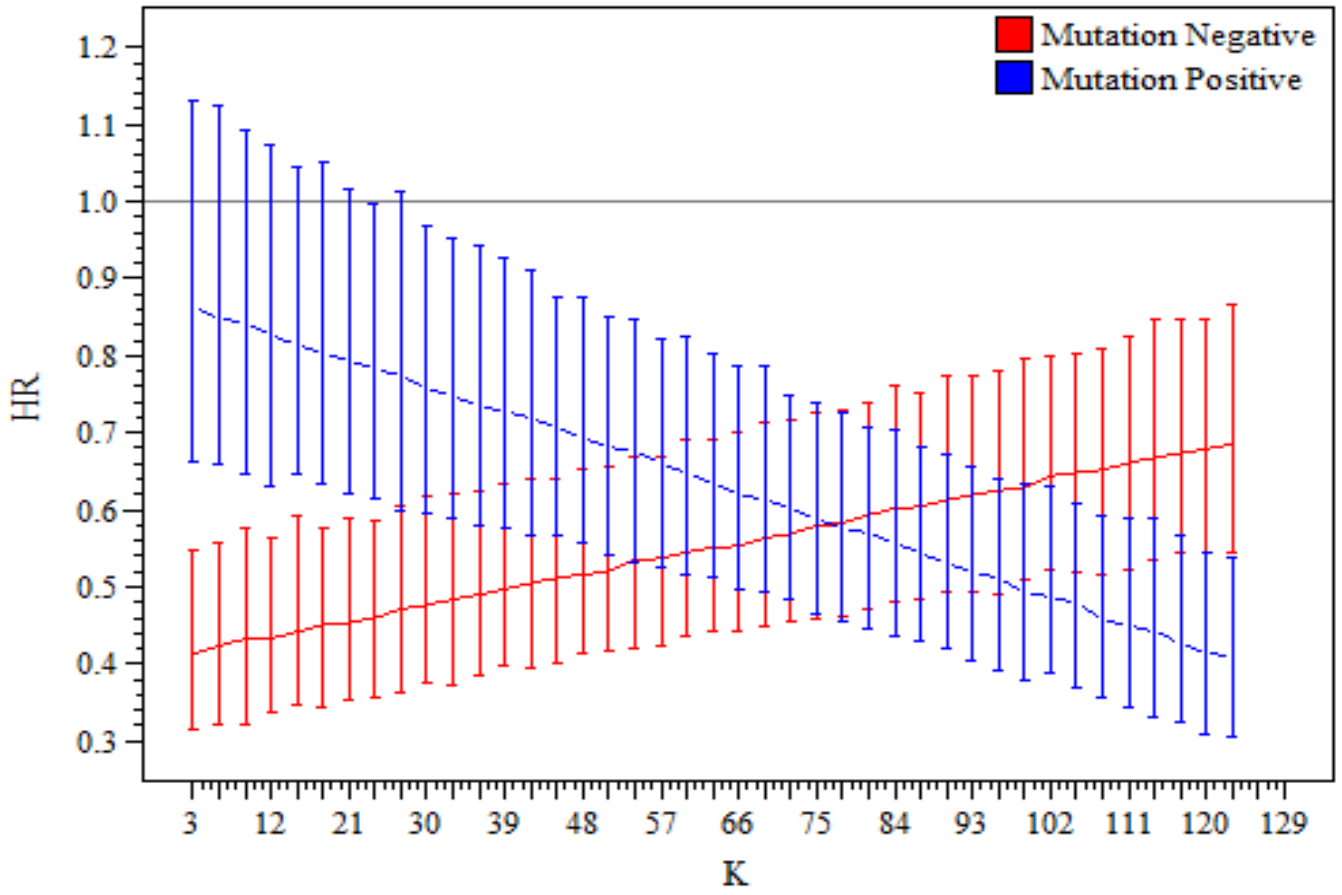
*Denne, Pennello et al. 2014, Statistics in Biopharmaceutical Research

OS (HR) Changes by KRAS Status as Determined by the cobas® KRAS Mutation Test by Moving Subjects from Concordance to Discordance (Criterion 5)



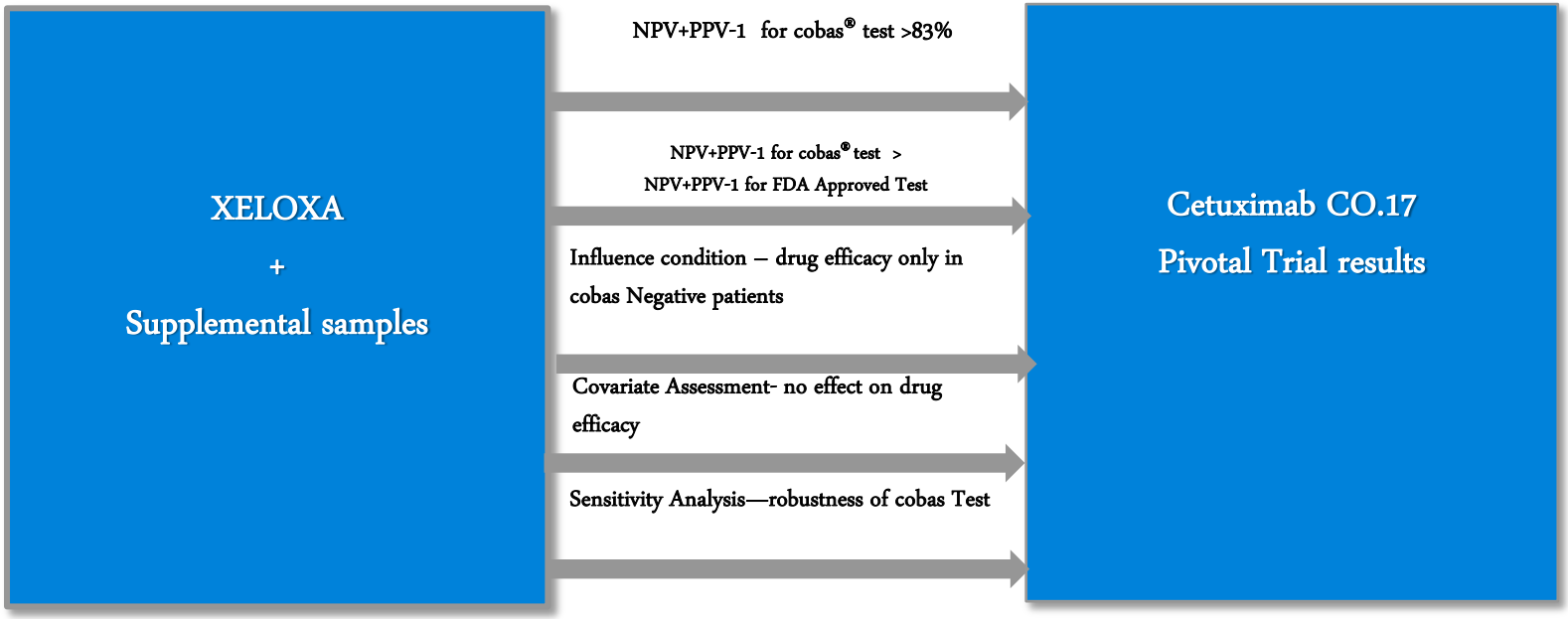
when k = 45, which corresponds to 21% more discordance between the **cobas®** KRAS Mutation Test and Sanger sequencing to change the drug efficacy

PFS (HR) Changes by KRAS Status as Determined by the cobas® KRAS Mutation Test by Moving Subjects from Concordance to Discordance (5)



when k = 27, which corresponds to 12.6% more discordance between the **cobas®** KRAS Mutation Test and Sanger sequencing to change the drug efficacy

Five Bridges to Demonstrate Clinical Utility



Analysis described was performed for the cobas® KRAS Mutation Test as a companion Diagnostic Test for cetuximab

Similar analysis was done for the **cobas® KRAS Mutation Test** as a CDx for panitumumab

Conclusions

- The approach described here proposes an innovative approach for evaluating the clinical utility of a follow on companion diagnostic test.

- We appreciate the support and collaboration from CDRH colleagues in defining and executing the innovative approach.

Doing now what patients need next