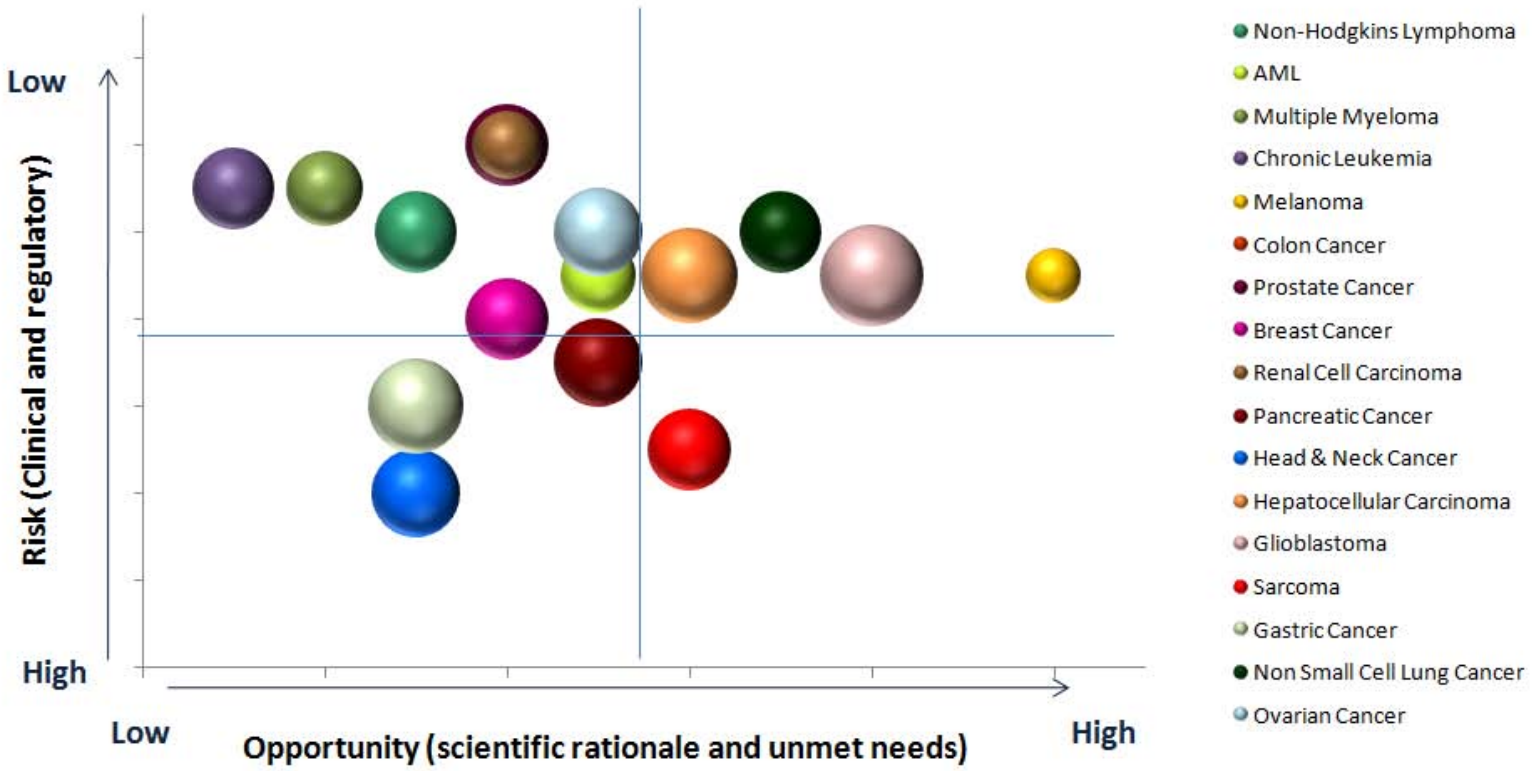
Designing an Optimal Label for Commercial Success: When and How?

Moderator:
Jeff Bockman, PhD, Vice President, Defined Health

Panelists:

- Steve Heller, Independent Consultant: Oncology Strategy, Development, Analysis
- Chandra Ramanathan, PhD, MBA, Head Early Pipeline Oncology Global Marketing SMBU, Bayer HealthCare Pharmaceuticals
- Usman Iqbal, MD, MPH, MBA Senior Director and Head of Oncology, Global Evidence & Value Development, R&D, Sanofi

Part of Getting to the Target Product Profile (TPP) Is Knowing Where You Want to Focus Development



Size of bubbles represent Commercial potential (market potential, current and future competition)

Note: Investment required for POC has been weighted 2x amongst risk parameters.

Developing a Provisional TPP for an Early Stage, Novel Asset Across Multiple Possible Tumor Types

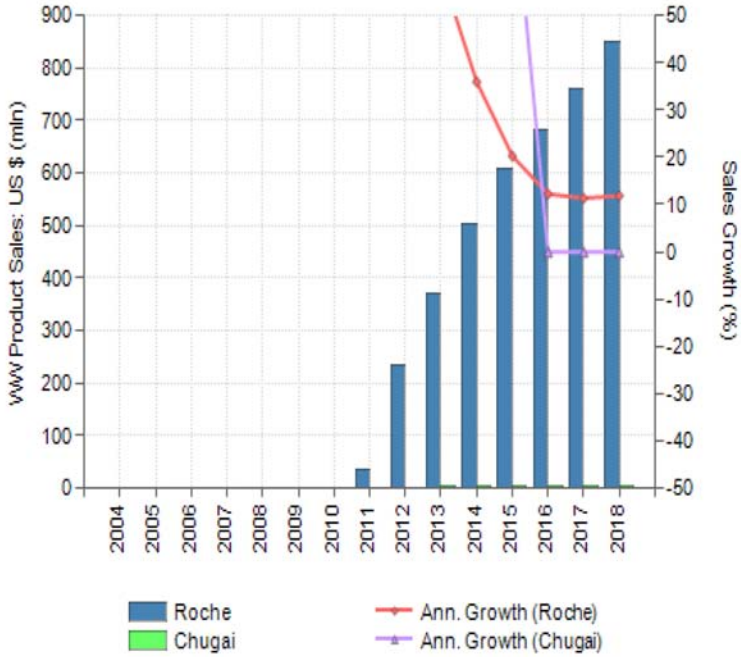
Benchmark for a product developed in second-line CRC, KRAS Mutants

	Efficacy	Safety	Dosing/Administration
Target ***Summary of Profile: Improved efficacy***	Patients receiving Product X + FOLFIRI in KRAS mutations experienced superior response and improved PFS compared to FOLFIRI alone and comparable to KRAS wt patients treated with FOLFIRI + Anti-EGFR MAb Minimal Efficacy*: • 2 months improvement in PFS, • Significant improvement in response rate Ideal Efficacy: >10% improvement in OS	• Diarrhea is seen with irinotecan-based therapies, so ideally any new agent should not increase the background rate (~10%) • Heme tox – approx. 10% neutropenia is seen with FOLFIRI	• Fitting into FOLFIRI schedule
SOC ***Current***	Comparator Regimen: - FOLFIRI + EGFR antibody Efficacy (181 study panitumumab + FOLFIRI vs. FOLFIRI): •- 14.5 months median survival (wt KRAS arm) vs. 12.5 months in control arm •5.9 months PFS (wt KRAS arm) vs. 3.9 months PFS in control arm •Response rate of 35% (wt KRAS arm) vs. 10% in control arm •In Mutant KRAS, analyses of multiple studies (not solely FOLFIRI+Anti-EGFR Mab), TTP was 3 months and OS 6.9 months, compared to wild-type where TTP was 6.1 months and OS 11.5 months.	Comparator Regimen: • FOLFIRI + EGFR antibody Safety (181 study panitumumab + FOLFIRI vs. FOLFIRI): ❖ The incidence of several grade 3 and 4 adverse events in panitumumab arm include rash (37% vs. 2%), diarrhea (14% vs. 9%) and stomatitis (8% vs. 3%)	•2-hour infusion of 400 mg/m2 of leucovorin, given simultaneously •followed by a bolus of 400 mg/m2 of 5FU and then a 46-hour infusion of 2400 mg/m2 of 5FU •Infusion of 180 mg/m2 of irinotecan instead of the infusion (1 cycle = 14 days)

*Sanofi is going for strong data package to displace Avastin – OS in second-line VELOUR study, but previous approvals have been on PFS

PoR Built Into PoC: Biomarker Strategy + Strong Differentiation = Short Term Value Creation

Date	Event	Terms
October 3, 2006	• Plexxikon files IND application for PLX4032 (B-Raf^{V600E} inhibitor)	
October 4, 2006	• Partnership with Roche for PLX4032 and follow-on products targeting other BRAF kinases • Agreement with Roche Molecular Diagnostics for companion diagnostic	**$40M upfront $6M research $660M total**
January 1, 2009	• Second agreement with Roche for PLX5568 (Raf kinase inhibitor) for polycystic kidney disease	$60M upfront $335M total
June 2009 – January 2011	PLX4032 • metastatic melanoma P1 results reported • first patient dosed in pivotal P2 & P3 metastatic melanoma trials • colorectal cancer extension trial P1 results reported • metastatic melanoma preliminary P2 results reported • metastatic melanoma interim P3 results reported	
January 6, 2011	• Plexxikon signs agreement with Genentech (Roche) to co-promote PLX4032 in the US (option from 2006 agreement)	
February 28, 2011	• **Daiichi Sankyo to acquire Plexxikon**	**$805M upfront $130M milestones**
August 17, 2011	• Zelboraf approval	



Plexxikon, EvaluatePharma, Defined Health

The Challenge of an Optimal Label

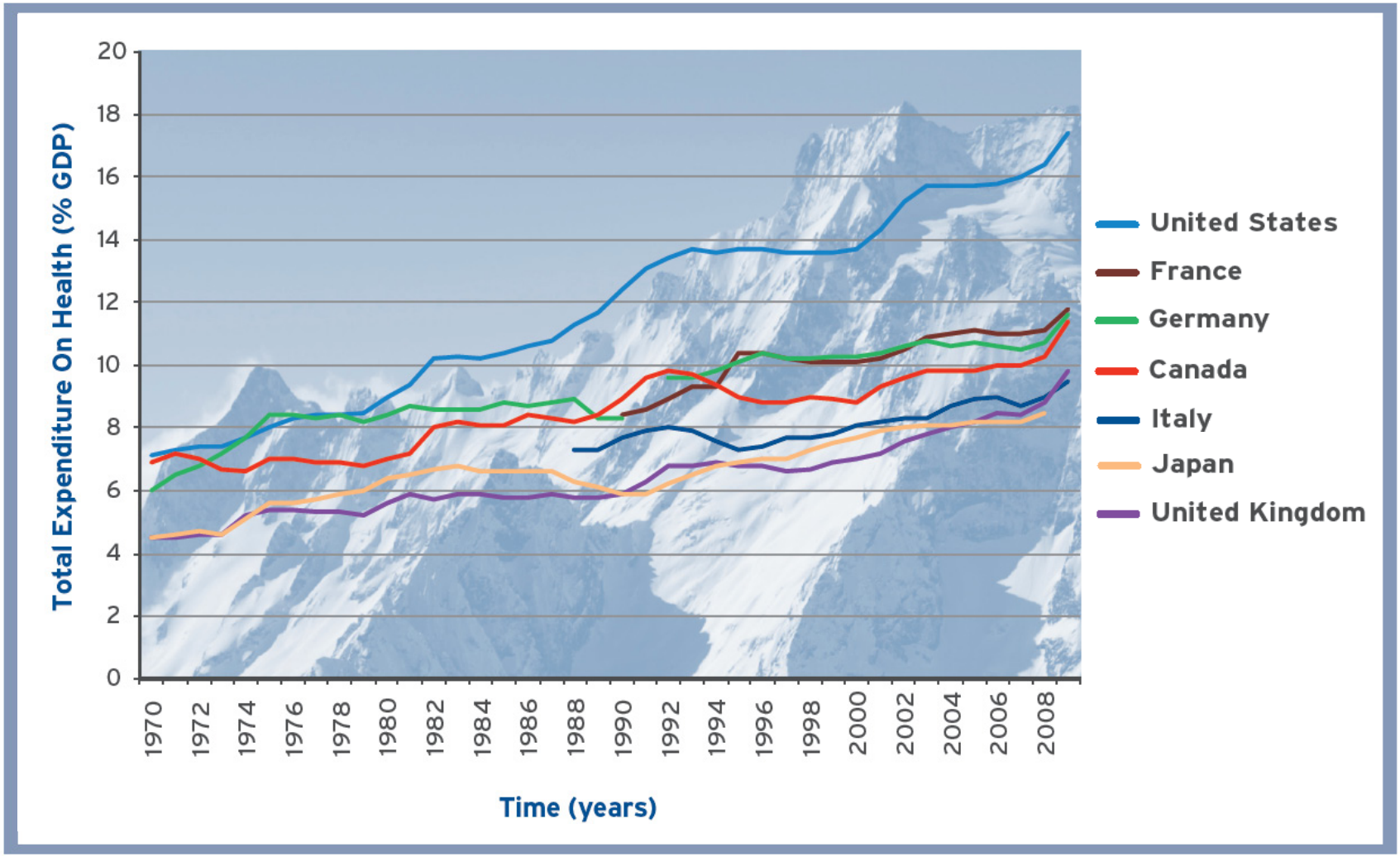
Activity $\neq$ Efficacy

Efficacy $\neq$ Regulatory Approval

Regulatory Approval $\neq$ Access for Patients

Clinical & Market Success Require Evidence of Differentiation AND Value

Unsustainable Health Care Cost*



*1) Organization of Economic Cooperation and Development, OECD Social Expenditure Statistics (database), 2011

THERAPEUTIC INSIGHT by DefinedHealth

DefinedHealth unconventional insight

CANCER PROGRESS by DefinedHealth

U.S. Late to the Party, but is Ready to Tango

1970's 1980's 1990's

1972
Office of Technology Assessment is established

1976
The term "meta-analysis" was first coined by Gene Glass (Metric)

1977
First publication on hospital purchasing committees

1986
Start of John Hopkins Program for Medical Technology and Practice Assessment

1989
AHCRP is created under the Omnibus Budget Reconciliation Act (103.Stat.2159)

1996
Gold et al. publish "Cost-Effectiveness in Health and Medicine" (US expert panel)

1999
Marked increase in implementation of three-tier product coverage (Restriction Measure)

Metrics/guidelines
Budget control measures
Access restrictions by payers

2000's

2000
AMCP`s guidance on clinical and economic data for private payer formulary listings

2004
U.S. health care spending is highest of all OECD countries

2006
Coverage with evidence development (CED) (Medicare U.S.) (Gatekeeper)

2007
AMCP Guide to Pharmaceutical Payment incorporates rebating
Congressional Budget Office (CBO) Report on Comparative Effectiveness

2008
WellPoint releases revised evidence requirements for pharmaceutical HTA

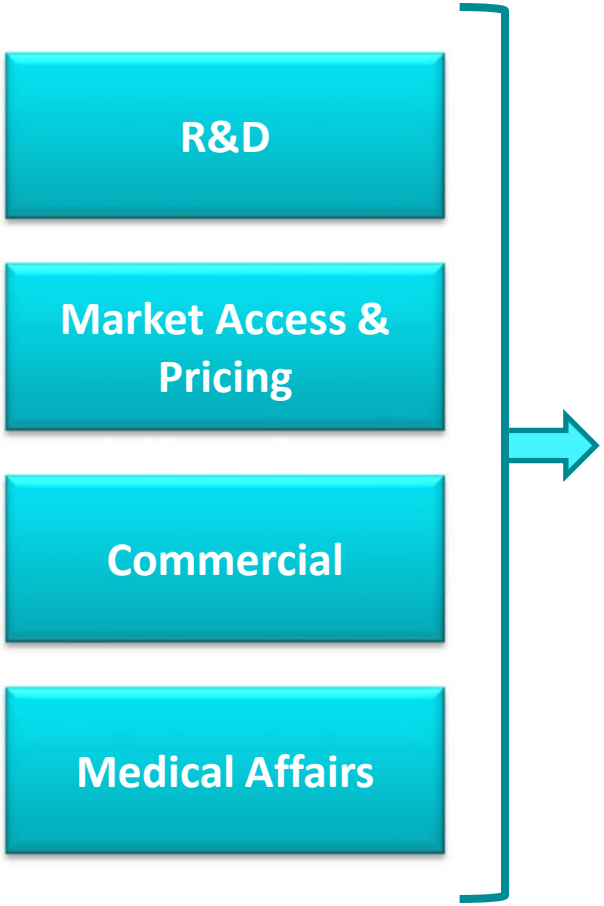
2009
$1.1 billion allocated for CER by ARRA

2010
Patient Protection and Affordable Care Act establishes Patient Centered Outcome Research Institute (PCORI)

2013
US Oncology Network and NCCN jointly developing "Value Pathways"

Adapted with permission from: Saadi et al., The Science of Commerce, 2012

Must Work Together Toward Global TPP that Captures Value for Critical Stakeholders



Target Product Profile

- Unmet need in setting ✔
- Defined patient population ✔
- Differentiation vs. future care ✔
- Meaningful endpoints ✔
- Limited uncertainty ✔
- Align price with clinical value ✔
- Affordable ✔

THERAPEUTIC INSIGHT by DefinedHealth DefinedHealth unconventional insight CANCER PROGRESS by DefinedHealth

Challenges of Differentiation vs. Future SOC: 1st Line Squamous NSCLC

Scenario	Evidence	TPP Implication
1) Platinum doublets remain SOC	• Uncertainty in pipeline • Abraxane/carbo improved on RR/tox. but not OS and adds cost	➢ Improved OS 30%+ (13 vs. 10 mths.) is moderate value prop[illegible]n. ➢ [illegible] positive [illegible]omics
2) FGFR class (Novart[illegible] Lilly, others)	• [illegible]	➢ FGFRs must exceed doublet SOC to reach
3) Nivolumab (PD-1 – BMS)	• P1: [illegible] elev[illegible] PD-L1 • Potential 2nd line to market 2015, then 1st line	➢ Nivolumab w/o biomarker would compete for all squamous. ➢ Biomarker would improve TPP and stratify squamous market
4) MET Mab (Roche)	• P2 w MET IHC biomarker	➢ If successful, hurdle is raised in biomarker segment.

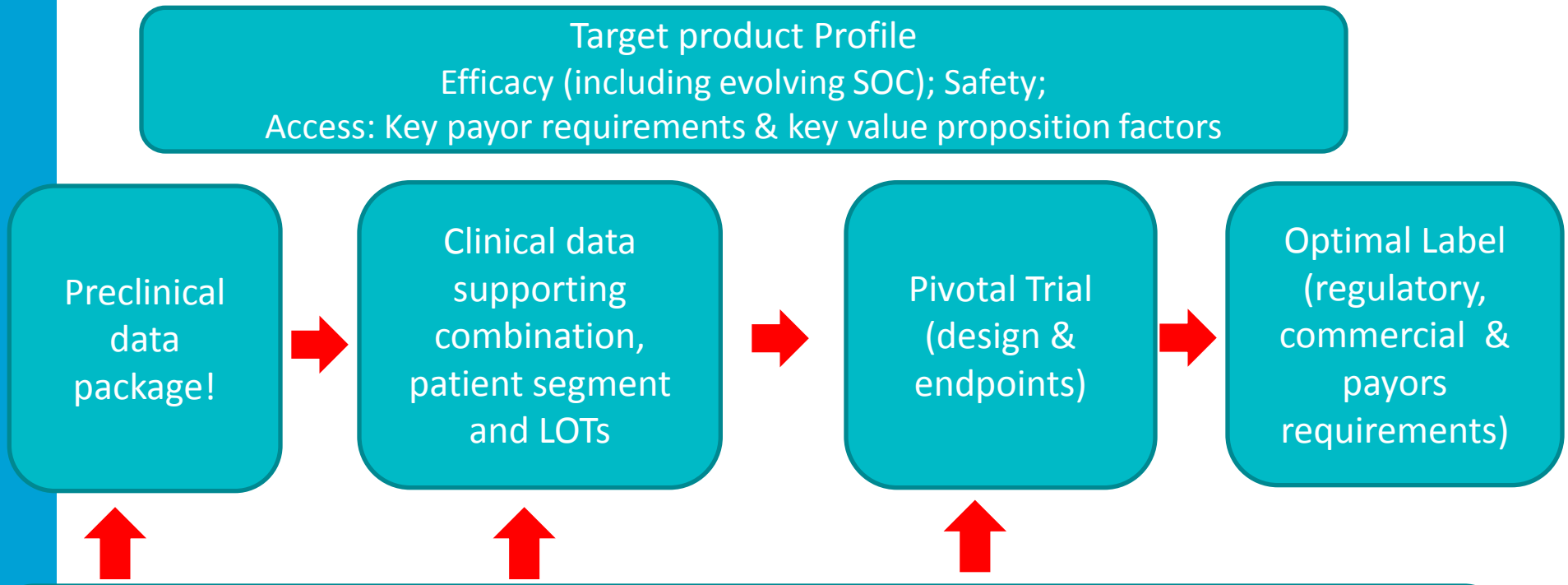
The probability of scenario #2 and #3 and #4 succeeding is LOW-MEDIUM

*But the probability of **EITHER** #2 or #3 or #4?*

Designing an Optimal Label for Commercial Success?

- Have a strategy – rigorously anticipate dependencies and linkages between clinical plan and market success
- Validate differentiation hypotheses early as possible - inform evidence plan, change strategy, or stop program
- Goal is evidence of Proof of Value

It is never too early to think about an optimal label!

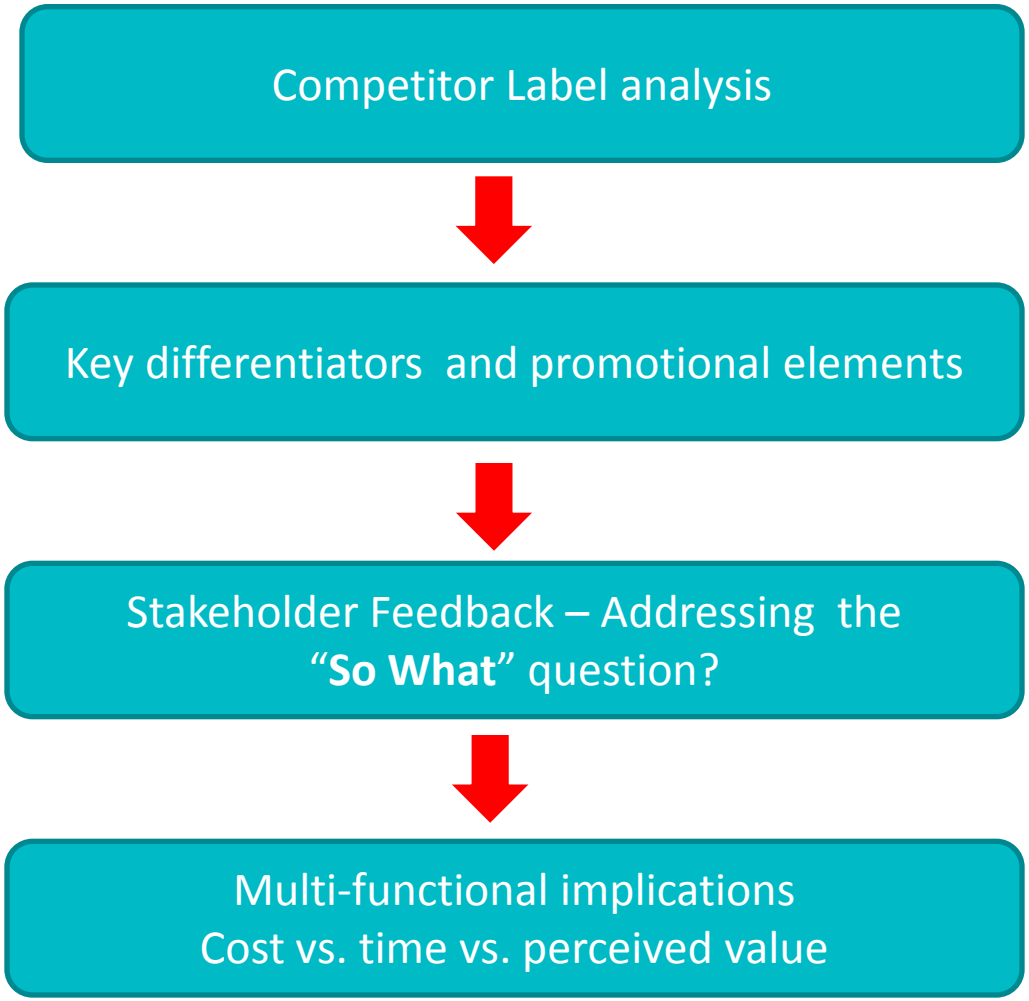


THERAPEUTIC INSIGHT by DefinedHealth

DefinedHealth unconventional insight

CANCER PROGRESS by DefinedHealth

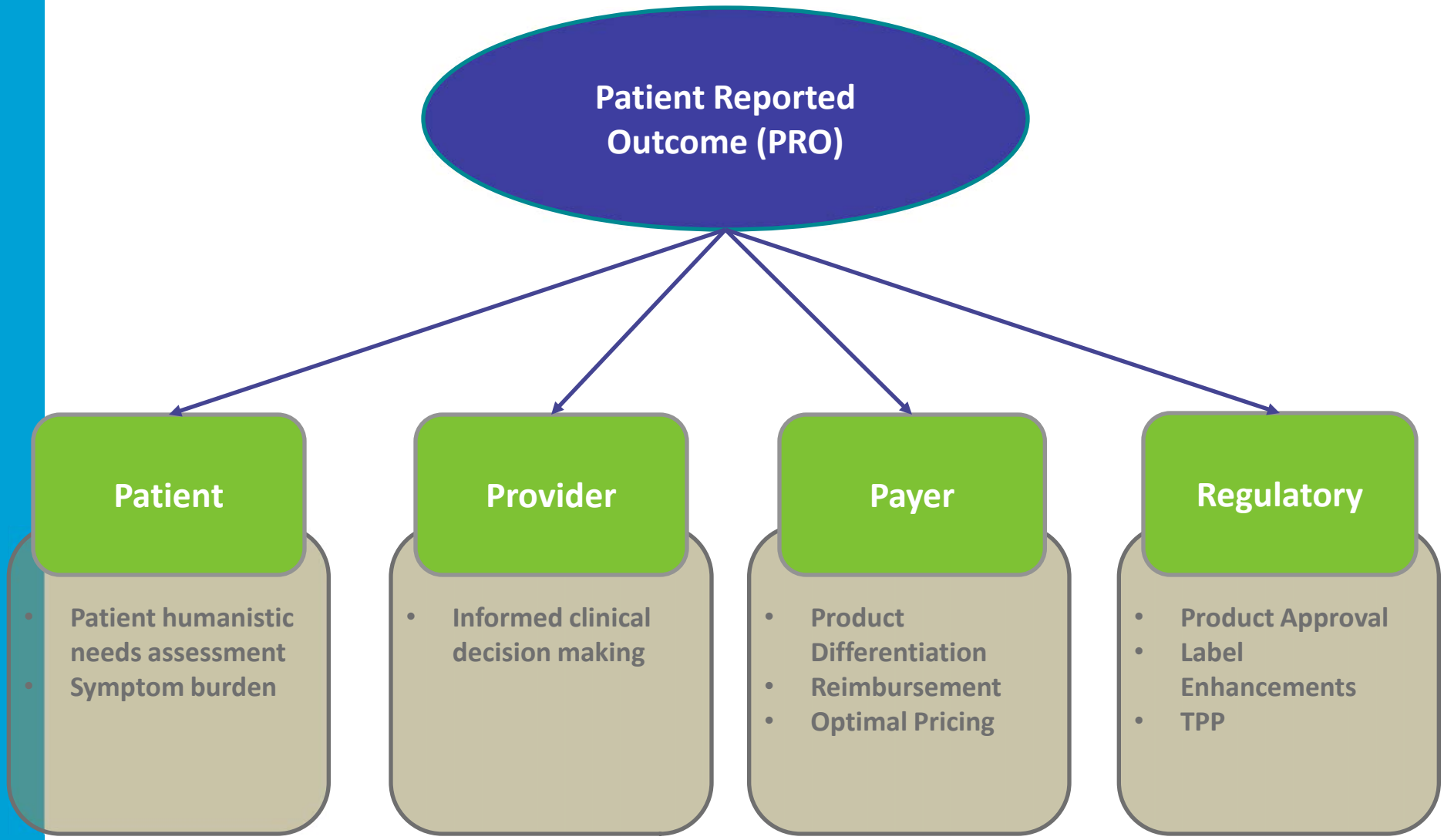
Capturing Value Through Label Analysis



Label Attributes - How do you translate them into competitive advantage?

Indication and Usage
Efficacy
Adverse Reactions (≥10% 3/4 AEs)
Black-Box Warning
Drug Interactions
Contraindications/ Precautions
Mechanism of Action
Dosage and Route of Administration
Health Economics & Outcomes Research

Patient-centered research has taken a principal position in enhancing value proposition for both registration & market access



PROs Value Proposition in Oncology: Label and Beyond!!

- **In the new era of "patient centricity" – PROs are in a principal position to provide product differentiation and label enhancements to Oncology products**
- Label Proposition incorporating PROs has to be based on **validated QOL instruments**
- PROs evaluating symptoms rather than health-related quality of life most successful because seen as more proximal to disease, treatment, resource utilization and costs.
- PRO evidence of patient benefit and response to treatment can influence treatment-related decisions made by **physicians, patients**, patient advocacy groups, **national health authorities, reimbursement agencies**, managed care organizations, and **hospital formularies**

Quality Adjusted Life Years Concept- Cost Utility Analyses and Importance in Oncology Patient Access

- "Quality modifier" of duration of life - life years versus quality adjusted life years

- **<u>Observations from QOL instruments converted into a summary index called utility-preference value associated with a given health state</u>**

- Utilities incorporated into Pharmacoeconomic analyses to compute quality adjusted life years (QALYS)- Survival multiplied by QOL driven utilities

  2 yr OS x 0.5 quality = 1QALY

Cost/QALYs is considered most appropriate CE criterion for assessing a product's Patient-centric value (HTA/ payers)

Real World Research is the KEY to understanding unmet need and limitations of current therapies, and positioning a value based label proposition for new products

Registration trials reflect stringent patient populations, limited observation period and outcome end points reflecting substantial gaps in efficacy vs. effectiveness

Regulators/Payer/Pharma awareness of the real world effectiveness of current therapies can be low

Compelling Value Based Label Proposition and Successful entry into the market is driven by the ability to capture and understand real world data on competitors and utilize that systematically for Development and Protocol Enhancement

Real World Observational Research and CER frameworks provide an Effective & Robust Medium to :

- Capture real world health outcomes & changes in treatment/disease landscape (Algorithms, Heat Maps)
- Highlight Associated limitations of existing therapies & Document Unmet Need
- Position development Program, TPP and end point optimization towards plugging the Gaps in current therapies and fulfilling the unmet needs

The New World of Evidence

-What type of evidence is needed to Optimize a successful Label

-Convergence of evidence being used by stakeholders

-Future Trends

- <u>What kind of evidence base</u>
  - Importance of real world research and its strategic application into development:
    - Protocol feasibility, pt recruitment, quantification of un met need/limitations of current therapies, end point optimization
  - PRO differentiation- Generic, Disease Specific, Fit for purpose instrument development customized to your TPP and patient population – QOL profile needed to show either better safety OR coupling of OS with the notion of improvement (first line) or no decrements in QOL (late lines)
  - Economic Evidence/end points (hospitalizations, no. of transfusions, growth factors)

  <u>Regulatory and Payer convergence</u>
  - EUNETHA, IMI, GreenPark initiative

- <u>Future:</u> Inter pharma collaboration on pathway validations and co- development of compounds- addressing the need for differentiation by collaboration.
  Joint regulatory and Payer dossier submissions and assessments