Reimbursement Landscape Assessment and Payer Relations Support for Company X's Technology X® Personalized 5-FU Dosing Platform

tJun17 Life Sciences Advisors

July 2018

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Project Overview

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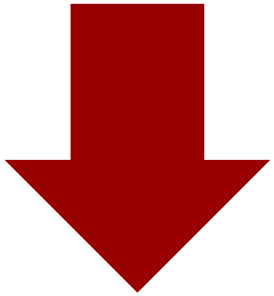
Statement of purpose and approach

Company X's Statement of Purpose

Company X seeks to optimize the value of its Technology X® personalized 5-FU dosing platform by refining its US payer relations strategy in order to maximize coverage and payment for the platform by Medicare and private payers



tJun17 Life Sciences' Approach

To support Company X' reimbursement objectives, tJun17 Life Sciences, LLC conducted a comprehensive market access landscape assessment based on both secondary and primary research with payers from each geographic region of the US

Project Objectives

1	Conduct a comprehensive US reimbursement coverage landscape assessment for personalized 5-FU dose optimization in the adjuvant and metastatic colorectal cancer setting
2	Detail current US private and Medicare funding pathways for personalized 5-FU chemotherapy dose optimization for colorectal cancer patients, environmental factors that may impact funding opportunities, and requirements for optimal coverage and payment
3	Develop actionable strategies to optimize the US market access and reimbursement landscape for Company X' Technology X® testing platform
4	Develop a time and events pathway to support future tactical initiatives to maximize the reimbursement potential for the Technology X testing platform
5	Align the Technology X reimbursement strategy with associated clinical and economic evidence development and regulatory strategies

Project Methodology

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In order to meet the project objectives, tJun17 Life Sciences' analytical methodology leveraged both secondary and primary market access research

To develop a comprehensive understanding of current US market access trends and perceptions for personalized 5-FU chemotherapy management, tJun17 Life Sciences:

1	Identified comparator technologies to provide insights into Medicare and private payer coverage policy and potential market access barriers
2	Conducted primary research with payers from each US geographic region to better understand market perceptions of the Technology X® testing platform, drivers of adoption, and financial incentives for use
3	Integrated primary & secondary data into actionable recommendations that address the potential market opportunities for the Technology X testing platform in current clinical practice, and optimization of Company X's current reimbursement strategy

In analyzing the current US reimbursement landscape for Technology X® tJun17 Life Sciences conducted an evaluation of clinical, economic and environmental variables

A comprehensive reimbursement evaluation was conducted within the scope of this project and incorporated:

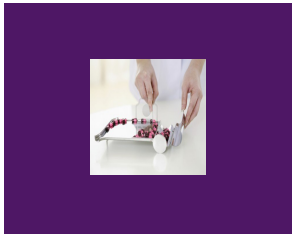
- Identification of the key decision-makers/thought leaders in the US payer community
- An assessment of the payer issues in favor and against 5-FU chemotherapy dose management
- An assessment of current US market conditions for 5-FU chemotherapy dose management
- An understanding of the location of service since different reimbursement paradigms exist for hospital inpatient, hospital outpatient, physician offices and long term care facility and the home healthcare environment
- An understanding of current oncology provider concerns, issues, or satisfaction utilizing secondary research
- An assessment of the need for patient assistance and reimbursement support

tJun17 Life Sciences conducted primary research with US payer stakeholders to inform Company X' key strategic questions

30 US stakeholder in depth interviews with small, medium and large payer organizations was conducted

2 Pharmacy Directors

19 Medical Directors



2 Doctors of Pharmacy

7 Chief Medical Officers

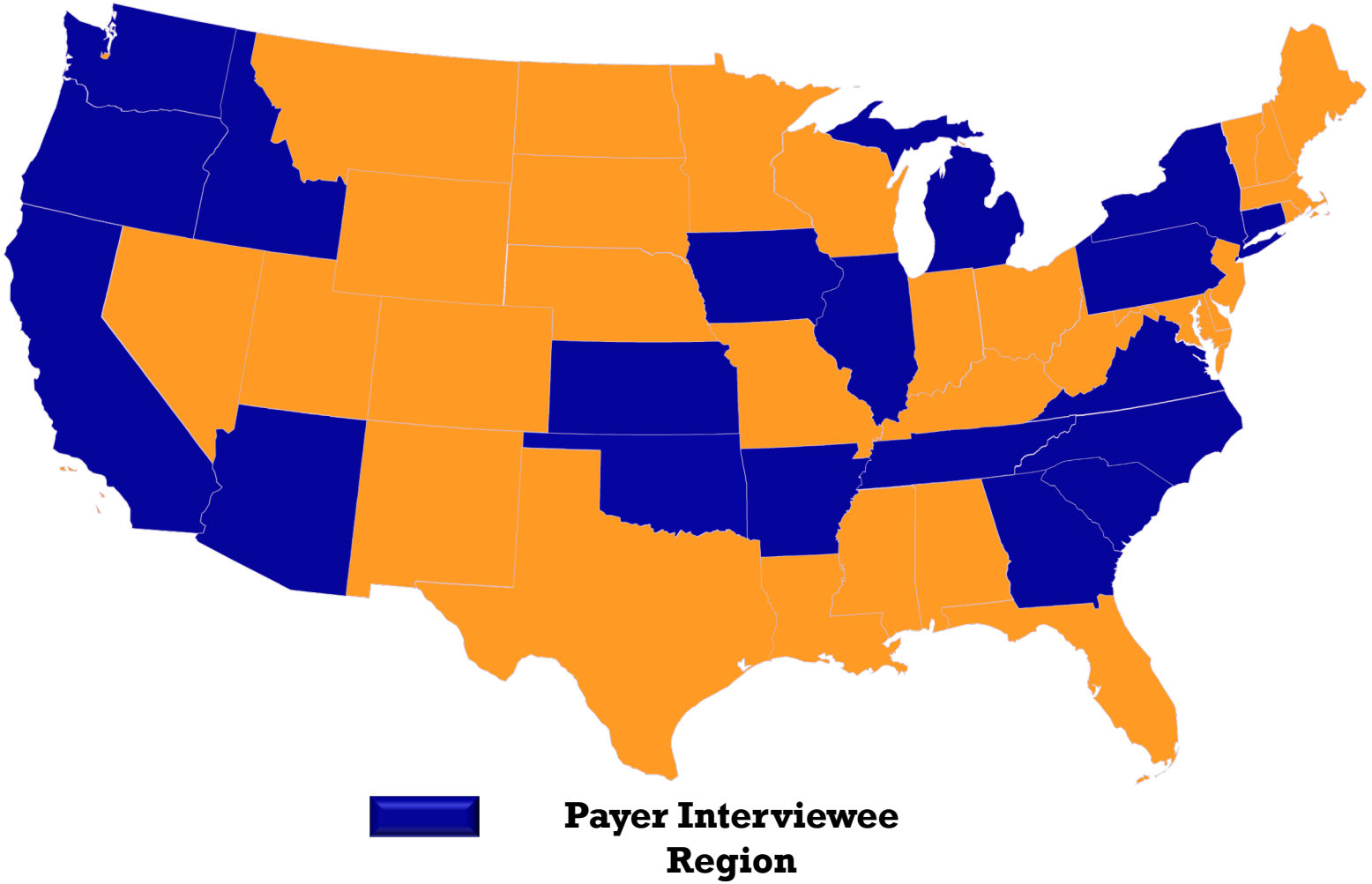
UnitedHealthcare
Healing health care. Together.®

CIGNA®

BlueCross BlueShield

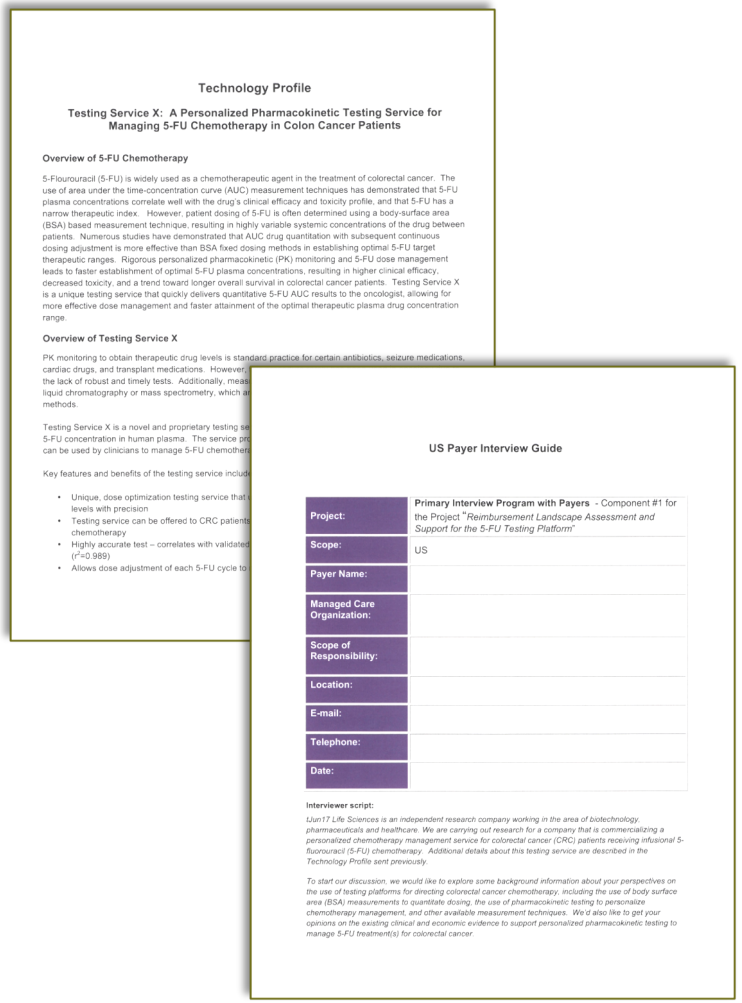
aetna℠

tJun17 Life Sciences conducted interviews with payers representing over 93.5 million covered lives and patient populations in 21 different states, including Alaska and Hawaii



A Technology Profile and Discussion Guide were developed to standardize the in-depth interview program

- A Technology Profile was developed to inform interviewees about Technology X® targeted indications, value proposition, and existing clinical data to support utilization of personalized pharmacokinetic 5-FU dose management – this was distributed prior to the interviews
- A Discussion Guide was developed to formulate a platform of dialogue centered around Medicare and private payer reimbursement coverage, adoption barriers, and reactions to the Technology X product within the current US paradigm(s) for 5-FU dose management



Technology Profile

Testing Service X: A Personalized Pharmacokinetic Testing Service for Managing 5-FU Chemotherapy in Colon Cancer Patients

Overview of 5-FU Chemotherapy

5-Flourouracil (5-FU) is widely used as a chemotherapeutic agent in the treatment of colorectal cancer. The use of area under the time-concentration curve (AUC) measurement techniques has demonstrated that 5-FU plasma concentrations correlate well with the drug's clinical efficacy and toxicity profile, and that 5-FU has a narrow therapeutic index. However, patient dosing of 5-FU is often determined using a body-surface area (BSA) based measurement technique, resulting in highly variable systemic concentrations of the drug between patients. Numerous studies have demonstrated that AUC drug quantitation with subsequent continuous dosing adjustment is more effective than BSA fixed dosing methods in establishing optimal 5-FU target therapeutic ranges. Rigorous personalized pharmacokinetic (PK) monitoring and 5-FU dose management leads to faster establishment of optimal 5-FU plasma concentrations, resulting in higher clinical efficacy, decreased toxicity, and a trend toward longer overall survival in colorectal cancer patients. Testing Service X is a unique testing service that quickly delivers quantitative 5-FU AUC results to the oncologist, allowing for more effective dose management and faster attainment of the optimal therapeutic plasma drug concentration range.

Overview of Testing Service X

PK monitoring to obtain therapeutic drug levels is standard practice for certain antibiotics, seizure medications, cardiac drugs, and transplant medications. However, the lack of robust and timely tests. Additionally, meas liquid chromatography or mass spectrometry, which a methods.

Testing Service X is a novel and proprietary testing se 5-FU concentration in human plasma. The service pr can be used by clinicians to manage 5-FU chemother

Key features and benefits of the testing service includ

- Unique, dose optimization testing service that levels with precision
- Testing service can be offered to CRC patients chemotherapy
- Highly accurate test – correlates with validated (r^2=0.989)
- Allows dose adjustment of each 5-FU cycle to

US Payer Interview Guide

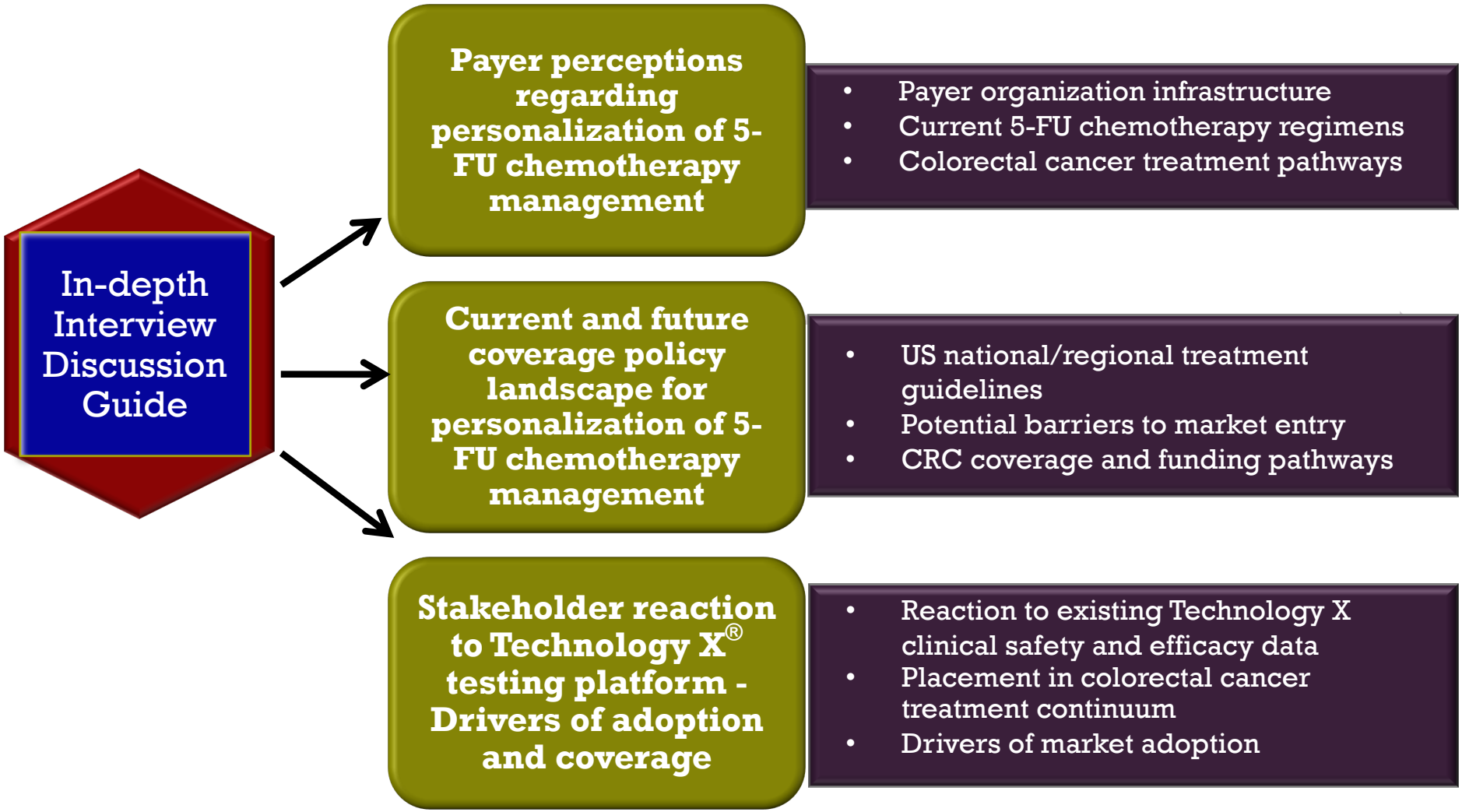
Project:	**Primary Interview Program with Payers** - Component #1 for the Project "*Reimbursement Landscape Assessment and Support for the 5-FU Testing Platform*"
Scope:	US
Payer Name:	
Managed Care Organization:	
Scope of Responsibility:	
Location:	
E-mail:	
Telephone:	
Date:	

Interviewer script:

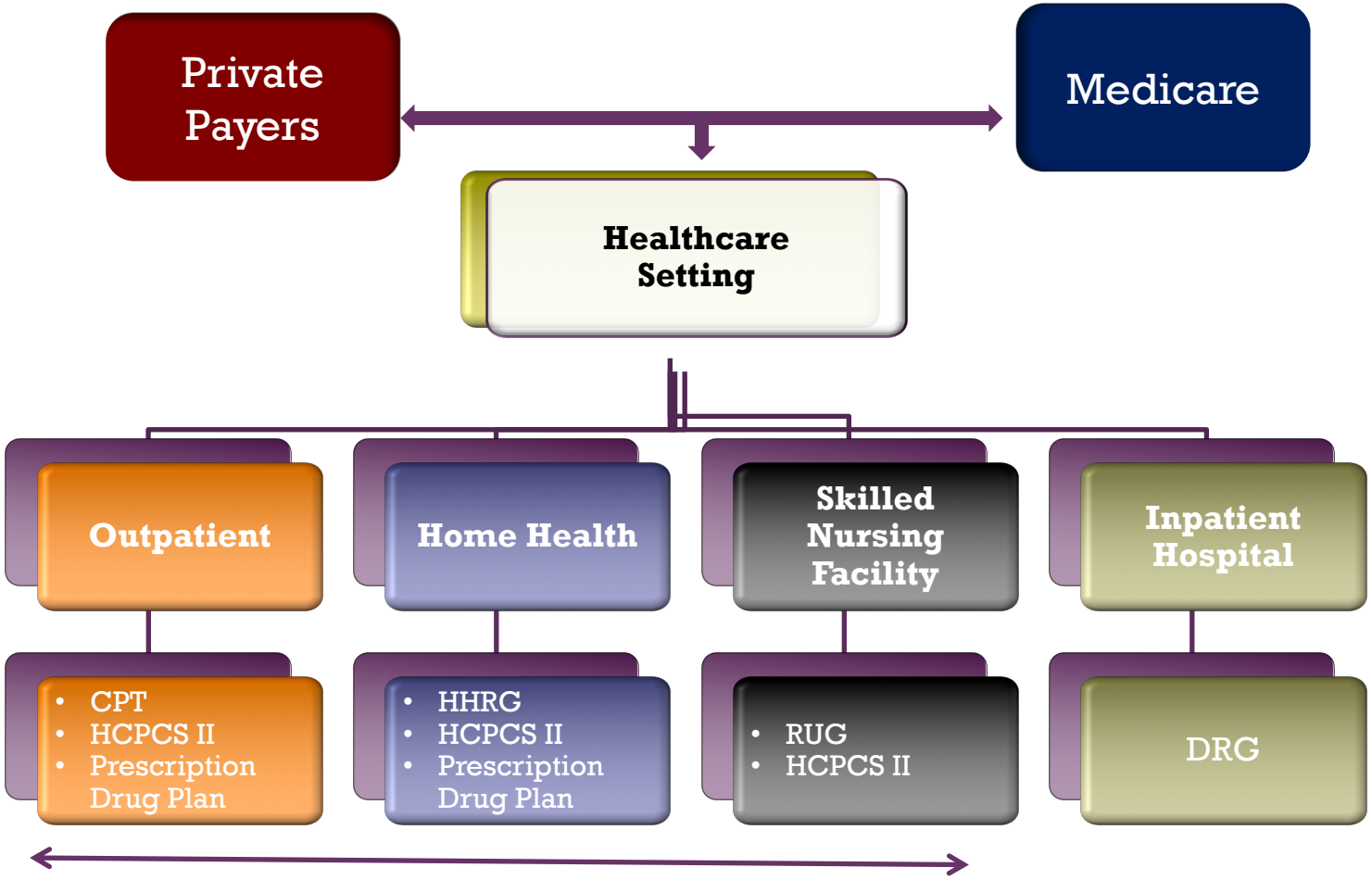
Uuni17 Life Sciences is an independent research company working in the area of biotechnology, pharmaceuticals and healthcare. We are carrying out research for a company that is commercializing a personalized chemotherapy management service for colorectal cancer (CRC) patients receiving infusional 5-fluorouracil (5-FU) chemotherapy. Additional details about this testing service are described in the Technology Profile sent previously.

To start our discussion, we would like to explore some background information about your perspectives on the use of testing platforms for directing colorectal cancer chemotherapy, including the use of body surface area (BSA) measurements to quantitate dosing, the use of pharmacokinetic testing to personalize chemotherapy management, and other available measurement techniques. We'd also like to get your opinions on the existing clinical and economic evidence to support personalized pharmacokinetic testing to manage 5-FU treatment(s) for colorectal cancer.

The in-depth interview program was designed to obtain detailed, US market specific insights on the reimbursement landscape for personalized 5-FU dose management



tJun17 Life Sciences analyzed the potential coverage and coding systems utilized in major US healthcare settings that may be applicable to Technology X® testing



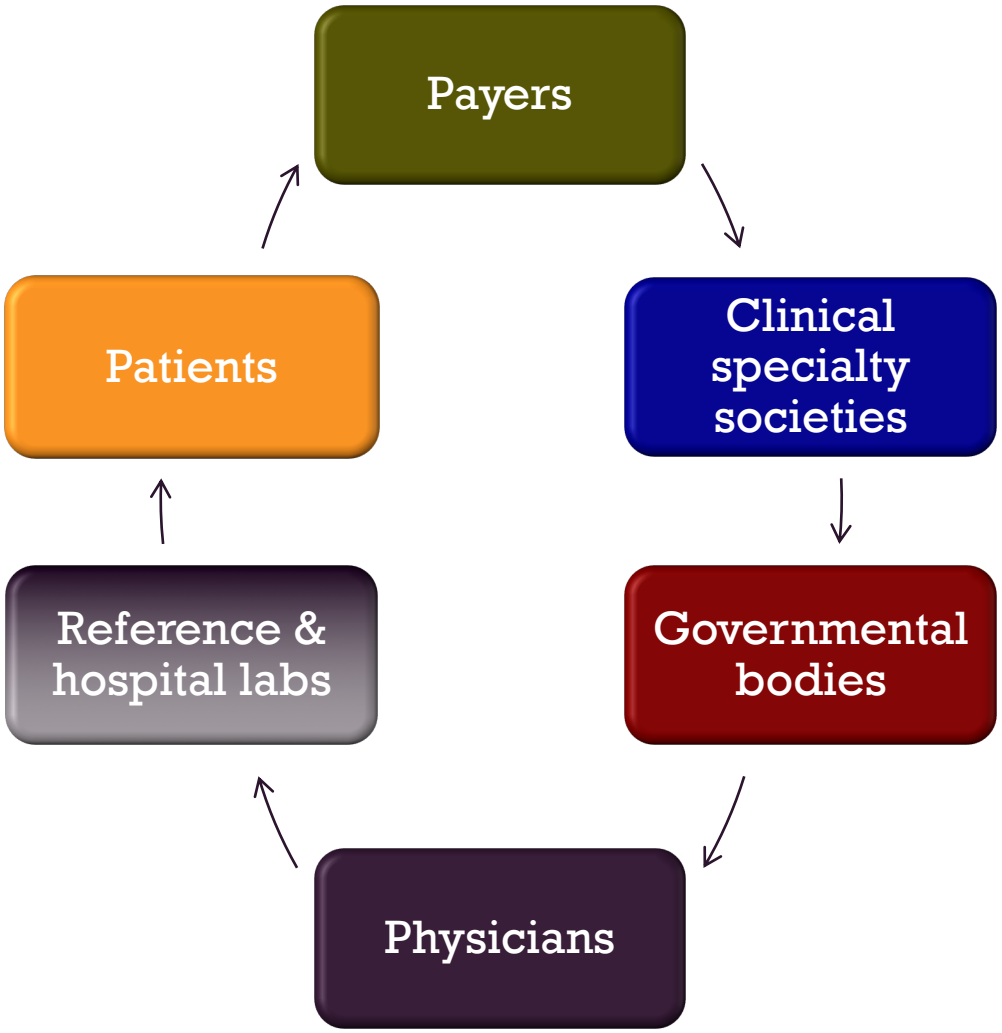
Most 5-FU therapy occurs outside the inpatient setting[1] unless toxicity is an issue

1. Society for Translational Oncology, Guidelines for Hospitalization for Chemotherapy, 2017

General Coverage Parameters for Personalized 5-FU Pharmacokinetic Testing in Colorectal Cancer Patients

03

Interviewees identified numerous Technology X® testing coverage stakeholders in the US *in vitro* testing market



- **Who are the payers making coverage decisions?**

  Private payers, public payers, self pay

- **What type of coverage policies will impact the technology?**

  Explicit or implicit coverage policies

- **What will coverage look like?**

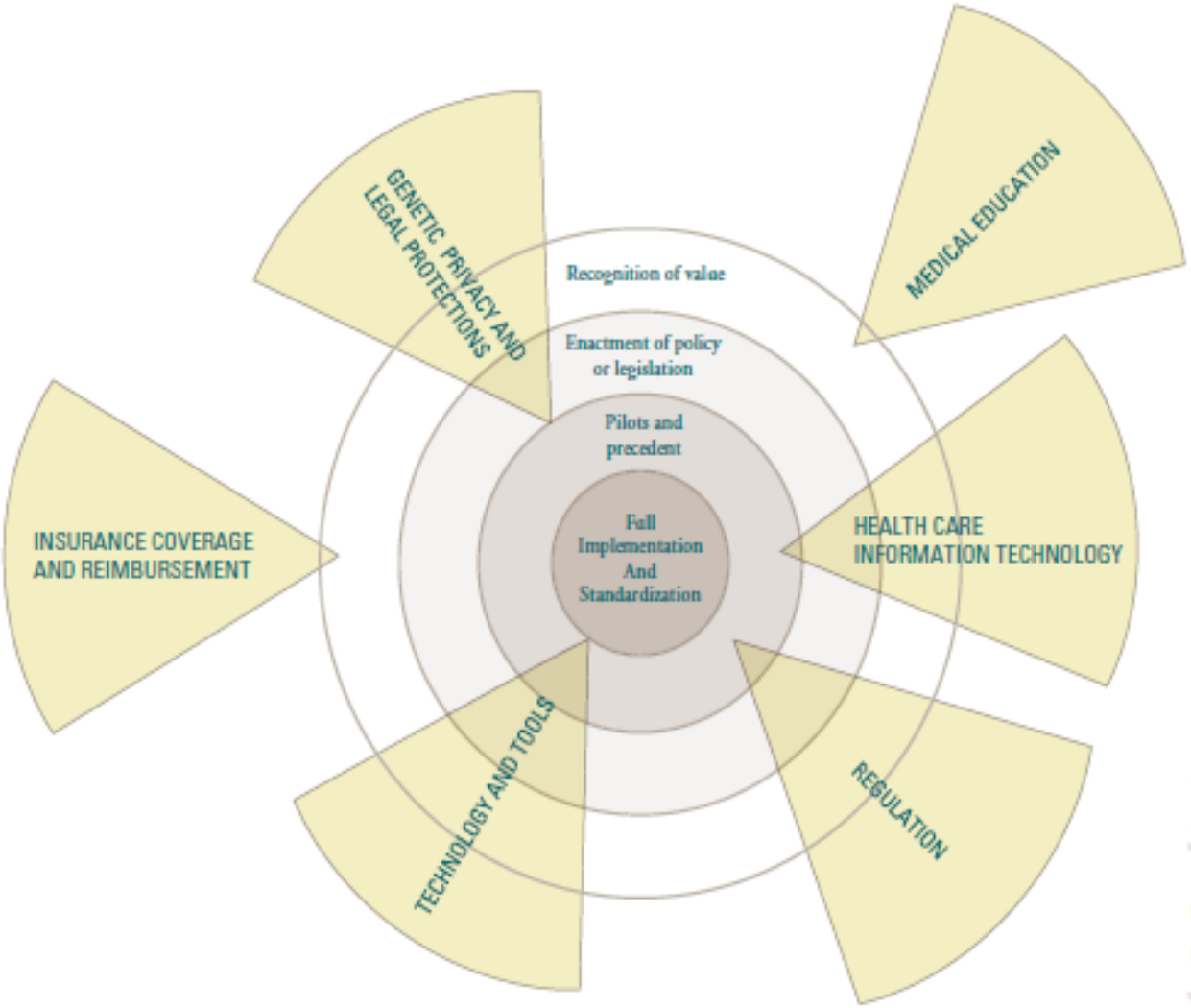
  For example, variable, consistent across payers, require prior authorization and/or be otherwise restricted

- **Are there any governmental laws or influential oncology bodies that will impact coverage?**
  - Federal health insurance mandates (i.e. CMS)
  - Clinical oncology societies
  - Industry groups or patient lobbies
  - Other government agencies (i.e. FDA)

Payers believe that a convergence of market forces is required to establish personalized 5-FU chemotherapy dose management as clinical standard of care

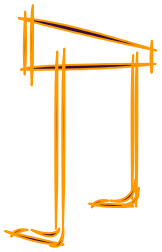
"The implementation of personalized medicine ***requires a confluence of several sectors****….public or stakeholder recognition of the value of personalized medicine, the establishment of supporting policies and laws, the launch and execution of smaller scale pilot programs and projects, to the final stage of full implementation and widespread use.* ***Full implementation of personalized medicine can only be achieved when all sectors converge toward the center."***

-Personalized Medicine Coalition, 2017



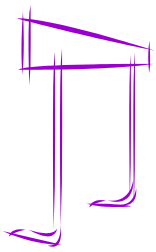
Reimbursement coverage is the 4th market access hurdle required to optimize coverage for *in vitro* testing products, including the Technology X® platform

In addition to proof of Quality, Safety and Efficacy, formal demonstration of economic value is increasingly required for coverage placement on US national or regional payment systems



Safety

Efficacy



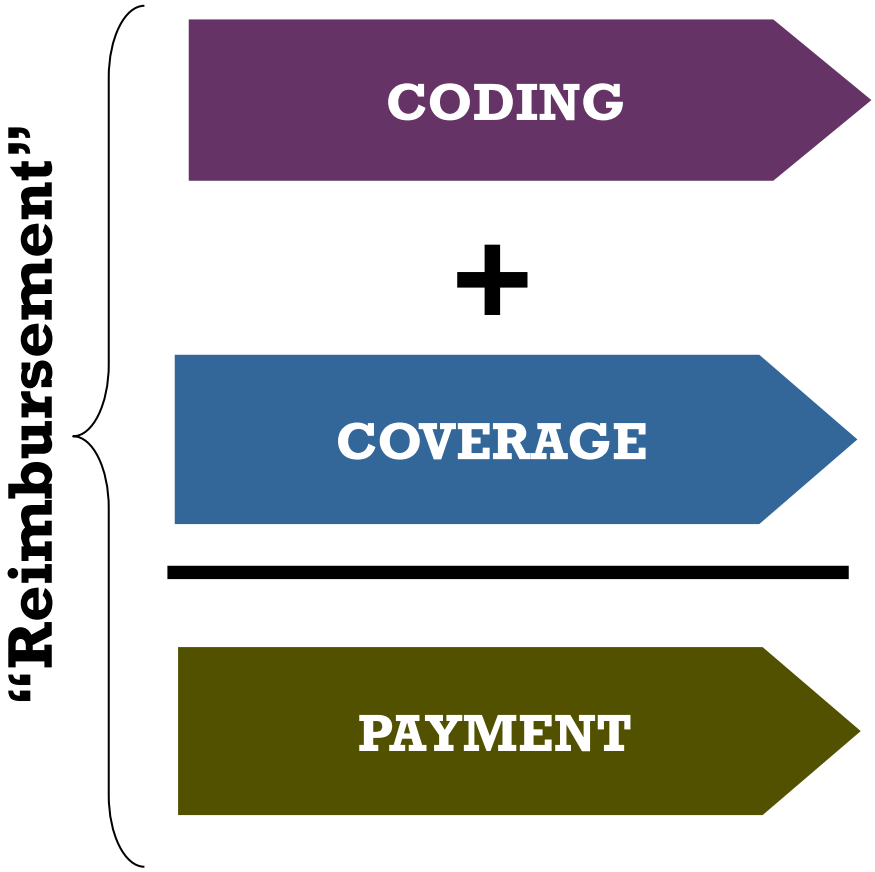
Quality

Reimbursement coverage, pricing and total market access

Market authorization from a CLIA or an FDA regulatory perspective

4th hurdle to complete market access

Optimization of Technology X® coverage also requires consideration of coding and payment strategies



The language that characterizes procedures and products rendered to patients by physicians/institutions and the rationale for providing them

The range and extent of services and products for which the insurer will pay

Payment is the amount rendered for the product/procedure that is covered by the insurer

Typical reimbursement process for *in vitro* testing products utilized in the US market

Providers

Typically, physicians order tests that are run by hospital labs or reference laboratories; Lab bills the payer based on CPT code

Coverage

Many **routine *in vitro* tests are not explicitly described in payer coverage policy, but some of the more high profile outpatient tests are subject to explicit coverage policy**

Coding

- **Primarily CPT coding for *in vitro* testing in 80000 series (CPT 84999 for Technology X® testing)**
- **Some tests use non-specific codes or 'stack codes',**

Payment

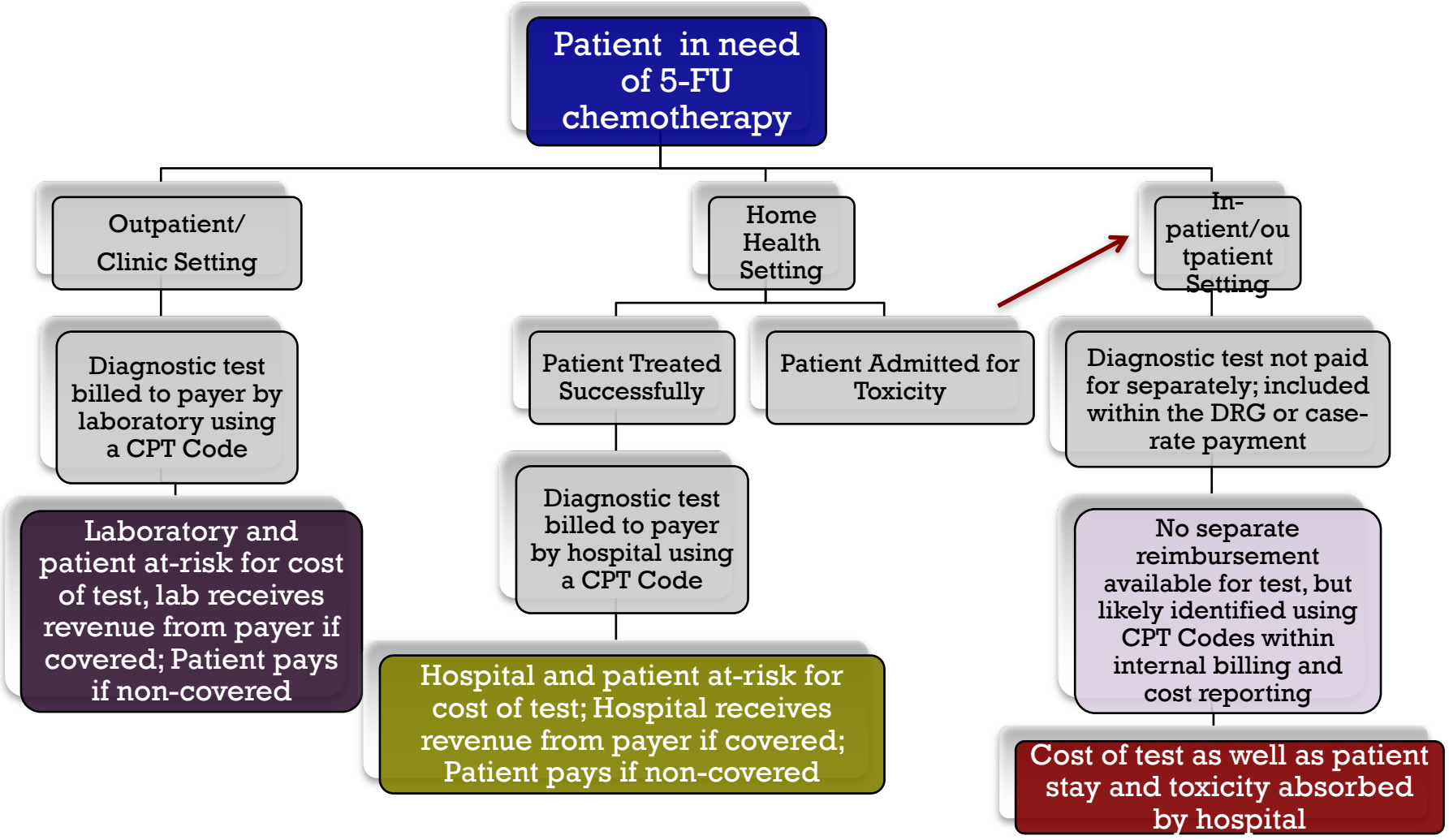
- **Outpatient test payment usually benchmarked from the Medicare Clinical Laboratory Fee Schedule**
- **Inpatient testing is included in the DRG, no separate payment**
- **In many areas routine laboratory services are covered within a capitated (per member per month) fee**

Reimbursement for Technology X® testing is based on payer type, though is predominantly case rate within a capitated environment or DRG global payment

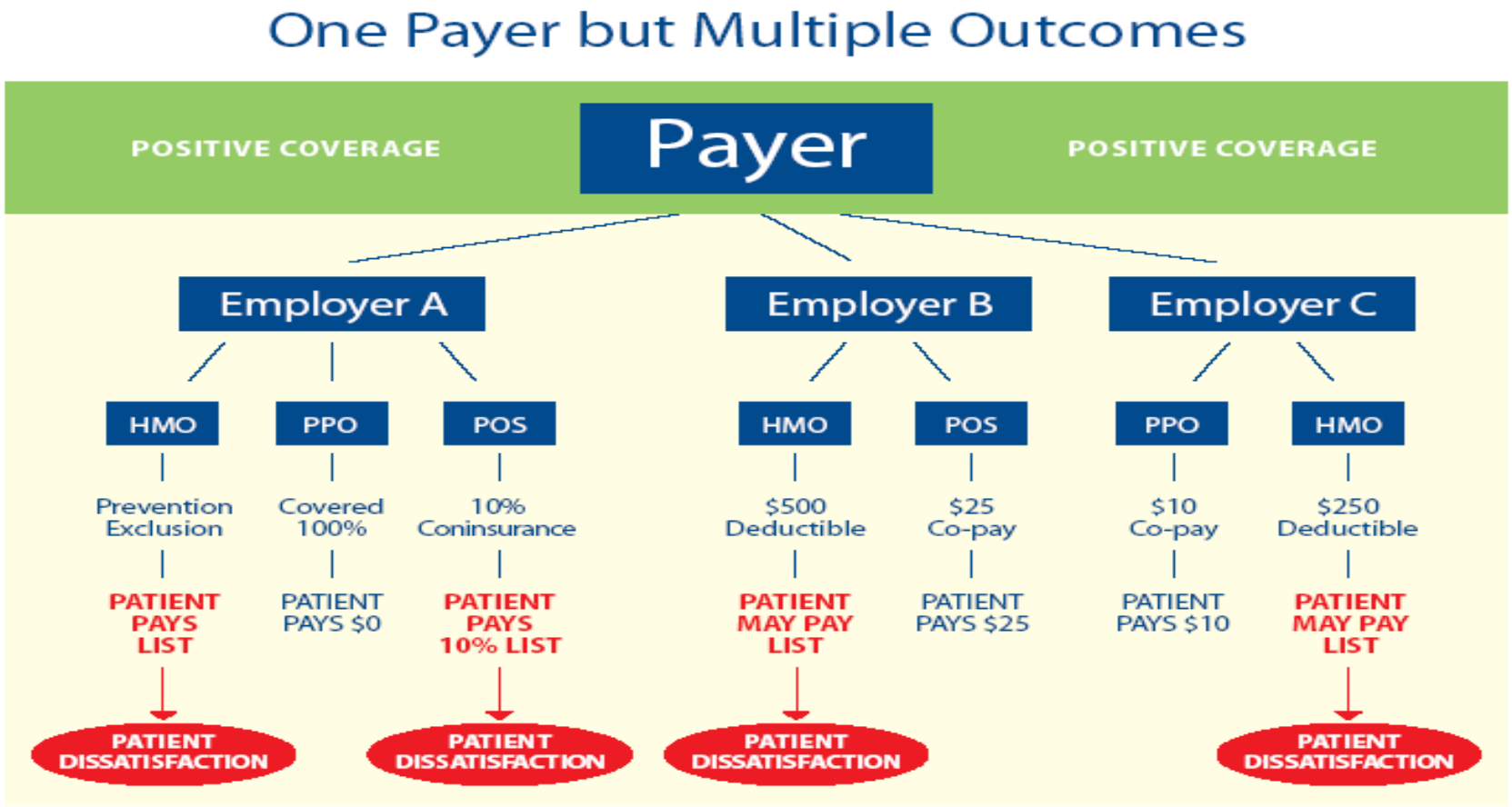
Depending on the type of insurance, the payment options for *in vitro* testing may differ:

	Name	Description
Applicable for Medicare & some private insurance plans	**DRG payment**	Hospital receives a single DRG payment for all services and products used; some DRGs are split into "normal" admissions, those with "complications and co-morbidities" CC, and those with "severe" CC. If the patient's medical record supports it, the higher paying, more severe DRG could be assigned for that admission, triggering higher reimbursement
Applicable for private insurance only	**Per diem payments**	Hospital receives a daily payment for specific cases. These rates can be renegotiated, usually on an annual basis
	Case rate payments ***(S3722 may be utilized here)***	Hospital or facility receives a specific case. These rates can be renegotiated, usually on a contracted annual basis. This may involve assignment within a capitated environment
	Percentage of charge payments	Hospital receives a payment based on their charges for services used. Insurer usually does not reimburse for full charges, but rather sets a percent of the charges

Inpatient hospitals with outpatient clinics or home healthcare services have a financial incentive to utilize personalized 5-FU dose management tools since they will absorb multiple costs if the patient is admitted for toxicity treatment



Universal reimbursement coverage for Technology X® testing could be obtained, but with multiple outcomes depending on the plan(s) offered by payers



Private Payer Coverage Landscape for Personalized 5-FU Pharmacokinetic Testing

04

Many payer interviewees cited rising costs in various areas as a significant driver of their interest in supporting personalized chemotherapy dose management

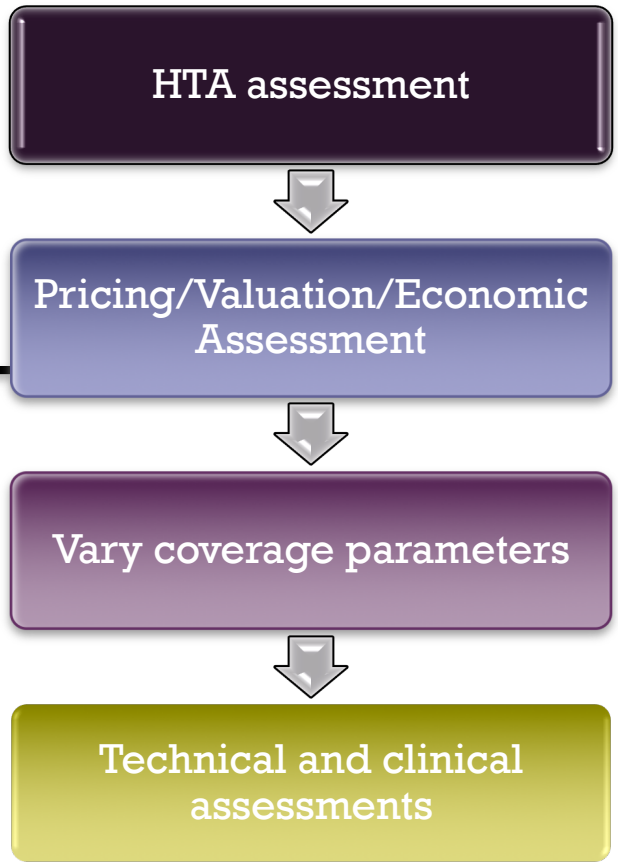
- Clinical laboratory industry today is ~$50 billion, with 5% average growth[1]
  - Predicted to grow to $98.4 billion by 2017
  - Fueling this growth is esoteric testing, growing at ~15% each year
- Pharmaceutical spending, especially among high cost biopharmaceuticals like chemotherapy is increasing dramatically
  - Growth in Oncology, Rheumatoid Arthritis, Cardiology, Neurology is driving the overall spend
  - Maintenance chemotherapy alone accounts for almost 4% of all colorectal cancer hospitalizations due to toxicity related issues[1]
- Opportunity to minimize the empirical practice of medicine
  - Avoiding trial-and error chemotherapy dosing inherent with body surface area (BSA) based regimens
  - Pharmacogenetic testing may prevent adverse drug reaction due to DPYD gene product deficiencies

1. *Healthcare cost and utilization project, AHRQ, 2017*

The Technology X® testing platform is part of an increasingly complex global *in vitro* testing market that has nuances that are not familiar to many payers

- Molecular diagnostics
- In-vitro diagnostics
- Diagnostic imaging
- Biomarkers
- Point of care diagnostics
- ASRs
- FDA approved/CE marked
- Companion diagnostics
- Nanodiagnostics
- Pathology
- Genetic markers

How should payers consider novel diagnostics or supportive measures within the scope of their existing activities?



"Most of the time manufacturers of fancy specialized and expensive tests come to us and ask us to cover them but don't really show us why we should"

-Southwest Payer

Private payers interviewees reported a desire to examine overall value offered by the Technology X® testing platform in addition to its clinical benefits

Payers are interested in:

- **Clinical benefits**
- **Economic information**, e.g.
  - •Savings
  - •Improved quality but no cash saving
- **Quality of life** benefits
- **Economic information** on local investment/ impact/ opportunity cost

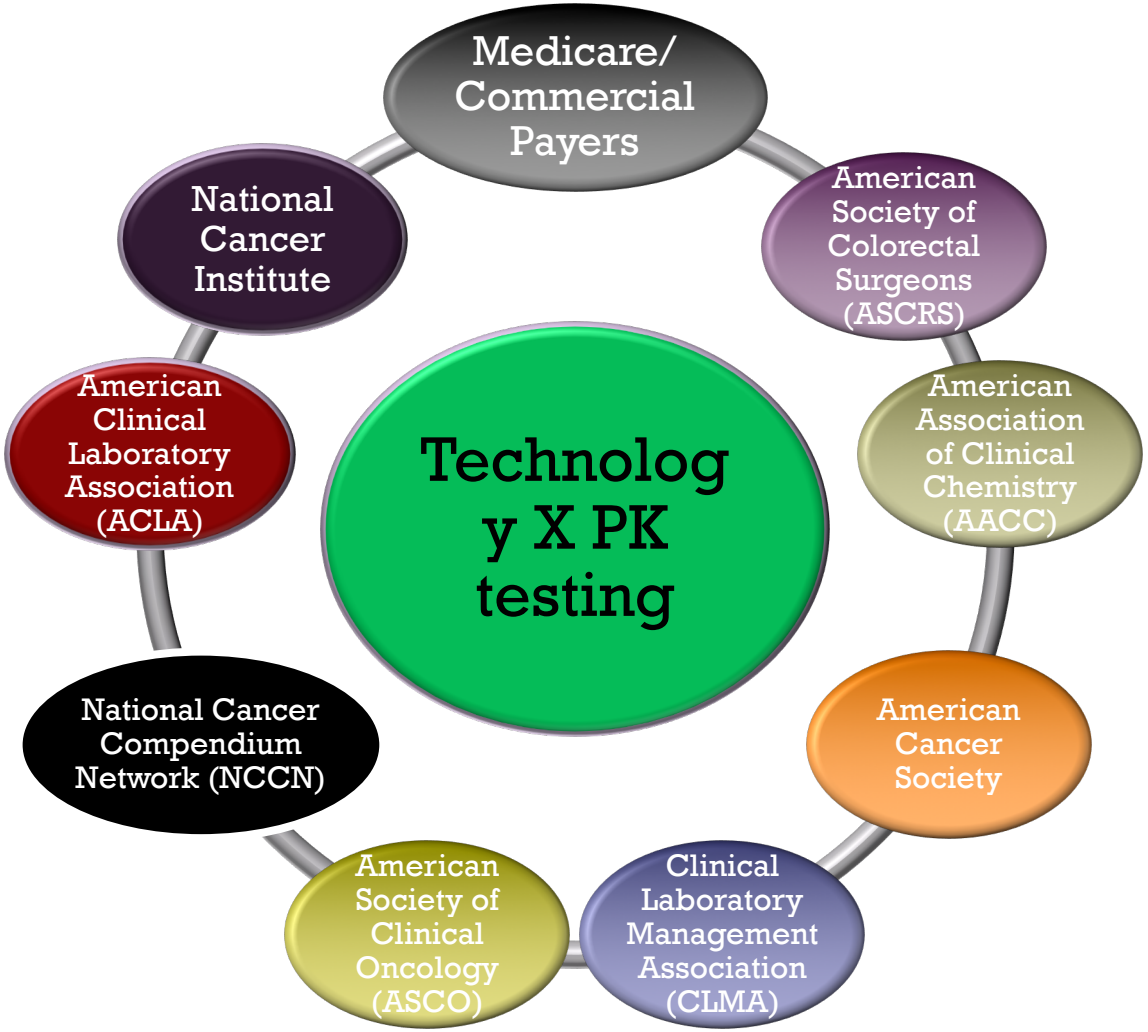
It is essential to generate the evidence to address these concerns

Demonstration of clinical value
- Clinical trials
- In Real-life'

Demonstration of economic value through health-economic data

Requirements are often **comparative**, against current or "standard" therapy, which in 5-FU dosing for colorectal cancer is body surface area (BSA) measurement

Payer interviewees referenced numerous organizations that could impact utilization and coverage for Technology X® testing through their treatment guidelines



"I want to see the test either included in the NCCN guidelines or cleared by FDA before I will support a unique coverage position for it"

- Southeast payer

"If your client creates demand among oncologists and that demand manifests itself through changes in ASCO treatment guidelines then we will pay for (the test)"

- Southwest payer

Private payer coverage decisions are based on technology assessment although payment is possible in the absence of explicit policy

- Private payers conduct internal technology assessment or leverage external resources
- Consider clinical efficacy first, and then economic impact of coverage
- Coverage policies indicate whether:
  - Technology is considered medically necessary
  - Utilization controls will be put into place like prior authorizations or step edits
  - There are specific conditions the technology is covered for
  - Use of the technology is restricted to certain specialists
- Even when coverage is in place, there is no guarantee of payment
  - Payment is based on individual policies, contracting, and cost-sharing schemes
  - Payment may be responsible for co-payment, co-insurance, or deductible
  - Employers may carve-out certain benefits within the plans they offer

Blue Cross/Blue Shield Technology Evaluation Center conducted an assessment of pharmacokinetic 5-FU dose management – while the report does incite concern among payers, it is not explicitly prohibiting Technology X® coverage[1]

- The evaluation was published in June 2010 and stated that:
  - In current clinical practice, 5-FU dosing is reduced when symptoms of severe toxicity appear, but seldom increased to promote efficacy
  - Clinical evidence supports the wide variability of 5-FU plasma levels when patients are placed on a fixed BSA based dose regimen
  - Clinical evidence is insufficient to draw conclusions about the impact of pharmacokinetic 5-FU does management to support universal adoption of the Technology X testing platform for colorectal cancer
- Over 80% of payers interviewed reported an awareness of the test but none expressed the opinion that this evaluation alone would prohibit coverage for the test in their organization

"Yes, we have seen this (BCBS) report – it does state that there is insufficient evidence to support universal coverage but we do our own internal technology assessments and make decisions based on those"
Southwest Payer

1. *Blue Cross Blue Shield Technology Evaluation Center, June 2018*

The clinical impact of 5-FU chemotherapy toxicity is high and is a significant incentive for Technology X® platform adoption

CRC Prevalence - 1.1 million people with history of colorectal cancer in the US[1]

275,000 US patients per year receive 5-FU chemotherapy[2]

Grade III-IV toxicity attributed to 5-FU occurs in up to 15% of patients treated [3]

The DPD enzyme is responsible for the degradation and inactivation of greater than 80% of 5-FU[3]

Up to 0.5% of patients receive a fatal overdose of 5-FU due to DPD deficiency[2]

"Pharmacogenetic testing for DPD deficiency prior to 5-FU administration could significantly reduce these occurrences"
-Southwest Payer

1. National Cancer Institute, 2009
2. National Institutes of Health, Public Health Service. Washington DC: HH Federal Register/Vol. 73, No. 129
3. *5-Flourouracil Sensitivity, 8 mutations, 2011 Arup Laboratories, www.aruplab.com*

Payers perceive that patients with late Grade 1 through late Grade III CTC scores are the most valuable targets for Technology X® testing

Purpose of National Cancer Institute (NCI) Common Toxicity Criteria (CTC) Guidelines:

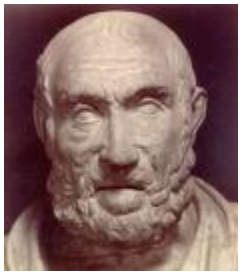
- Facilitate evaluation of new therapies & supportive measures like Technology X
- Standardize reporting of adverse events across groups
- Develop a more complete characterization of both early and persistent events of chemotherapy

"Any CRC patient with late Grade III toxicity or above should not receive dose management therapy – they should either start another regimen or else receive palliative care"
Northeast payer

CTC Guideline	
Grade 0: No adverse events	% payers perceiving value – 5%
Grade 1: Mild adverse event	% payers perceiving value – 30%
Grade II: Moderate adverse event	% payers perceiving value – 68%
Grade III: Severe adverse events	% payers perceiving value – 62%
Grade IV: Disabling adverse event	% payers perceiving value – 4%
Grade V: Death related to adverse event	% payers perceiving value – 4%

Perceived Valuable Target Patient for Technology X Testing

Payers interviewed believe that pharmacogenetic testing in concert with personalized chemotherapy management will help to target limited resources more effectively

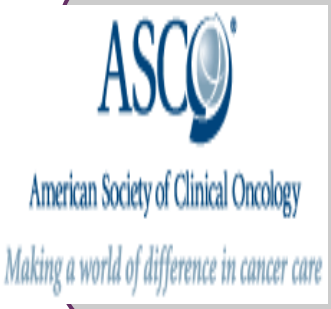


"It's far more important to know **what person the disease has** than **what disease the person has.**"
-Hippocrates

"We want to cover personalized oncology *ivd* testing since it may save us from paying for unnecessary chemotherapy costs"
-Northeast payer

- Payers interviewed are looking for ways to determine the value of new technologies and pass that value along to employer customers or health systems
- Increasing costs associated with novel oncology chemotherapies and other bio-therapeutic innovations, combined with relatively low population level efficacy of many of these products, creates substantial opportunity for a more targeted approach
- Personalized pharmacogenetic testing offers the potential to help target therapies to specific subpopulations where they will have greater efficacy and can be utilized more cost effectively
- Therefore, payers interviewed perceive that having a clear understanding the evolving role of personalized pharmacogenetic, as well as pharmacokinetic testing to payer business and technology evaluation models is critical for their future growth and success

The American Society of Clinical Oncology (ASCO) has recommended that pharmacogenetic along with pharmacokinetic approaches be considered in guiding chemotherapy dose management



The use of fixed-dose chemotherapy is rarely justified, but the Panel does recommend fixed dosing for a few select agents. The Panel recommends further research into the role of pharmacokinetics and pharmacogenetics to guide appropriate dosing of obese patients with cancer. [1]

"If oncologists come to us and demand that pharmacogenetic testing be administered prior to 5-FU dose management to avoid toxicity complications that may lead to hospitalization then we will certainly cover the testing"

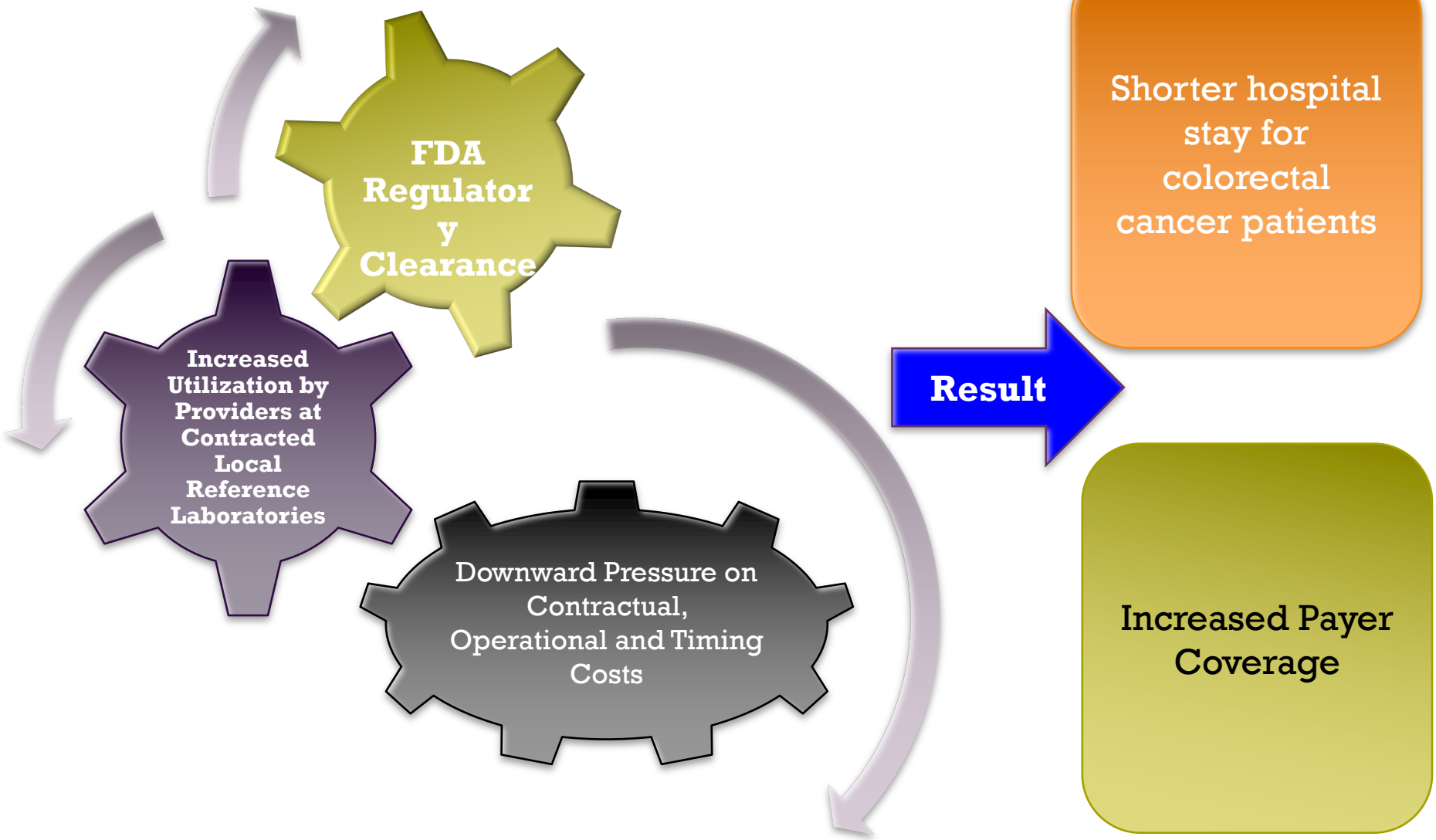
- Midwest Payer

"Oncology societies have convinced us of the value in covering FDA validated biomarkers for cancer treatment – if they do the same for pharmacogenetic testing than we will pay for it"

- Southeast Payer

1. Appropriate Chemotherapy Dosing for Obese Adult Patients With Cancer: American Society of Clinical Oncology Clinical Practice Guideline *April 2012*

Payers perceive that FDA regulatory clearance/approval for Technology X® could increase clinical utility, drive down costs and increase coverage



Payers are attempting to create coverage pathways for personalized oncology disease management - though the process continues to evolve

- Historically, evaluation of drugs and diagnostics have been completed by different decision-making groups within payer organizations - Decisions made by P&T committees, HTA groups, or other pharma oriented bodies
- Pharmaceuticals, for the most part, have gained coverage once regulatory approval is granted, for example through Medicare Part D; the degree of cost sharing or access limitations usually in question
- Diagnostic evaluation often has a less formalized process, though that is changing
  - In the US, Technology Evaluation Groups evolving to consider drug/diagnostic combinations; Groups like Medco conducting internal evaluations of cost/efficacy
  - In Europe, groups like NICE and IQWiG have developed diagnostics specific evaluation arms, and are in process of developing evaluation methodologies
  - Diagnostic reimbursement being established with consideration of drug/diagnostic value proposition in some cases; while in others diagnostics are being given away as a pathway to high cost therapeutics

"We want to cover these (personalized dose management) tests in the oncology setting, but no one has shown us clear clinical efficacy or a decrease in hospital re-admissions or complication rates due to decreased toxicity"

-Southwest Payer

Medicare Coverage Landscape for Personalized 5-FU Pharmacokinetic Testing

05

Medicare is the largest single payer in the United States and plays a significant role in setting reimbursement for *in vitro* testing

What is Medicare?

- Federal health insurance program enacted in 1965 to provide healthcare coverage for those aged 65 and older regardless of income or medical history
  - Expanded in 1972 to include those under the age of 65 with permanent disabilities or end-stage renal disease (ESRD)
  - Expanded in 2001 to include those under the age of 65 with amyotrophic lateral sclerosis (ALS)
- As of November 2008, over 45 million Americans covered through Medicare's various programs
  - 38 million over the age of 65
  - 7 million under the age of 65 with disabilities

- **Part A Coverage**
  - Covers inpatient hospital services, skilled nursing facility, home health, and hospice care
  - Accounted for approximately 40% of Medicare benefit spending in 2008
  - Individuals are entitled to Part A if they or their spouse are eligible for Social Security payments and have made the appropriate payroll tax contrib**utions for 10 or more years**
- **Part B Coverage**
  - Helps pay for physician, outpatient, home health, and preventive services
  - Accounted for 27% of benefit spending in 2008
  - Individuals are entitled to Part A services may enroll in Part B benefits, but this coverage is considered voluntary (95% of Part A participants also enroll in Part B benefits)
- Medicare Advantage (Part C) plans are available in many areas. People with Medicare Parts A and B can choose to receive all of their health care services through one of these provider organizations under Part C
- Prescription drug coverage (Part D) that helps pay for medications doctors prescribe for treatment

Medicare: A Primer, January 2009 http://www.kff.org/medicare/upload/7615-02.pdf

Medicare regulates all laboratory testing in the U.S. through the Clinical Laboratory Improvement Amendments (CLIA)

- In total, CLIA covers approximately 200,000 laboratory entities
  - The Division of Laboratory Services, within the Survey and Certification Group, under the Center for Medicaid and State Operations (CMSO) has the responsibility for implementing the CLIA Program
  - Research programs are not included
- The objective of the CLIA program is to ensure quality laboratory testing
- Laboratory tests are categorized as one of the following by complexity:

  (1) Waived tests.

  (2) Tests of moderate complexity, including the subcategory of PPM procedures

  (3) Tests of high complexity

Medicare can create national or local coverage policies, however most *in vitro* testing services, including Technology X® are paid without explicit policies

National Coverage Determination (NCD)

- NCD process consists of 3 steps: initiation, review and completion
- Formal requests for an NCD can be initiated either by:
  - An outside party who identifies an item or service as a potential benefit (or to prevent potential harm) to Medicare beneficiaries
  - Or by internal agency personnel
- Once received, the Center for Medicare Management (CMM) will make a benefit category determination
- The item is then posted on list of pending coverage issues on the CMS website until final determination is made

Local Coverage Determination (LCD)

- Medicare contractors develop LCDs when no NCD exists, or when further clarification of an NCD is needed
- LCDs can be established with the intent to create payment policy or manage utilization
- Some contractors have quotas on establishing a certain number of LCDs

NCDs will preempt LCDs only when a final NCD is issued; local contractors must amend or withdraw any inconsistent LCDs

Medicare covers *in vitro* tests that are deemed 'reasonable and necessary' – Technology X® does not have this designation in all cases

- Medicare covers the cost of personalized *in vitro* diagnostic testing, if the care is deemed medically ***reasonable and necessary*** by a physician
- Coverage for Technology X testing currently requires submission of an Advance Beneficiary Notice of Non-Coverage (ABN) by the patient prior to administration of the test – if denied the cost for the test it must be borne by the patient
- Either an NCD or individual LCDs must be established for Technology X testing before Medicare will establish universal coverage for the test

"We service about 2 million Medicare patients in our organization. In order to have an LCD established in our local area, the manufacturer must do more to create demand for the test in the oncology community and also must clearly show us the value of the test – once we have a good understanding of why the test is needed, if it has demonstrated efficacy then an LCD will likely be established"

Midwest Payer

In 2008, Medicare began to enforce the Debt Reduction Act (DRA) of 2005, by refusing to pay for 10 categories of Hospital Acquired Conditions (HAC)

For example, if Stage 3 or Stage 4 pressure ulcers (ICD-9 702.23, 702.24) are acquired while the patient is admitted into a hospital, the hospital will receive no reimbursement from Medicare for their treatment

- Diagnosis of pressure ulcers cost $400 more per day than other inpatients
- Under this new policy, Medicare reported a $5,000 savings per patient, for which hospitals received no reimbursement[1]

The DRA of 2005 creates a need for inpatient facilities to utilize products targeted at preventing the progression of pressure ulcers to stage 3 and 4, and a loss of reimbursement

1. Breisacher, Pay for Performance in Nursing Homes, 2009, *Healthcare Financing Review* , 30(3) 1-13

Treatment facilities distinguish between present on admission (POA) vs. non POA medical conditions, which could positively impact adoption for Technology X® testing

- When a patient is admitted into the treatment facility, clinicians must designate which medical conditions are Present on Admission (POA)
- If a patient develops a secondary condition while in the hospital that is one of the 28 HAC's or "never events" the hospital must report the incidence to CMS[1]
- The development of toxicity represents a potentially significant cost to the facility if designated as a non POA medical condition
- Several payers prognosticated that at some point, providers may be held responsible for the development of extreme cases of 5-FU based toxicity in cancer patients and hold the facility responsible for the cost of treatment

"Your client seems to have a technology platform that would eliminate or greatly reduce the potential for 5-FU based toxicity in colorectal cancer patients at least in extreme cases. If you combine this with DPD testing, there is no way that the treatment facility could not be held responsible for 5-FU toxicity cases, given the cuts we are about to see in Medicare and in the commercial payer setting."

-Northwest Payer

1. Agency for Healthcare Research and Quality, National Quality Forum (2006). 2. Healthcare Cost and Utilization Project, National Inpatient Sample, 2009

Payer Primary Research Quantitative Results

06

Payers appear to have some concern for the costs associated with 5-FU dose management but not enough to track them

- Overall, the payers queried are aware of the cost associated with inappropriate 5-FU dosing, however they are not quantitatively tracking it
- The majority believe that personalized pharmacokinetic testing will become standard of care if the efficacy base is clearly communicated

- Some payers believe that 5-FU overdosing toxicity will incentivize providers to utilize personalized pharmacokinetic or even pharmacogenetic testing to optimize 5-FU dosing

"We don't track this in the slightest. A lot of the cost is rolled into the capitated diagnostics contracts."
Medical Director

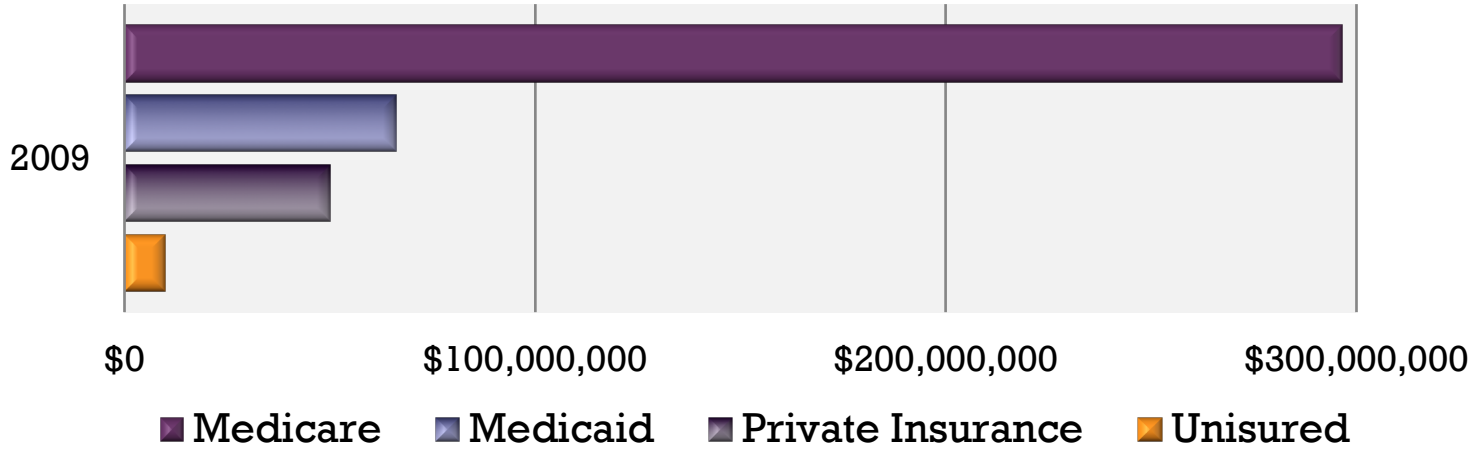
"I can't tell you what our total spending on chemotherapy is. We don't track it, but it is meaningful and should be tracked especially for at risk populations"
Medical Director

"We don't have the detail to know what percentage of cost 5-FU toxicity represents. Maybe 5% of our budget goes to CRC in general."
Medical Director

"Roughly 70% of what we do spend on CRC is dedicated towards screening and surgical treatments"
Medical Director

Payers are cognizant of increased spending on 5-FU overdose toxicity, but they do not track its impact on their expense budget(s)

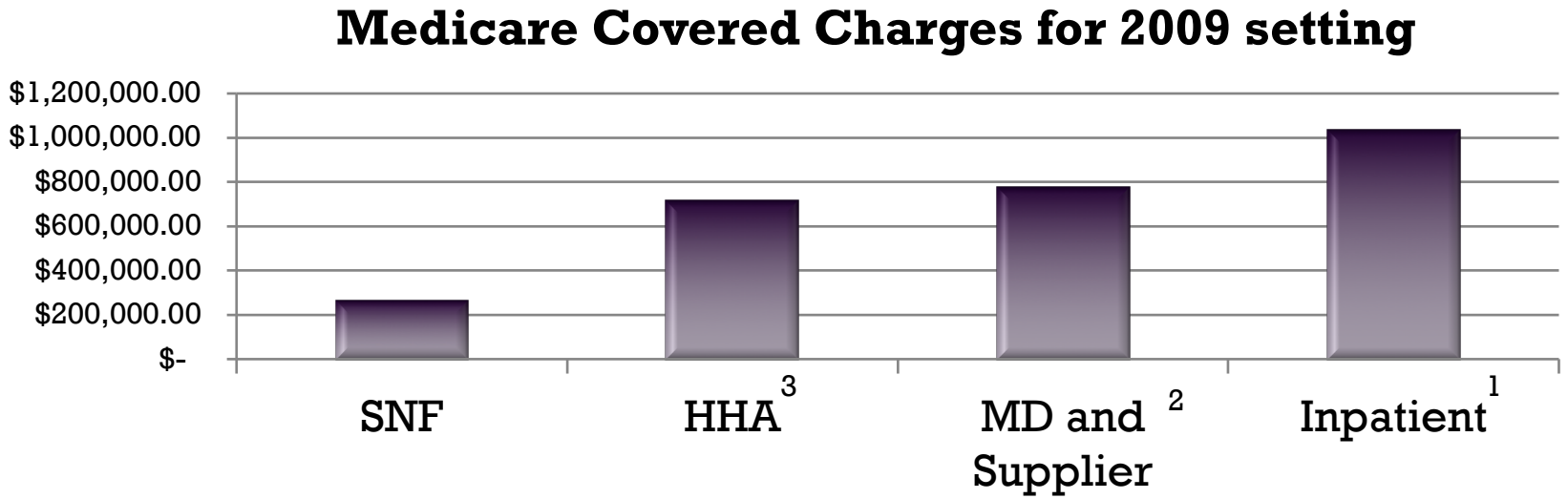
Aggregate Costs of Treating Colorectal Cancer Chemotherapy Toxicity in Inpatient Hospital Settings[1]



- Of the 30 payers interviewed only 5 (150,000 covered lives, 100% Medicare) was aware of the cost of inpatient 5-FU treatment, and was developing internal guidelines to increase outpatient treatment of the condition
- Two of the payers interviewed stated that chemotherapy for colorectal cancer patients are tracked in their organization only if the toxicity leads to complications or readmissions triggering an increase in payment above the DRG

1. Healthcare Cost and Utilization Project, National Inpatient Sample,

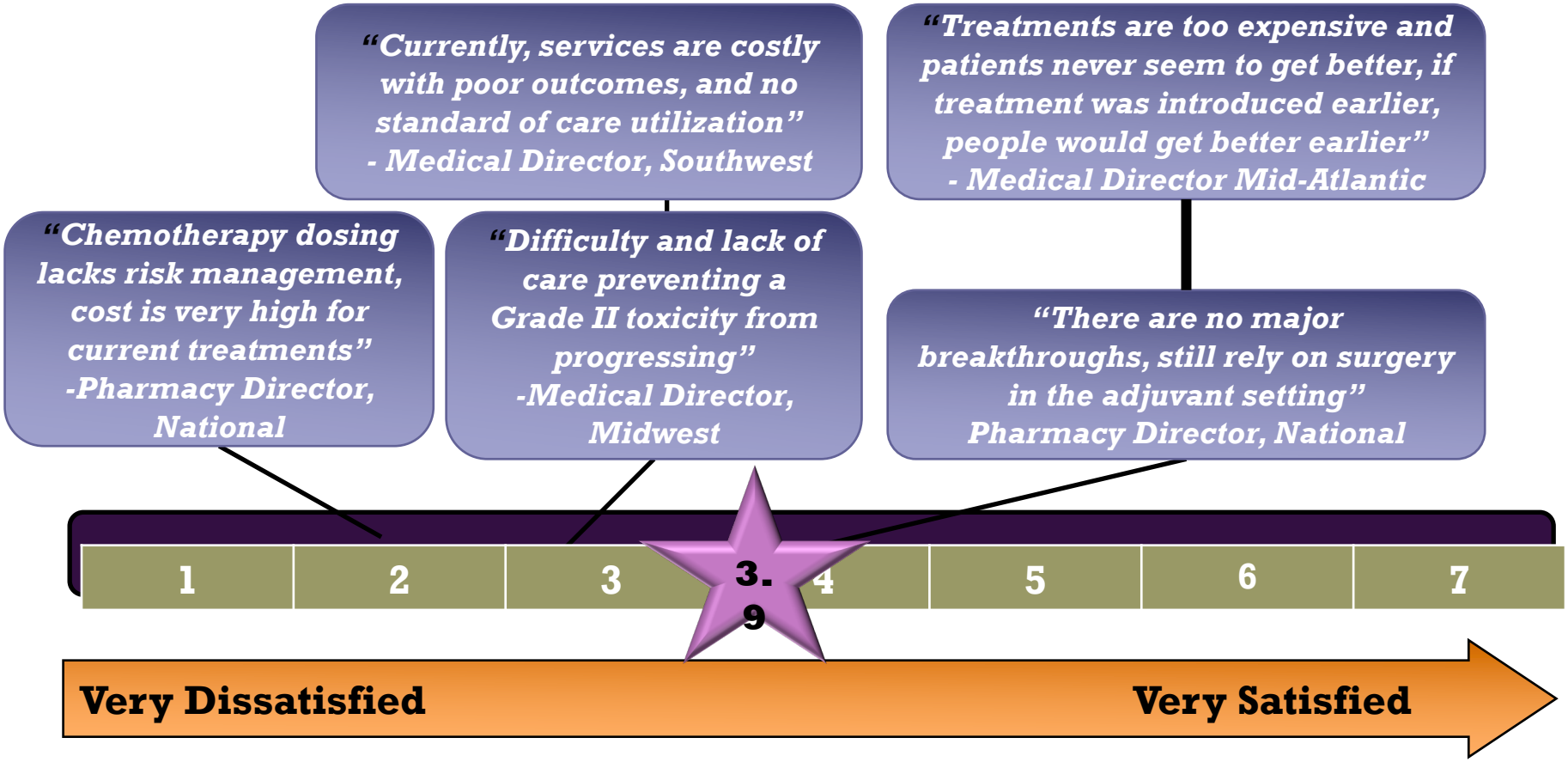
A significant concern for payers is the number of hospital admissions and bed days a patient spends in a hospital due to 5-FU chemotherapy overdosing



- SNF's are only qualified for a certain level of medical care and it is in their best interest to re-admit a patient to the hospital who requires a higher level of care than the original RUG score
- Multiple interviewed payers emphasized their concern for patients "bouncing back " to inpatient care from a SNF or HHA due to chemotherapy complications
- One payer quoted inpatient beds were $4,000/ day while a SNF was $800

1.CMS Coding Datasets CY 2009 Inpatient DRG's
2.MD and Supplier – Allowed Charges; 3. HHA – Program Payments

Payers expressed frustration in the lack of options for personalized 5-FU dose management for colorectal cancer patients



Payer Interviewee Reaction to Technology X® Technology Profile

07

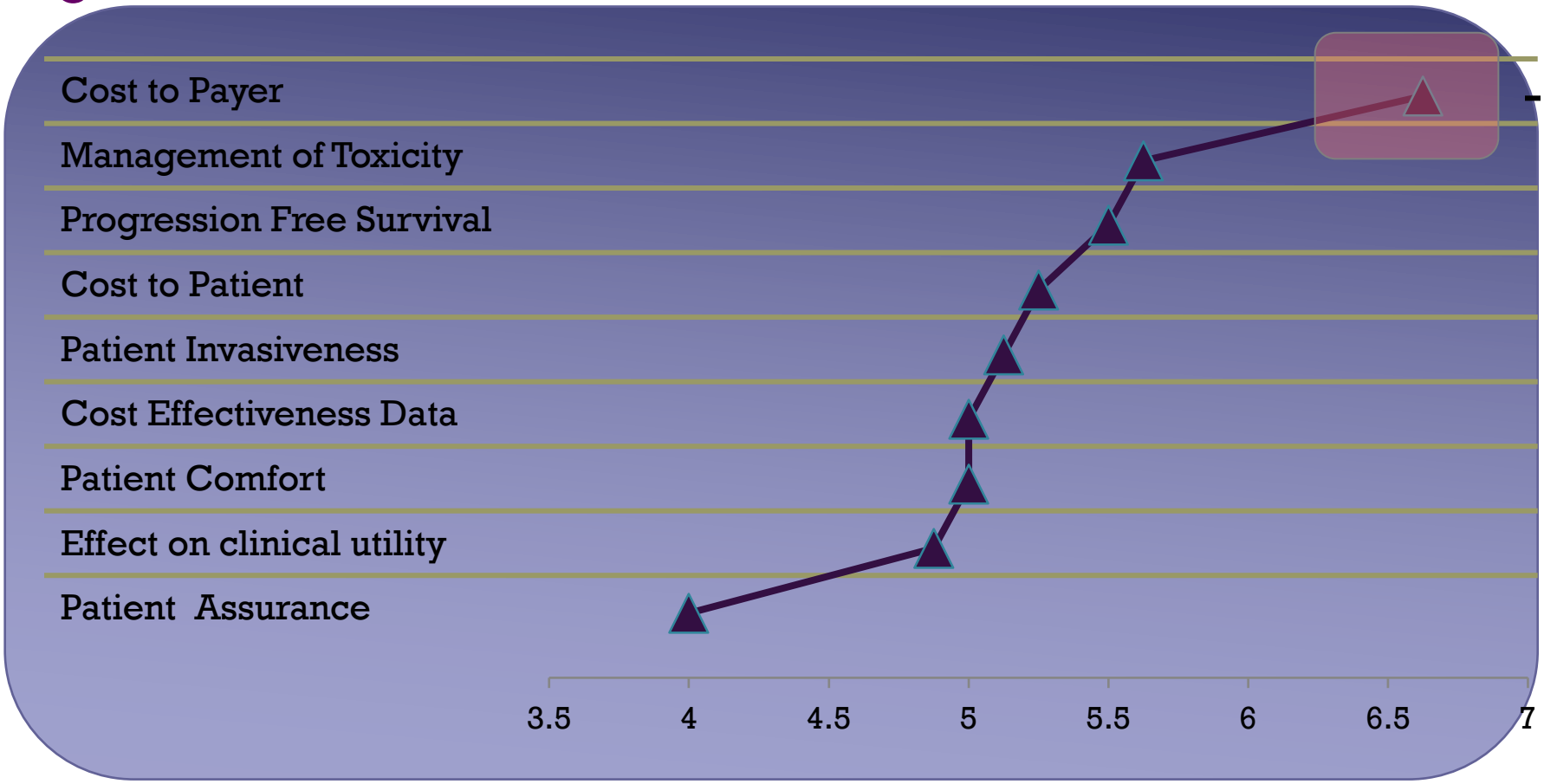
Of payers interviewed, many noted that the committee which would evaluate the Technology X® platform is variable

Q: Who in the organization is responsible for determining coverage policies? Who are the stakeholders?

	MCO Medical Directors (n=6)		MCO Pharmacy Directors (n=2)	
P&T Committee	✓	Our P&T Committee makes all of our formulary decisions	✓	"This would go to our P&T committee. Medical Affairs only has an impact on the policies conducted in a physician's office."
Medical Affairs / Policy Committee	✗	"For this type of product [we] would go through the Technology Assessment committee."	✓	"[This is the responsibility of the] Medical Policy and Technology Committee. If these are outpatient drugs, it would be a P&T issue. It is therefore not dependent on diagnosis, it is more dependent on the product and setting."
Medical Tech Committee	✓		✓	

Key
✓ Yes
✗ No

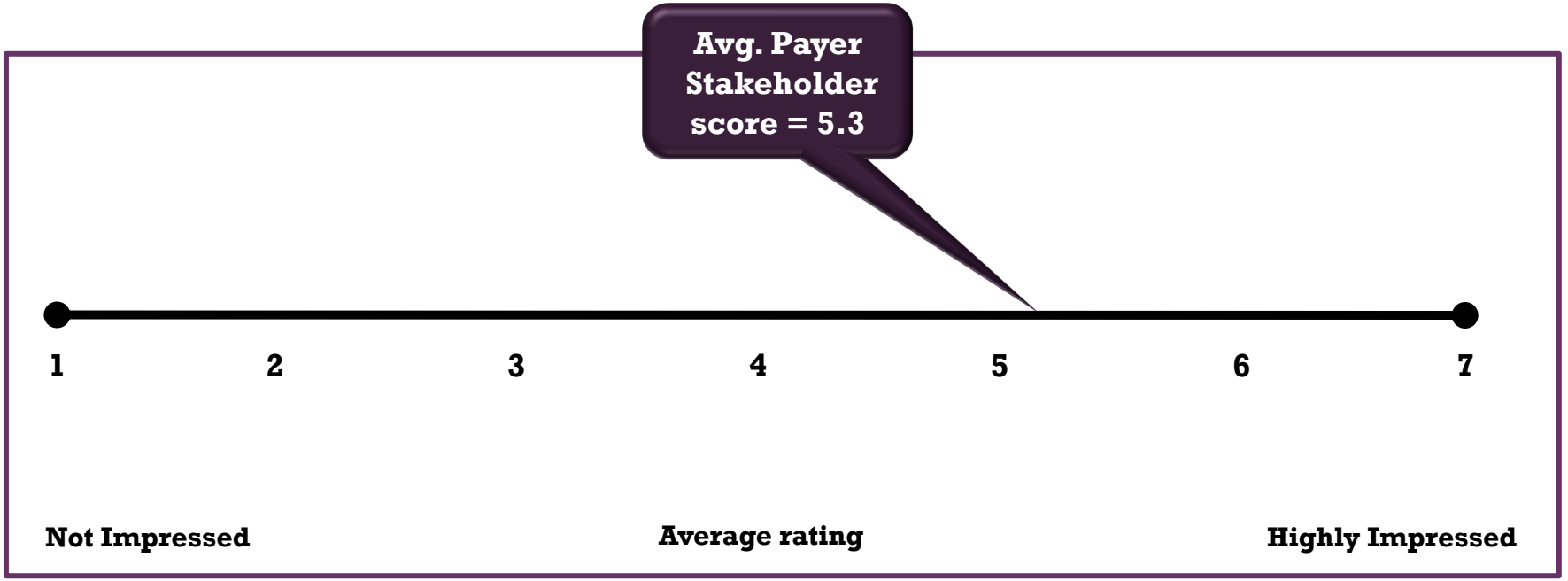
When reviewing Technology X® platform utilization, payers will consider clinical capabilities and cost to their organization



Although the cost of the product was highlighted as the determining factor when evaluating a new *in vitro* testing product, management of toxicity was ranked as an important variable

Stakeholders had a significantly positive reaction towards the clinical evidence detailed in the Technology Profile

Q: How would you rank the clinical evidence presented in terms of its coverage supporting potential?

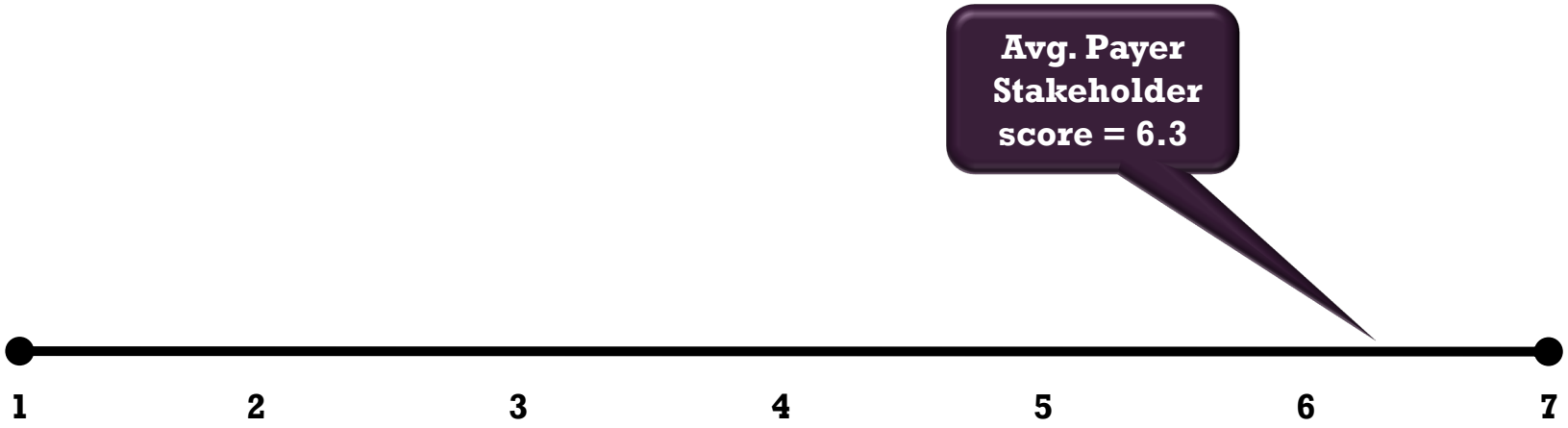


"I would like to see evidence from a trial in the home healthcare setting. Results of clinical trials in terms of effectiveness: how often does the test need to be conducted, what is its efficacy in late Stage III/Stage IV. These things need to be evaluated."

– Southwest Payer

Payers perceive significant added value when pharmacogenetic testing for DPYD gene deficiency is paired with pharmacokinetic testing for 5-FU dose optimization

Q: Would bundling a pharmacogenetic test for DPD deficiency along with the pharmacokinetic 5-FU dose management test add value?



"There are too many colorectal cancer patients that do very poorly with 5-FU chemotherapy not because of the dosing but because they cannot adequately metabolize the 5-FU; oxiplatin is a different story but there is no excuse for a patient receiving a dose of 5-FU and then progressing to Stage IV toxicity because they have DPD deficiencies

-Southwest payer

Payers reported that an ideal study to support coverage should demonstrate clinical efficacy, include statistically significant patient numbers and multiple centers

- Prospective, randomized multi-center comparative trials are preferred by payers
- Clinical endpoints should be gathered at key intervals like 3, 6, 12 and 18 month
- Follow-up data should be published after 12 and 24 months

"Pick the patients for the trial carefully. Maybe this isn't a product for every patient, but you can demonstrate improved outcomes for a targeted sub-population, for example older patients."
- Midwest Payer

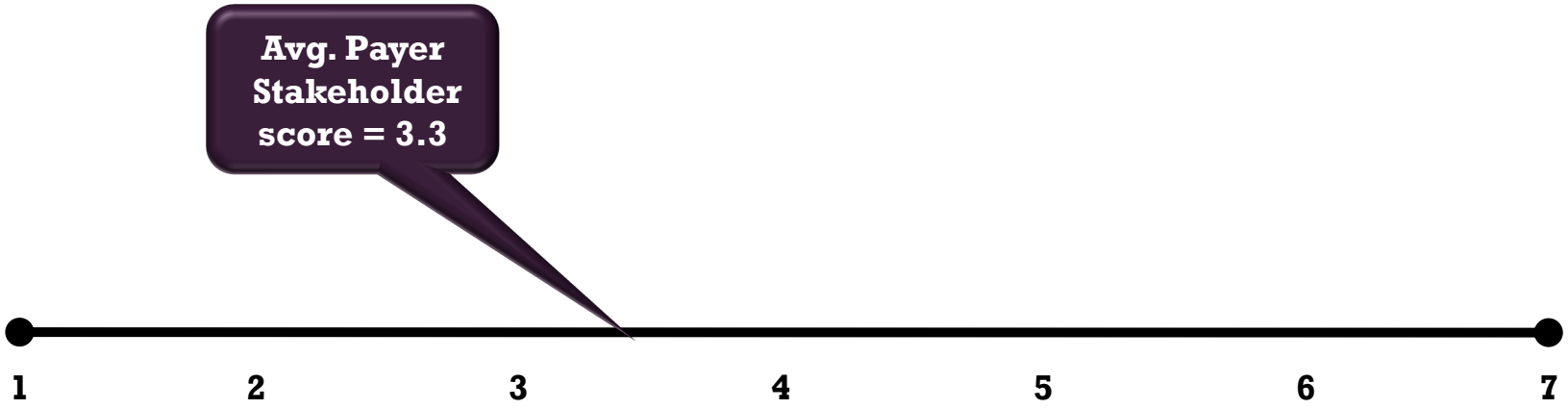
"Maybe the likelihood of developing toxicity decreases, but the root cause of the problem may still be present if the patient is DPYD deficient – these must be addressed or else toxicity is a constant threat. I want to see the whole picture."
-Northeast Payer

Desired Endpoints

- Progression free survival and QoL
- Readmission rates
- Durability/Recurrence
- Resource utilization
- Ease of testing
- Total cost of care
- Bed Days
- Impact on disease progression

Recently published clinical oncology paper added significant value to payer perception of Technology X® clinical utility[1]

Q: Is additional clinical evidence needed to support coverage in your organization?



"I would like to see evidence from a trial in the acute care setting. Results of clinical trials in terms of effectiveness in a prospective study. These things need to be evaluated. Data from a home health care setting or skilled nursing facility – that would be great."

– Southwest Payer

"I would say the the evidence presented in the technology profile would be sufficient for us to cover utilization of the test at a reasonable payment level. There is no need for level 1 evidence here if multiple trials have already demonstrated increased clinical efficacy in colorectal cancer patients"

-Northeast Payer

1. Capitain, et al. Clinical Colorectal Cancer June 2012

Payers require education about the importance of early optimization of 5-FU chemotherapy though payment policies increasingly incent focus on enhancing efforts

- Oncology clinical guidelines don't specifically mention chemotherapy dosing optimization in their guidelines but do not recommend against this practice
- Due to fear from CMS 'never pay' clauses some treatment facilities are already educating clinicians and staff on the importance of chemotherapy dose optimization as a way to improve care and to produce an overall cost savings in their patient care
- Perception of severity for 5-FU overdosing by clinicians is lower in priority than ensuring chemotherapy is effective in increasing progression free survival

Advantages derived from the use of Technology X® need to be clearly communicated to significantly impact payer attitudes

"I am not familiar with this product but its attributes need to be clearly communicated in order for us to cover the test"
Southeast Payer

"What is the cost of the test? What are its drawbacks? How often must it be repeated – these would be significant variables in our coverage determination"
Northeast Payer

	Pros	Cons
Product Attributes	• Ease of use for practitioner • Lower cost versus home brew liquid chromatography testing • Repeatability of the test	• Questions about data; one payer wondered why none of the large academic centers had endorsed Technology X if the claims of higher efficacy, lower toxicity, were proven
Patient Management	• Adjustability of 5-FU dosing • Data can alter clinical actions quickly • Long-term management of potential toxicity issues	• How often does the product need to be repeated? • Long term utilization unknown • Repeatability of results

Several interviewees mentioned that alternative arrangements between payers and providers, like ACOs, will incentivize investment in prevention of 5-FU toxicity by rewarding positive clinical outcomes

Accountable Care Organizations (ACO)

- A collaborative of hospitals, physicians, and other ancillary providers
- Incentivized by healthcare outcomes and quality care measures
- ACO's actively seek more effective treatments and products to improve the quality and cost of care
- Organizations are moving away from Fee for Service (FFS) and in the future will likely be reimbursed through global capitation, partial capitation and bundled payments

Health and Human Services Secretary Kathleen Sebelius recently cited the important role ACO's will play in the reduction of readmission and spending on poorly managed chemotherapy toxicity[1]

1. 2nd Annual National Accountable Care Organization Summit, June 27, 2011

Recommendations and Next Steps

08

The Technology X® testing platform should be cleared or approved by FDA to maximize its coverage potential from private payers

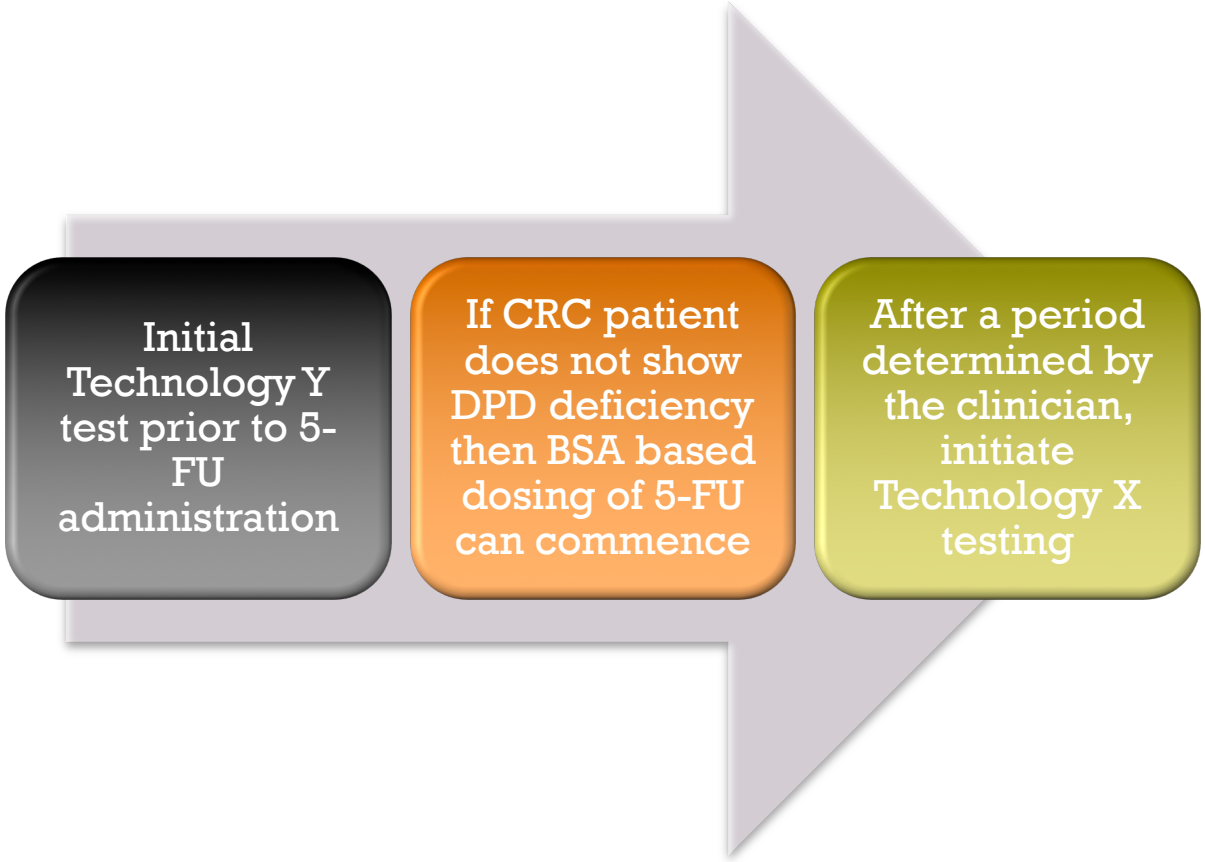
- Virtually all payer interviewees reported that FDA clearance/approval would increase the chances that their organization would cover the test
- Many clinical facilities contract *in vitro* testing with local reference laboratories – conducting Technology X testing either locally or at point of care is likely to improve operational efficiencies, decrease costs, and improve clinical efficacy due to shorter time to result - FDA clearance/approval will be required for Technology X test distribution
- It is likely that Technology X could be cleared for marketing by FDA through the 510(k) premarket notification process

Implication

Return on investment could be significantly improved by creating barriers to entry for competitive 5-FU dose management products

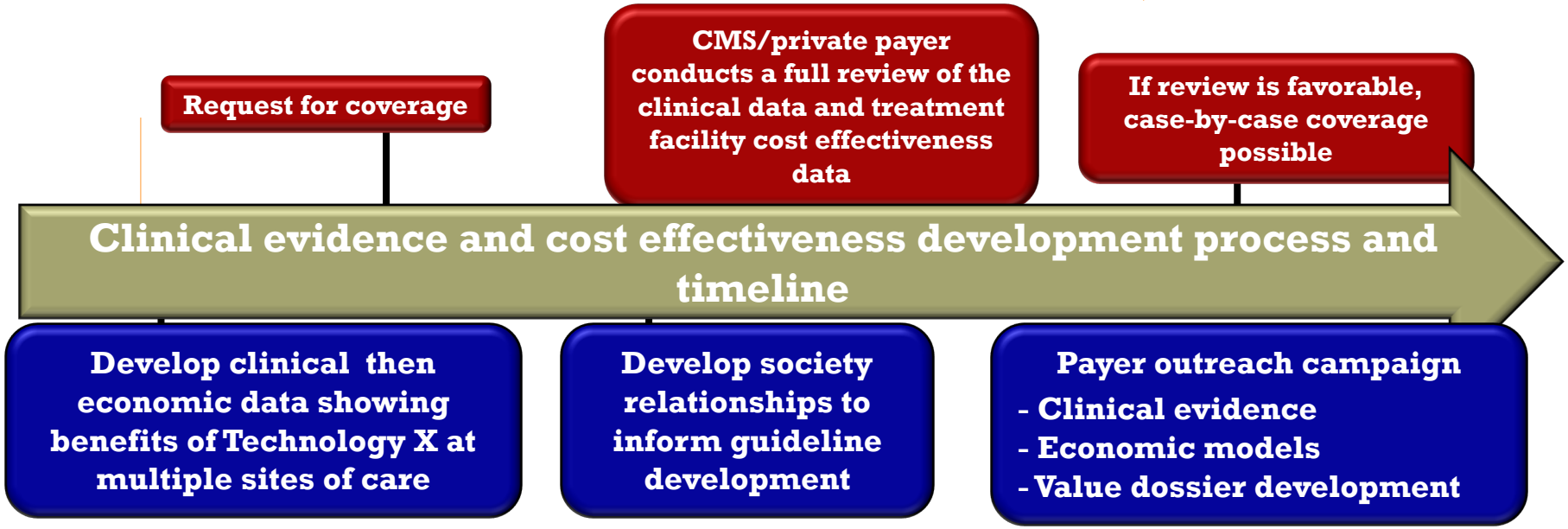
Company X should consider bundling the Technology X® and Technology Y® testing platforms together for utilization in 5-FU dose management in colorectal cancer patients

- A significant number of payer interviewees commented that there would be significant value added by bundling the tests
- ASCO has recommended consideration of bundling pharmacogenetic testing with pharmacokinetic testing in 5-FU dose management
- Bundling the two testing platform would create marketing differentiation from service, product and potentially pricing perspectives



Technology X® coverage will benefit from an oncology clinician and payer outreach campaign that leverages evolving clinical safety and efficacy as well as economic data

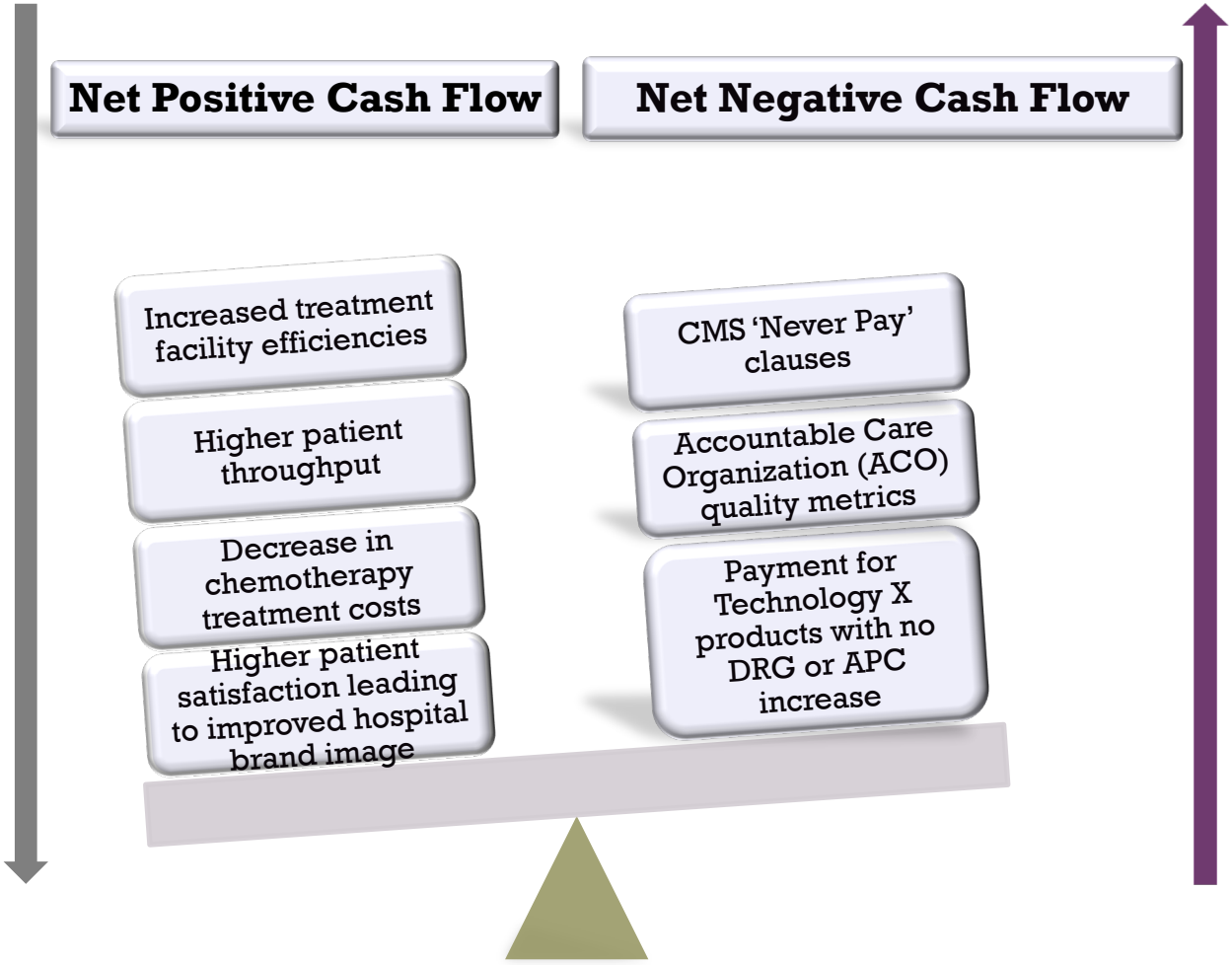
- Develop a network of oncology clinicians who recognize the patient benefits of Technology X, become early adopters and conduct evaluation studies independently
- Utilize the clinician network of support to advocate 5-FU dose optimization to minimize toxicity as a component of societal colorectal cancer treatment guidelines
- As the clinical evidence base develops and personalized chemotherapy management is included in treatment guidelines, develop a payer outreach campaign that focuses on clinical benefits of product safety and efficacy



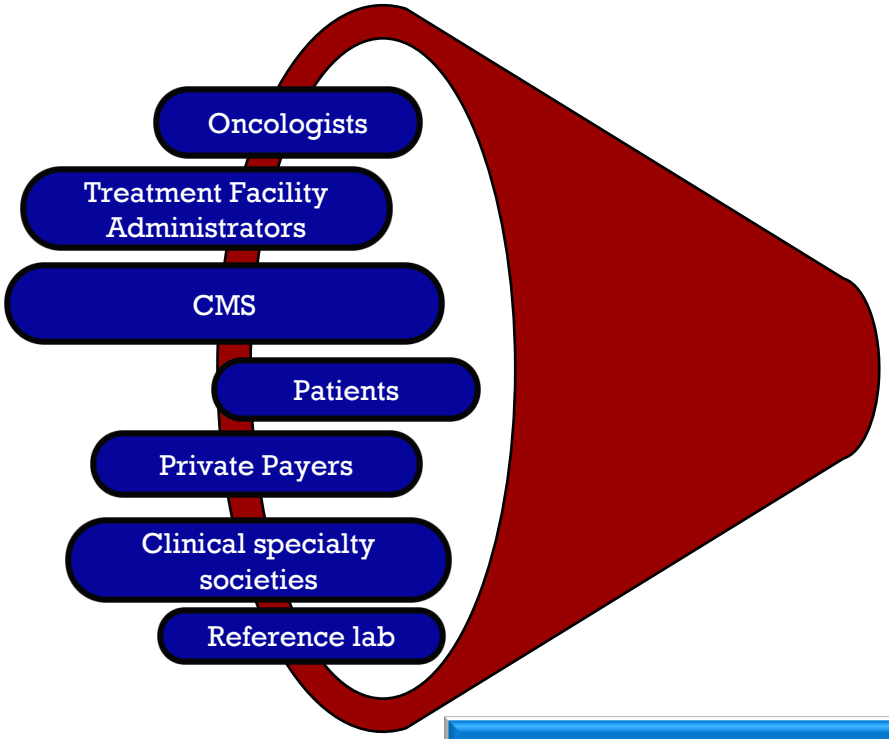
Myriad should develop a marketing campaign for Technology X® to emphasize that its utilization may lead to a net positive cash flow for provider facilities

"Providers are under tremendous cost pressures in the current healthcare environment - If you can show the provider that they can reduce their costs in the long run through active management of 5-FU dosing then they will be more likely to do so"

Northwest Payer



A value development strategy for Technology X® should demonstrate the need for personalized 5-FU dose management products to reduce the likelihood of toxicity development in high risk patients



Advocate for chemotherapy toxicity prevention and facilitate decision making

Encourage continued evaluation and demonstration of economic modeling and overall cost impact savings to treatment facilities

"Once a new 5-FU dose management test is trialed and ultimately brought into the hospital the provider will conduct its own internal product evaluation for quality purposes to assess efficacy and impact on treatment costs"

Northeast Payer

Company X should develop a set of tools that treatment facilities can utilize to conduct cost impact analyses for Technology X® testing within their institutions

Literature review on the role of pharmacogenetic and pharmacokinetic testing in the personalized management of 5-FU dosing in colorectal cancer patients

Data package to demonstrate the safety and efficacy of Technology X in reducing the likelihood of development of chemotherapeutic toxicity in high risk patient populations

Comprehensive set of colorectal cancer treatment guidelines with explanations of applicability to Technology X product

Economic model to demonstrate the potential cost-savings associated with use of pharmacokinetic testing in personalized 5-FU dose management

A set of clinical study protocols designed to evaluate the usage of pharmacokinetic testing in personalized 5-FU dose management at the institutional level

Educational tools that instruct the clinical oncologist and support staff on use of Technology X testing

An oncology provider advocacy base at outpatient clinics and home healthcare providers should be developed to maximize Technology X® uptake

Outpatient Clinic	Home Healthcare Provider
• In order to get coverage beyond the miscellaneous CPT code, an additional modifier and/or a unique CPT code should be obtained • In order to get an additional code, data from outpatient facilities should be collected in a registry and analyzed	• A significant percentage of chemotherapy for colorectal cancer patients is conducted in the home healthcare environment • S code 3722 can be utilized to gain additional payment in the home healthcare environment

Strategies/tactics for success:

- Develop a comprehensive target list of outpatient and LTC treatment facilities
- Identify Key Opinion Leaders and decision making stakeholders at each site
- Publish and advertise in leading outpatient and specialty LTC journals
- Participate and present in clinical specialty conferences for outpatient/long-term treatment care
- Use sampling and aggressive pricing at launch to penetrate key facility targets once identified

Recommendation Summary

- Obtain FDA clearance for the Technology X® testing platform through the 510(k) premarket notification pathway
- Continue to build demand for Technology X testing among clinical oncologists and healthcare providers at the facility level
  - Potential for increased efficacy of treatment
  - Decreased 5-FU toxicity
  - Potential treatment facility quality measure
- Combine Technology X testing with an initial Technology Y® test to identify patients that are DPYD deficient
- Ensure that Technology X is included in NCCN and other oncology clinical societal treatment guidelines, including ASCO
- Construct cost effectiveness models to show return on investment includes fewer complications and less hospital readmissions

Recommendation Summary (cont)

- A value development strategy for Technology X® should be created to demonstrate the need for products to reduce 5-FU toxicity in high risk colorectal cancer patient populations

- Company X should facilitate construction of cost impact models for the utilization of pharmacokinetic testing for personalized 5-FU dose management at the treatment facility level – such models along with KOL support should be incorporated into Company X' payer negotiation strategies given prevalence of global payment schemes

- Company X should use the recent implement of "never pay" clauses as well as CMS and/or ACO quality measures to incentivize inpatient facilities to adopt use of the Technology X testing platform

Next Steps

- Finalize the Technology X® regulatory strategy, including determining the product classification and indications for use
- Initiate bundling of the Technology X and Technology Y® testing platforms from a marketing perspective
- Initiate dialogue with clinical societies to expand the scope of personalized 5-FU dose management in treatment guidelines
- Facilitate development of treatment facility level cost-impact models to support payer negotiation strategies
- Determine what, if any additional clinical studies will be done to support regulatory applications, as well as reimbursement coverage submissions to CMS and private payers
- Create and implement a marketing strategy for hospitals that demonstrates the potential positive cash flow to these institutions for using Technology X even without additional reimbursement
- Develop payer education tools including value dossiers, payer cost-impact models, and HTA support presentations

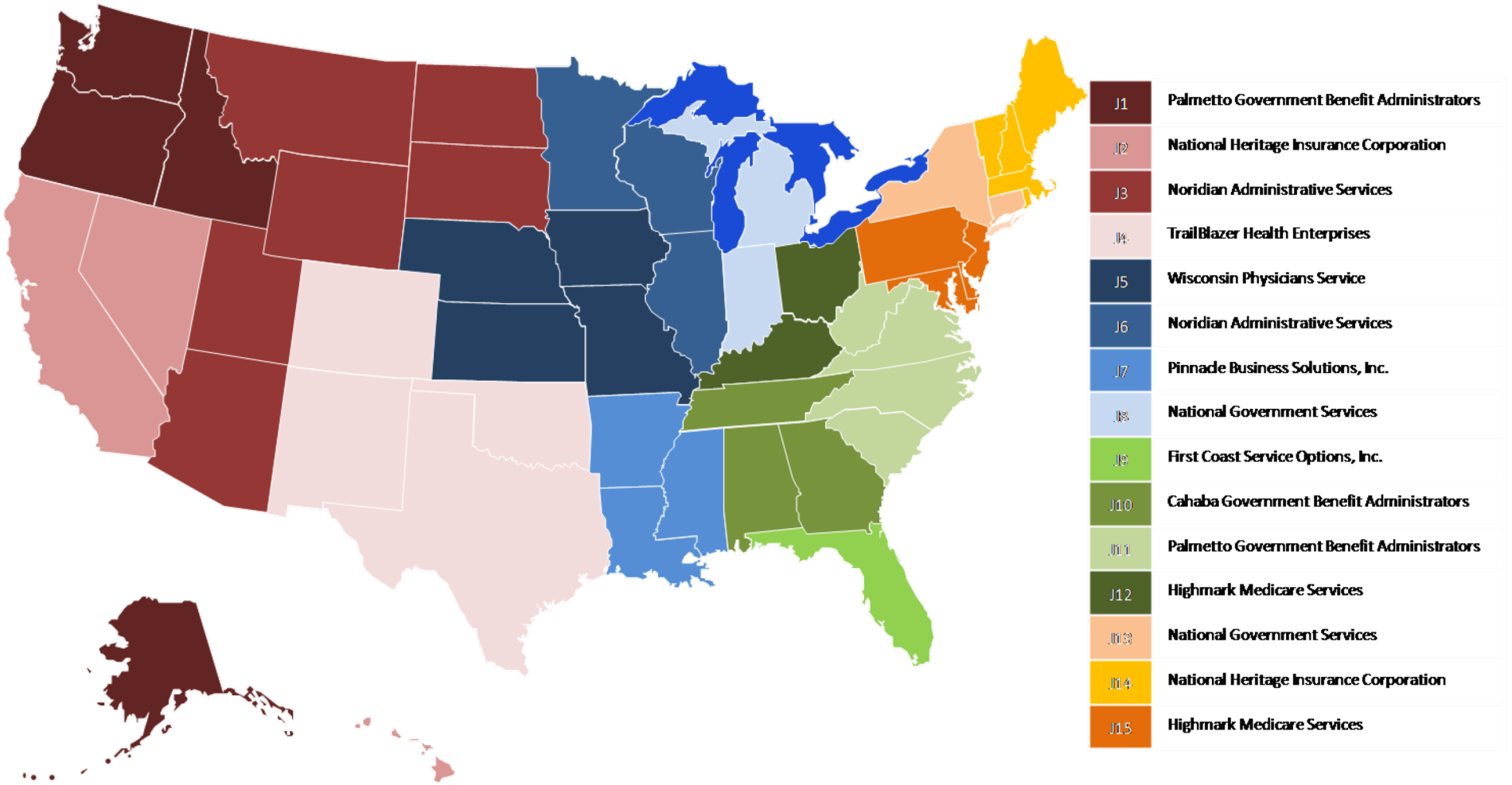
Appendices

09

Medicare Part A Intermediaries and Part B Carriers are being consolidated into Medicare administrative contractors (MACs)

- The Medicare Prescription Drug, Improvement and Modernization Act of 2003 (MMA), authorized the Centers for Medicare & Medicaid Services (CMS) to make significant changes to Medicare fee-for-service (FFS) administration
- Under Medicare Contracting Reform, CMS will combine the administration of Medicare Parts A and B (FFS benefit) into Medicare Administrative Contractors (MACs) – Work will be transitioned by 10/09
- By consolidating Part A & B, Medicare hopes to gain efficiencies and enhance the delivery of care
- Positive Implications of this transition will be greater consistency across Part A and B diagnostics used in both settings, likely to have greater recognition of value as MAC has domain over both settings
- There will also be less variability with LCDs given the smaller number of MACs

Medicare Part A/B MAC Jurisdiction



Technology-appropriate coding is vital to ensure appropriate reimbursement of *in vitro* testing products

- Before a strategic coding path can be determined, reference the latest version of Current Procedural Terminology (CPT) codes or consult with a certified coding professional to ascertain if an existing code accurately identifies the test in question
- If new code(s) are needed, three major steps need to be addressed to allow for appropriate coverage, documentation and payment for the specific test
  - *Coverage*
    - Determine effectiveness of test
    - Role of Medicare in coverage policy
    - Impact of Medicare on private payers
  - *New code creation*
    - Process for applying for novel CPT code
    - The use of miscellaneous or unlisted CPT codes
  - *Establishing payment*
    - Medicare cross-walking
    - Clinical lab fee schedule (CLFS)

CPT Codes offer pathways to technology specific reimbursement

Three distinct categories for CPT Codes

- *Category I CPT Codes*

  Describe a procedure or service identified as being consistent with contemporary medical practice and being performed by many physicians in clinical practice in multiple locations

- *Category II CPT Codes*
  - Supplemental tracking codes that can be used for performance measurement and minimize administrative burden
  - Use of these codes is optional
- *Category III CPT Codes*
  - Temporary set of tracking codes for new and emerging technologies
  - Can be used to support FDA approval or substantiate widespread usage
  - Payment for the service would be at the discretion of the payer and codes are not included in CMS fee schedules

If new codes are needed, code proposals must follow submission dates established by the AMA

Proposals for 2014 CPT Code

Deadline for Submission of CPT Proposals	CPT Agenda Books Mailed	Pathology Coding Caucus Meeting	CPT Meeting
March 4, 2013	May 4, 2013	Prior to June meeting	June 4-6, 2013
July 15, 2013	September 15, 2013	Prior to October meeting	October 15-17, 2013
November 11, 2013	January 11, 2014	Prior to February meeting	February 11-13, 2014

CMS Clinical Lab Fee Schedule Determination

Public Meeting For Payment Recommendations	Public Comments and CMS Proposed Payment Posted	Comment Period on Proposed Payment Determinations	Final Payment Determinations Posted	New Clinical Lab Fees Effective
Mid July 2013	Mid September 2013	Open until early October 2013	Mid December 2013	January 1, 2014

Key Milestones in a Novel CPT Code Application Process

1. After FDA approval, manufacturer develops CPT application and submits to AMA
2. Application initially reviewed by AMA staff and the CPT Advisory Committee (Pathology Coding Caucus in some cases)
3. Staff and Advisory Committee then refer file to the 17 member CPT Editorial Panel to address application
4. Outcomes of the Laboratory CPT application include:
   - Add a new code or revise existing nomenclature

     New code can either be a Level 1 CPT Code or a Level 3 tracking code
   - Postpone/table an item to obtain further information
   - Reject an item
5. CMS then assigns rates to the novel codes through a process called "cross-walking"; new code and rate published in January of the following year
6. The entire process, from initial application to creation of a novel code, can take between 13 and 21 months

   In the interim, new technologies may be coded using "miscellaneous" codes

Key research organizations support payer health technology assessments for personalized 5-FU dose management that will influence coverage decisions

- The Cochrane Collaboration, established in 1993, is an international network that conducts reviews to assist health care provider and payer decision-making
- Hayes, Inc. is an independent health technology research and consulting company dedicated to promoting better health outcomes. Hayes performs unbiased, evidence-based healthcare technology assessments of the safety and efficacy of new, emerging, and controversial health technologies and evaluates the impact of pressure technologies on healthcare quality, utilization, and cost.
- ECRI Institute is a nonprofit organization dedicated to bringing the discipline of applied scientific research to discover which medical procedures, devices, drugs, and processes are best.
- BCBS Technology Evaluation Center (TEC) has been recognized for its leadership in evidence-based healthcare technology assessment. Its mission is to provide healthcare decision makers with timely, objective and scientifically rigorous assessments.

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ECRI Institute
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