Development and Implementation of a Formal Process for Addressing the Off-Label Uses of Medications

Background

- Many of the newer, expensive oncology agents are being studied for multiple indications outside of their FDA-approved labeling
- Observed increase in off-label use of medications at all practice sites
  - Concerned for both safety and financial reasons
- Identified need for formal process and policy
  - Pharmacists initially serving as the gatekeeper

Policy Development

- Multidisciplinary team is necessary
  - Physician champion
  - Pharmacy
  - Nursing
  - Finance
  - Compliance
  - Risk management

Policy Development

- Steps of the process:
  - Define:
    - Off-label use
    - A process for predeterminations
    - A process for handling off-label requests
  - Establish a timeline for advance notification
  - Develop a method for tracking off-label requests
  - Establish a peer review process
  - Explore alternative means of payment
  - Educate staff
  - Anticipate exceptions and unexpected scenarios
    - e.g. rare conditions, therapy already initiated, etc.

Policy Development

- Definitions
  - Off-label medication use: use of a medication for any indication that is not stated/included in the FDA-approved labeling
    - Dose
    - Administration frequency
    - Administration route
    - Line of therapy (sequence)
    - Age of patient
    - Combination therapy

D Leveque. Lancet Oncology 2008; 9:1102-07

Policy Development

- CMS-approved compendia and recommendation levels:
  - Elsevier Gold Standard *Clinical Pharmacology*
    - Narrative assessment
  - American Hospital Formulary Service (AHFS) Drug Information
    - Indication is supportive
  - Truven Health Analytics Micromedex DrugDex
    - Class I, IIa, IIb
  - National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium
    - Category 1 or 2a
  - Wolters Kluwer Lexi-Drugs®
    - Level A

https://www.cms.gov/Regulations-and-Guidance/Guidance/Manuals/Downloads/bp102c15.pdf
https://www.cms.gov/Medicare/Coverage/CoverageGenInfo/compendia.html

Policy Development

- Definitions (cont.)
  - **Predetermination (Pre-D)**: process used with commercial payers to gain approval for off-label use prior to the patient receiving treatments
  - **Notice of Non-Coverage (NONC)** – a written notice to a patient who is covered under a commercial insurance plan before the patient receives a medication for an off-label indication that has been denied for payment and the patient may be responsible for payment

Policy Development

- Definitions (cont.)
  - **Peer-Reviewed Scientific Evidence**: two Phase II studies or one Phase III study reported in scientific, medical, or pharmaceutical publications in which original manuscripts are published only after having been critically reviewed for scientific accuracy, validity, and reliability by unbiased, independent experts. (e.g. Journal of Clinical Oncology)

Note: In-house publications of pharmaceutical manufacturing companies, case studies, or abstracts (including meeting abstracts), do not constitute Peer Reviewed Scientific Evidence.

https://www.cms.gov/Regulations-and- Guidance/Guidance/Manuals/Downloads/bp102c15.pdf

Policy Development

- Definitions (cont.)
  - **Advanced Beneficiary Notice (ABN):** a written notice which a physician or designee must provide a patient with Original Medicare that informs the patient that Medicare may not pay for the medication and that the patient may be responsible for payment if the claim is denied. An ABN should be issued prior to the patient receiving an item or service
  - Timeline for notification
    - Off-label request must be provided to reimbursement analyst **at least 10 business days** in advance of treatment

https://www.cms.gov/Regulations-and-Guidance/Guidance/Manuals/Downloads/bp102c15.pdf

Predetermination Process

- Formal process with a team approach
- Key players:
  - Pharmacist
  - Physician
  - Advanced Practice Provider (CNP or PA)
  - Reimbursement Specialist
- Effective and traceable form of communication is essential

Predetermination Process

- Pharmacist role
  - Discuss rationale for off-label use with the team
  - Retrieve supporting literature
  - Review CMS-approved compendia and NCD/LCD
  - Enter request into off-label use database
    - Entry triggers an email to pharmacy director, P&T committee chair, reimbursement specialist team

Predetermination Process

- Reimbursement Specialist role
  - Verify medical insurance
  - Obtain copies of pertinent information from patient medical record (treatment plan, diagnostic studies, etc.)
  - Retrieve supporting literature (if not already provided by team)
  - Verify compendia and NCD/LCD support
  - Identify appropriate ICD-10 code(s) and HCPCS code(s) for medications

Predetermination Process

- Reimbursement Specialist role
  - Draft letter of medical necessity
  - Fax letter and supporting evidence to payer
  - Confirm payer has received information
  - Continue to follow up until approval/denial received
  - Request approval number and individual name

James Off-Label Database

The James

The Ohio State University Arthur G. James Cancer Hospital
And Richard J Solove Research Institute

THE OHIO STATE UNIVERSITY
WEXNER MEDICAL CENTER

OFF-LABEL USE DATABASE
SEARCH RESULTS

Displaying submission record(s) 1 through 1 of 1 Record(s) Found

Patient Name	MRN	Submission Date	Off-Label Medications	Pharmacist	Claim Status	Payor	Submission Status
Patient, Test Again	99887766	06/29/2015		Smith2, Michael	Pending PC	Other Payors	Open

Click patient name to view/update submission details

| Start New Search | Off-Label Submission Form | Pharmacy Home | OneSource |

[Logout]

The James

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And Richard J Solove Research Institute

THE OHIO STATE UNIVERSITY
WEXNER MEDICAL CENTER

OFF-LABEL USE DATABASE
RECORD DETAIL

Patient Name: Patient, Test Again
MRN: 99887766
Dx Code(s): 1234
Pharmacist: Smith2, Michael
Phone: *Pager:*

Submission Date: 06/29/2015 **Rec ID:** 944
Location: 5-CCCT
Diagnosis: Sorry, This is another test submission. Please ignore. --Kim

TREATMENT REGIMEN					
Regimen Details *(please indicate treatment frequency/days, cycle length, etc)*					
Another test submission					
Medication	**Dose** (ex: mg/m^2)	**Patient's Calculated Dose**	**ACQ Cost Per Dose**	**No. Doses Per Cycle**	**Use Off-Label**
1.					
2.					
3.					
4.					

Planned cycles per regimen: 0
Cost per treatment cycle: $
TOTAL treatment cost: $0
Physician: Awan, Farrukh
Disease Service: GI Med/Onc
Reason for Off-Label Use:
Another test submission

PEER REVIEW SUPPORT			
Medication 1	**Medication 2**	**Medication 3**	**Medication 4**
☐ FDA Approved	☐ FDA Approved	☐ FDA Approved	☐ FDA Approved
☐ NCD-covered indication	☐ NCD-covered indication	☐ NCD-covered indication	☐ NCD-covered indication
☐ LCD-covered indication	☐ LCD-covered indication	☐ LCD-covered indication	☐ LCD-covered indication
☐ AHFS-DI-Indication is supportive	☐ AHFS-DI-Indication is supportive	☐ AHFS-DI-Indication is supportive	☐ AHFS-DI-Indication is supportive
☐ NCCN-Indication is Category 1 or 2A	☐ NCCN-Indication is Category 1 or 2A	☐ NCCN-Indication is Category 1 or 2A	☐ NCCN-Indication is Category 1 or 2A
☐ DrugDex-Indication is Class I, IIa, or IIb	☐ DrugDex-Indication is Class I, IIa, or IIb	☐ DrugDex-Indication is Class I, IIa, or IIb	☐ DrugDex-Indication is Class I, IIa, or IIb
☐ Two Phase II Studies	☐ Two Phase II Studies	☐ Two Phase II Studies	☐ Two Phase II Studies
☐ One Phase III Study	☐ One Phase III Study	☐ One Phase III Study	☐ One Phase III Study
☐ Other	☐ Other	☐ Other	☐ Other
☐ None Available	☐ None Available	☐ None Available	☐ None Available
If Other checked, please describe:	If Other checked, please describe:	If Other checked, please describe:	If Other checked, please describe:

MRN: Medical Record Number
Dx Code: diagnosis code

CLAIM DETAILS

Claim status:

- ○ Patient receiving medication
- ◉ Pending payment
- ○ Denied-pending appeal
- ○ Appealed
- ○ Denied-final
- ○ Completed-paid
- ○ Not given

Service Date(s): 07/12/15, 07/19/15

HAR(s): 07/01/2015, 07/07/2015

Total Amount Reimbursed: $20,345.00

Bundled or Inpatient: ○ Yes ◉ No

Reason if claim denied: ○ Medical necessity ○ No authorization ○ Experimental/investigational ◉ Other

If "other", please describe: other denied reason test- appeal submitted reference# 123456856

Total acquistion Cost of Denied Drug(s): $500.00

Total amount recovered by appeal: $500.86

Total amount replaced by manufacturer: $0.12

Claim comments: claim comments go here

Last modification date: 07/27/2015	**Last modified by:** S Hudson-DiSalle

UPDATE RECORD

The James

The Ohio State University Arthur G. James Cancer Hospital
And Richard J Solove Research Institute

THE OHIO STATE UNIVERSITY
WEXNER MEDICAL CENTER

OFF-LABEL USE DATABASE
SUBMISSION SEARCH FORM

Select Search Criteria

Select multiple criteria to narrow results

Patient Last Name:

Patient MRN:

Pharmacist:

Date range:

Beginning date: (m/d/yyyy)

Ending date: (m/d/yyyy)

Pre-Cert Status:
- Pending Pre-D
- Pending Admin
- Admin Approved
- Pre-D Submitted
- Pre-D Approved
- Pre-D Denied
- Pre-D Appealed
- Cancelled

Payor: Medicaid | Medicare | Self-pay | Other Payors

SEARCH | Reset

Key:
Pending Pre-D = waiting on reimbursement team
Pending Admin = Awaiting pharmacy administration review
Admin Approval = Administration approval
Pre-D = Predetermination

| Start New Search | Off-Label Submission Form | Pharmacy Home | OneSource |

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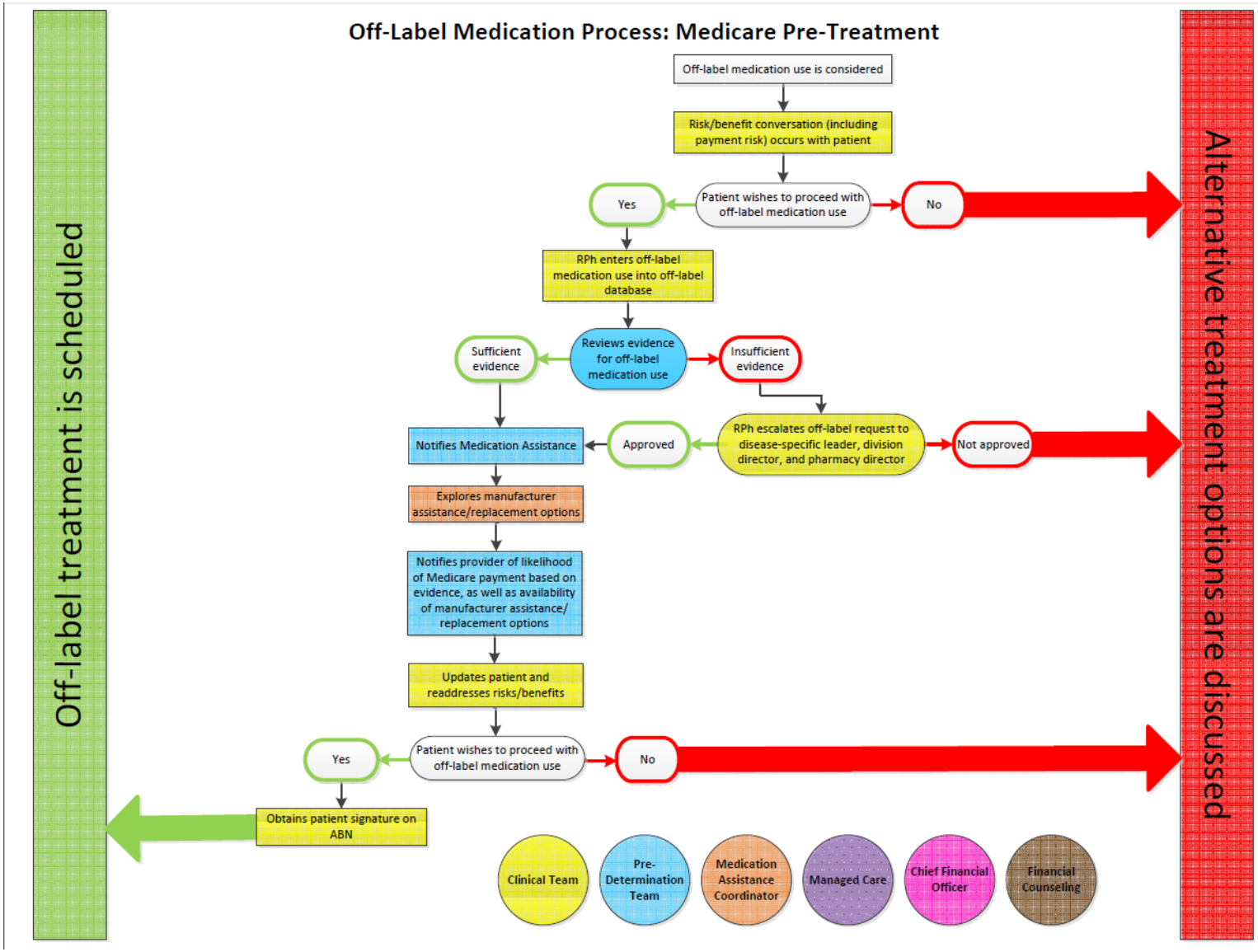
Peer Review Process

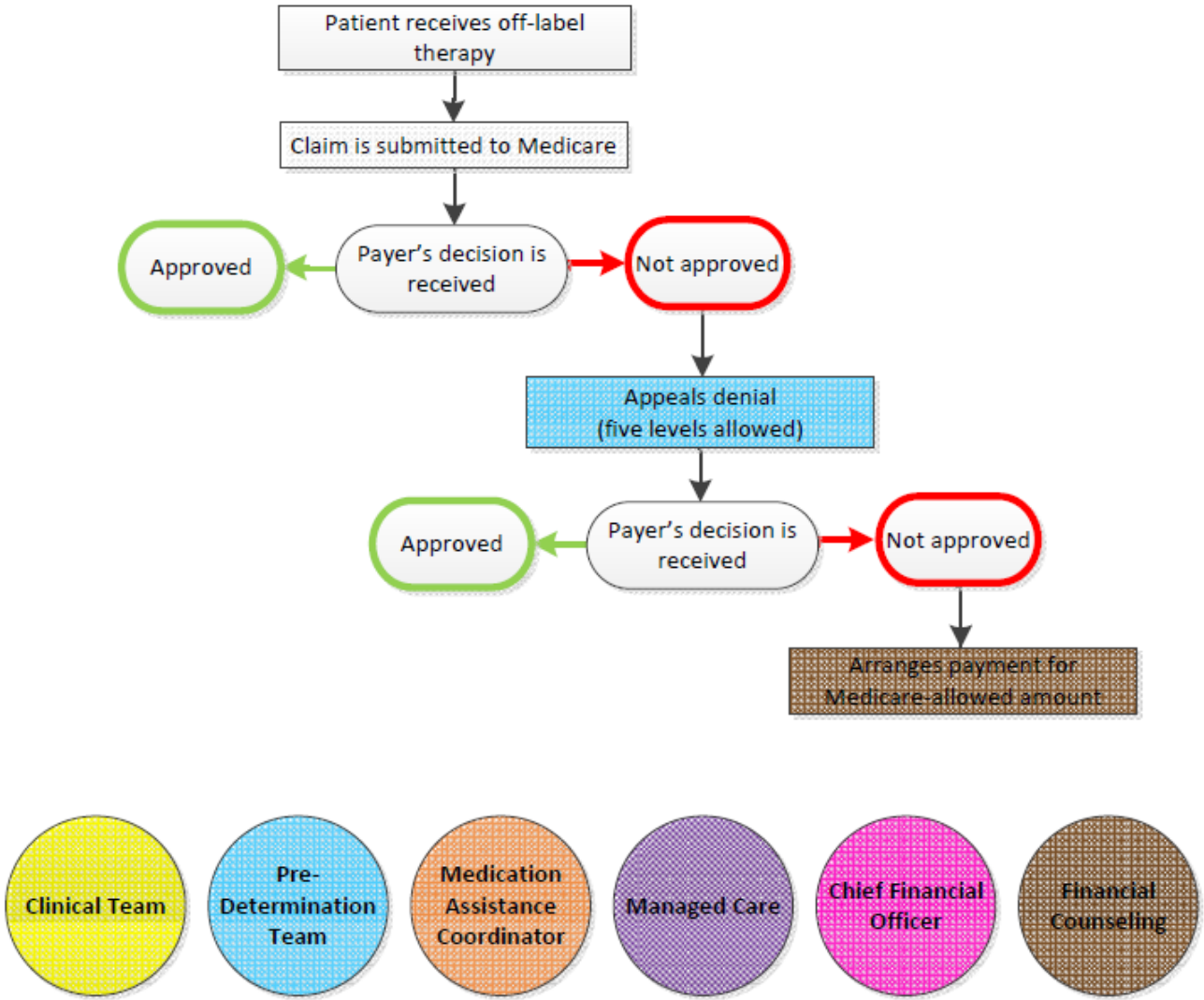
- Off-label requests lacking supportive evidence require approval by:
  - Disease-Specific Leader (GI, GU, Lung, etc..)
  - Division Director (hematology or oncology)
  - Pharmacy Administrator/Director
- Safety, efficacy, and cost must be considered
- Decisions may take up to 72 hours depending on availability of individuals

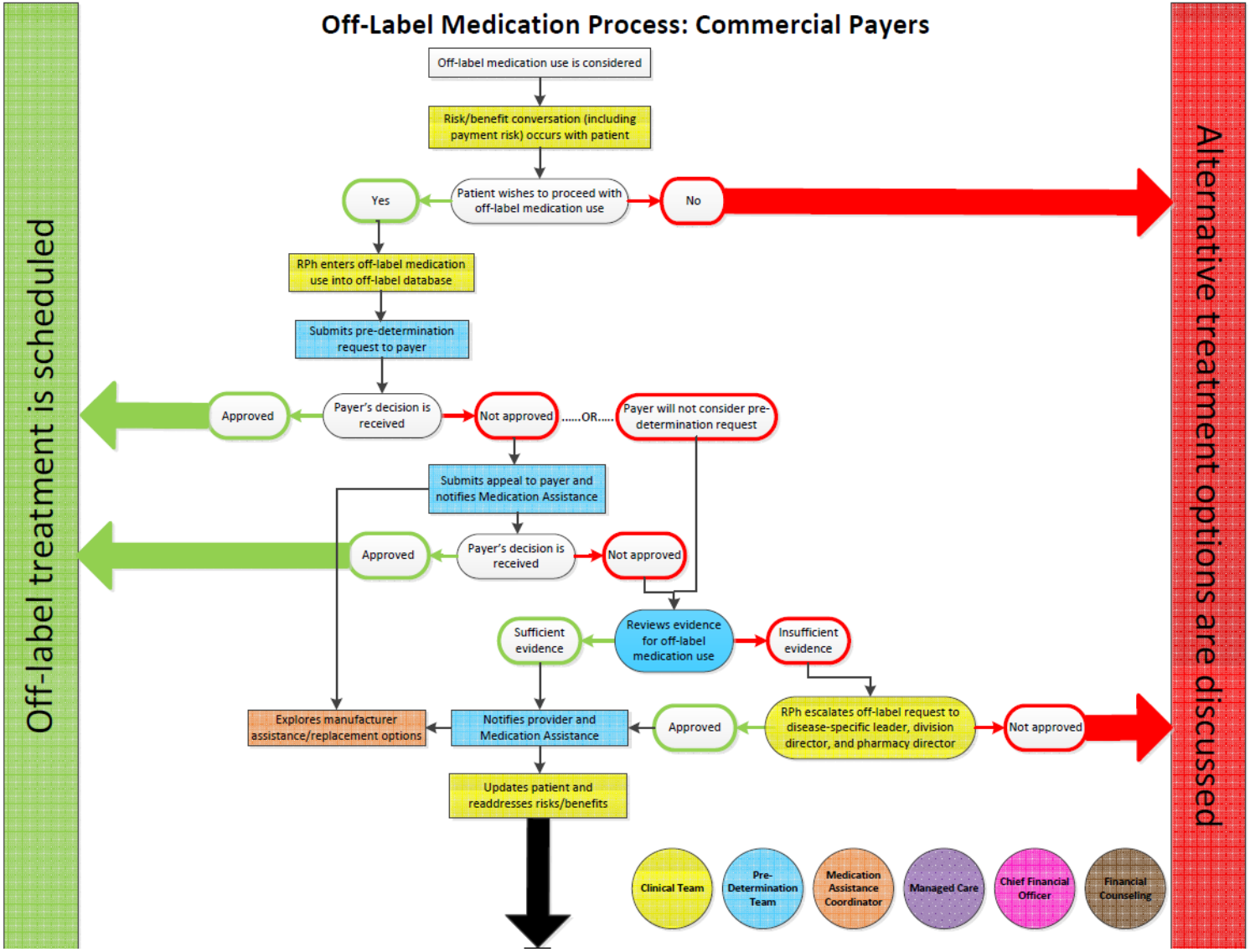
Alternative Payment Options

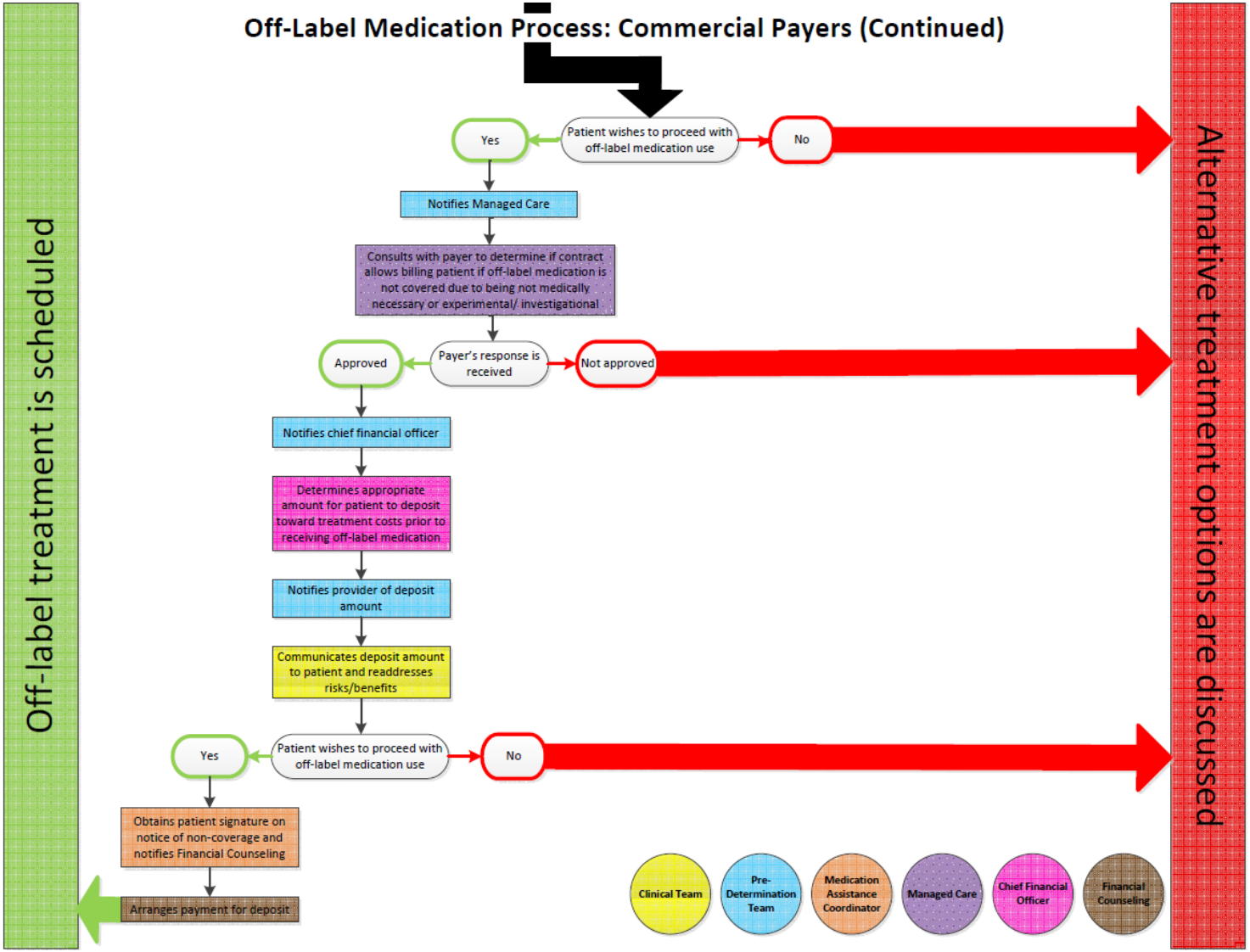
- Medication assistance program staff research options for pharmaceutical manufacturer assistance
  - Require copy of denial and appeals
  - Diagnosis dependent
  - Income dependent
- Chief Financial Officer makes final payment decision regarding deposit


Off-label treatment is scheduled
Off-Label Medication Process: Medicare Pre-Treatment
Off-label medication use is considered
Risk/benefit conversation (including payment risk) occurs with patient
Patient wishes to proceed with off-label medication use
Yes
No
RPh enters off-label medication use into off-label database
Reviews evidence for off-label medication use
Sufficient evidence
Insufficient evidence
RPh escalates off-label request to disease-specific leader, division director, and pharmacy director
Approved
Not approved
Notifies Medication Assistance
Explores manufacturer assistance/replacement options
Notifies provider of likelihood of Medicare payment based on evidence, as well as availability of manufacturer assistance/ replacement options
Updates patient and readdresses risks/benefits
Patient wishes to proceed with off-label medication use
Yes
No
Obtains patient signature on ABN
Clinical Team
Pre-Determination Team
Medication Assistance Coordinator
Managed Care
Chief Financial Officer
Financial Counseling
Alternative treatment options are discussed

Off-Label Medication Process: Medicare Post-Treatment



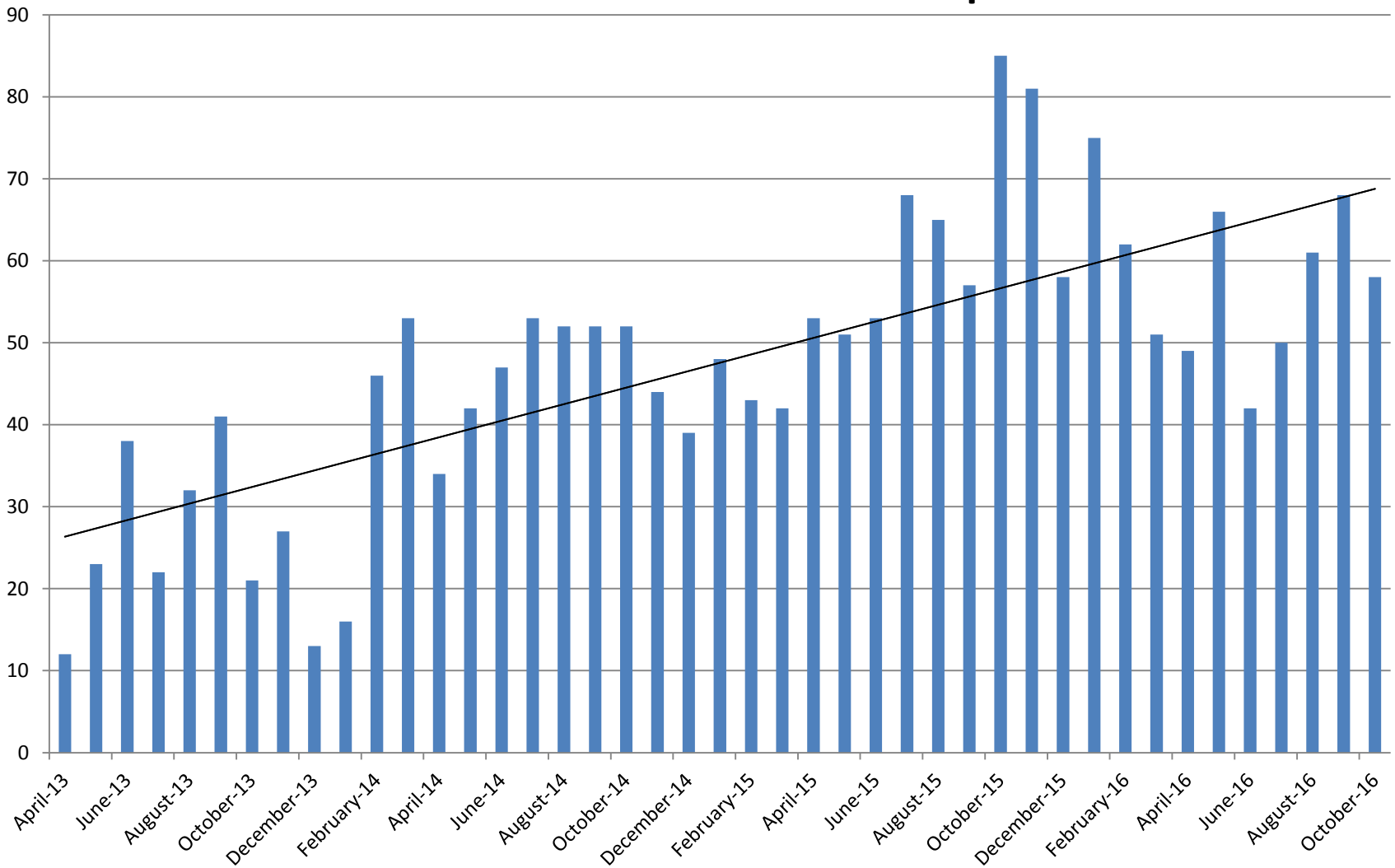

Off-label treatment is scheduled
Off-Label Medication Process: Commercial Payers
Off-label medication use is considered
Risk/benefit conversation (including payment risk) occurs with patient
Patient wishes to proceed with off-label medication use
Yes
No
RPh enters off-label medication use into off-label database
Submits pre-determination request to payer
Payer's decision is received
Approved
Not approved
.....OR.....
Payer will not consider pre-determination request
Submits appeal to payer and notifies Medication Assistance
Payer's decision is received
Approved
Not approved
Reviews evidence for off-label medication use
Sufficient evidence
Insufficient evidence
RPh escalates off-label request to disease-specific leader, division director, and pharmacy director
Approved
Not approved
Notifies provider and Medication Assistance
Explores manufacturer assistance/replacement options
Updates patient and readdresses risks/benefits
Clinical Team
Pre-Determination Team
Medication Assistance Coordinator
Managed Care
Chief Financial Officer
Financial Counseling
Alternative treatment options are discussed


Off-Label Medication Process: Commercial Payers (Continued)
Off-label treatment is scheduled
Alternative treatment options are discussed
Patient wishes to proceed with off-label medication use
Yes
No
Notifies Managed Care
Consults with payer to determine if contract allows billing patient if off-label medication is not covered due to being not medically necessary or experimental/ investigational
Payer's response is received
Approved
Not approved
Notifies chief financial officer
Determines appropriate amount for patient to deposit toward treatment costs prior to receiving off-label medication
Notifies provider of deposit amount
Communicates deposit amount to patient and readdresses risks/benefits
Patient wishes to proceed with off-label medication use
Yes
No
Obtains patient signature on notice of non-coverage and notifies Financial Counseling
Arranges payment for deposit
Clinical Team
Pre-Determination Team
Medication Assistance Coordinator
Managed Care
Chief Financial Officer
Financial Counseling

Education

- Begin education prior to release of policy
- Provide targeted education for all involved parties and clearly define roles
  - Include citations from
    - Social Security Act, Sec 1861(t)(1)- recognized compendia
    - Carriers Manual, Chapter 15, Section50.4.5.1
- On-board new pharmacist and provider staff
- Consider educational needs around ABN and NONC
  - Determine who delivers to patient and their needs
  - Ensure patient understanding through open-ended questions

Number of Off-label Requests



Off-Label Metrics

- Database entries:
  - Entries of 2,306 (Jan 2014-Nov 2016)
- Most requested agents:
  - Bevacizumab-297
  - Paclitaxel-296
  - Nivolumab-555
  - Rituximab-197
  - Carboplatin-199
- Payer:
  - Commercial (71%)
  - Medicare (18%)
  - Medicaid (10%)

Off-Label Metrics

- Database information
  - Medication
  - Diagnosis code
  - Insurance company
  - Time from submission to close
  - Healthcare providers involved
  - Diseases involved
  - Inpatient vs. outpatient
  - Bundled payment vs. fee-for-service
  - Total cost of drug
  - Status (i.e. approved, denied, no prior authorization required)

Challenges

- Physician buy-in
- Timing of application or signage of treatment plan in the electronic medical record
- Commercial payers can take up to 5-15 days to respond to predetermination request
  - Exceptions need to be made based on clinical situation
  - National Committee for Quality Assurance (NCQA) guidelines
    - Standard request
    - Expedited request

Challenges

- Communicating with payers
  - Need to be clear you are requesting approval for an OFF-LABEL use for cancer treatment
  - Need to state that you are calling about an intravenous infusion from an outpatient oncology clinic versus pharmacy benefit
  - Different requirements for approval (i.e. literature support)
  - Different insurance companies = different departments to contact
    - Medical Review, Case Management, Predetermination, etc.
  - Pre-D approval does not guarantee payment
  - Keep copies of all authorizations granted

Challenges

- Affecting change with payers
  - Internal payer medication policies often outdated
  - Develop reconsideration packet (for both commercial payer and Medicare) with evidence to support addition of covered diagnoses and/or regimens excluded from payer policies
- Successful and consistent communication back to clinicians and provider team

Tips for Success

- Education….early and often!!
- Designate ***dedicated*** staff to perform Pre-D
- Clinical experience necessary with knowledge of medical terminology, treatment plans, and payer-specific rules
  - Must have good resources at fingertips
- Collaboration between departments
- Timely communication of treatment plans
- Development of relationships with payer clinical teams and medical review personnel
- Share metrics and program impact with senior leaders

Patient Case – Off-Label Commercial Payer

- Request for rituximab 375mg/m2 weekly for 4-8 doses for immune thrombocytopenic purpura (ITP)
- Diagnosis code D69.3
- Insurance: The Healthplan
- Cost of therapy: $53,848
- Level of evidence:
  - Medicare LCD covered diagnosis
  - J Clin Oncol 21:1746-1751 (Phase II data)
  - No clinical coverage policy available for payer

Patient Case – Off-Label Commercial Payer

- Initial thoughts?
- Concern for reimbursement?
- Next steps?

Patient Case – Off-Label Commercial Payer

- Initial thoughts?-
  - Will this be covered since it is outside of the FDA label? Does payer have a coverage policy?
- Concern for reimbursement?
  - Phase II trial plus LCD support, but commercial plan with no coverage policy still a concern - PMAP support available?
- Next steps?
  - Submit a predetermination request

Patient Case – Off-Label Commercial Payer

- What we did:
  - Submitted a predetermination request with patient specific information and peer-reviewed literature support

- Final outcome:
  - Predetermination approved
  - Claims submitted for payment after approval of Pre-D

Patient Case – Off-Label Combination Commercial Payer

- Request for ipilimumab 10 mg/kg day 1 with dacarbazine 850 mg/m2 day 1 every 21 days for 2 cycles for malignant melanoma to liver
- Diagnosis code: C43.9
- Insurance: Ameriplan
- Cost of therapy: $97,473
  - Dacarbazine $78; Ipilimumab $97,395
- Level of evidence
  - Phase III data
  - FDA approval for single use, but not combination
  - Coverage policy for payer does not list combination

Patient Case – Off-Label Combination Commercial Payer

- Initial thoughts?
- Concern for reimbursement?
- Next steps?

Patient Case – Off-Label Combination Commercial Payer

- Initial thoughts?
  - Will combination therapy be reimbursed?
- Concern for reimbursement?
  - Will off-label combination therapy be considered a concern or will the medications be considered separately?
  - Coverage policy deems combination experimental and investigational without sufficient support (at that time)
- Next steps?
  - Submit a predetermination
  - Submit PMAP paperwork

Patient Case – Off-Label Combination Commercial Payer

- What we did:
  - Submitted a predetermination and enrolled the patient in the PMAP for appeals and Medication Assistance Program services
- Final outcome:
  - Predetermination denied for the ipilimumab and appeal submitted, but denial was upheld. Patient received free medication through the PMAP

Patient Case – Off-Label Combination Commercial Payer

- Request for combination of carfilzomib, dexamethasone, and cyclophosphamide for progressed multiple myeloma
- Diagnosis code: C90.0
- Insurance: United Healthcare
- Cost of therapy: $110,636
- Level of evidence: Combination not supported by NCCN

Patient Case – Off-Label Combination Commercial Payer

- Initial thoughts?
- Concern for reimbursement?
- Next Steps?

Patient Case – Off-Label Combination Commercial Payer

- Initial thoughts?
  - Carfilzomib and dexamethasone combination are NCCN approved (Level 2A) and the cyclophosphamide is oral and through the pharmacy benefit, therefore case should be approved without issues
- Concern for reimbursement?
  - None
- Next steps?
  - Submit a predetermination

Patient Case – Off-Label Combination Commercial Payer

- Final outcome
  - Received denial stating: Level of evidence did not warrant use of the oral cyclophosphamide (medical and pharmacy benefit are connected)
  - Peer-to-peer conducted with medical director
  - UHC follows the NCCN compendia and clinical guidelines
  - Regimen of the carfilzomib and dexamethasone changed to follow the ENDEAVOR trial (higher dose carfilzomib with dexamethasone, but no cyclophosphamide)
  - Authorization granted for therapy for one year

Patient Case – No Evidence Commercial Payer

- Request for pembrolizumab 2 mg/kg IV every 3 weeks for first-line metastatic melanoma to lung and lymph nodes. Patient has history of bowel perforation that prohibits use of ipilimumab
- Diagnosis codes: C43.9; C78.02
- Insurance: Anthem
- Cost of therapy: $88,046
- Level of evidence:
  - No available literature for use before failing ipilimumab (not approved for first-line at time of request)
  - No coverage policy published for payer

Patient Case – No Evidence Commercial Payer

- Initial thoughts?
- Concern for reimbursement?
- Next steps?

Patient Case – No Evidence Commercial Payer

- Initial thoughts?
  - New agent on the market and this is the first request after its launch- off-label
- Concern for reimbursement?
  - No published literature to support
  - No coverage policy
- Next steps?
  - Submit a predetermination
  - Submit PMAP paperwork

Patient Case – No Evidence Commercial Payer

- What we did:
  - Submitted a predetermination for the pembrolizumab
  - Enrolled the patient in PMAP services in the event of an insurance denial
- Final outcome:
  - Patient was denied predetermination based on the patient's GI risk. A peer-to-peer was completed and denied
  - PMAP was not available due to off-label, non-compendia supported diagnosis
  - Patient chose alternative therapy

Patient Case - Medicare

- Request for carfilzomib 20 mg/m2 for cycle 1 on days 1,2,8,9,15, and 16; carfilzomib 27 mg/m2 for cycle 2 on days 1,2,8,9,15, and 16 for multiple myeloma. Patient has not failed two lines of therapy. Patient cannot take lenalidomide due to inability to take oral medications
- Diagnosis code: C90.0
- Insurance: Original Medicare
- Cost of therapy: $34,553
- Level of evidence:
  - No FDA approval for sequence
  - Lack of LCD

Patient Case - Medicare

- Initial thoughts?
  - No formal LCD for Medicare Fiscal Intermediary
- Concern for reimbursement?
  - Off-sequence therapy (patient has not failed lenalidomide, but cannot take oral medications)
  - Do we need to have the patient sign an ABN?
- Next steps?
  - Request ABN signature
  - Seek approval from disease lead and division director

Patient Case - Medicare

- Initial thoughts?
- Concern for reimbursement?
- Next steps?

Patient Case - Medicare

- What we did
  - Verified the patient's Original Medicare, had the patient sign an ABN, enrolled the patient into the PMAP program, and sought division director authorization
  - Gained approval through peer-review process
- Final outcome
  - Medicare paid for claims

Patient Case – Medicare

- Request for bevacizumab 15 mg/kg on day 1 of each 21-day cycle (in conjunction with erlotinib 100 mg PO daily) for hepatocellular carcinoma
- Diagnosis code: C22.0
- Insurance: Original Medicare
- Cost of therapy: $205,329
- Level of evidence:
  - 2 phase II trials
  - Diagnosis not supported by Medicare LCD

Patient Case – Medicare

- Initial thoughts?
- Concern for reimbursement?
- Next steps?

Patient Case – Medicare

- Initial thoughts?
  - Diagnosis is outside the LCD
- Concern for reimbursement?
  - There are no third-line treatments available for HCC
  - Two phase II trials
- Next steps?
  - Request ABN signature
  - Submit PMAP paperwork

Patient Case – Medicare

- What we did:
  - ABN signed by the patient and the PMAP paperwork submitted

- Final outcome:
  - Claim denied and appealed at a first level appeal which was upheld by Medicare
  - Bevacizumab replaced through PMAP

Questions?