# Welcome!

# Please be seated by 7:55 am ET

## The teleconference will go live at 8:00 am ET

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# Assessment of Prevention, Diagnosis, and Treatment Options

## Advisory Panel Meeting

*November 16, 2016*

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# Welcome, Introductions, Overview of the Agenda, and Meeting Objectives

***David Hickam, MD, MPH***
*Program Director, PCORI, CER Methods*

***Yen-pin Chiang, PhD***
*Program Director (interim), PCORI, Clinical Effectiveness Research*

***Margaret F. Clayton, RN, PhD***
*Chair, Panel on the Assessment of Options*
*Associate Professor, College of Nursing and*
*Co-Director of the PhD Program, University of Utah*

# Housekeeping

- Today's teleconference is open to the public and is being recorded
  - Members of the public are invited to listen to this teleconference
  - Meeting materials can be found on the PCORI website
  - Comments may be submitted via email to advisorypanels@pcori.org; no public comment period is scheduled
- For those in the room, please remember to speak loudly and clearly into a microphone
- Where possible, we encourage you to avoid technical language in your discussion

# Panel Member Introductions

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# PCORI Staff


Yen-Pin Chiang, PhD


Diane Bild, MD, MPH


Anne Trontell, MD, MPH

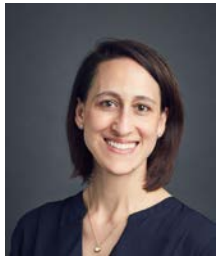

Stanley Ip, MD


Sarah Daugherty, PhD, MPH


Danielle Whicher, PhD, MHS


Layla Lavasani, PhD, MHS


Kim Bailey, MS


Laura Esmail, Phd, MSc


Holly Ramsawh, PhD


Jess Robb, MPH


Fatou Ceesay, MPH


Geeta Bhat, MPH


Katie Hughes, MA


Rebecca Barasky, MPH


Allison Ambrosio, MPH


Sarah Philbin, MPH


David Hickam, MD, MPH


Sandi Nayreau


Jillian Nowlin, MA


Jana-Lynn Louis, MPH

# Agenda Overview

| Time | Agenda Item |
|---|---|
| 8:00 – 8:45 am | Welcome, Introduction, Overview of the Agenda and Meeting Objectives |
| 8:45 – 8:50 am | Conflict of Interest Disclosure Forms |
| 8:50 – 9:20 am | Background and Status of Previous Topics |
| 9:20 – 9:30 am | Break |
| 9:30 – 10:45 am | Topic 1: Treatments for Asymptomatic Bacteriuria |
| 11:00a – 12:00 pm | Topic 2: Treatments for Non-Muscle Invasive Bladder Cancer |
| 12:00 – 12:45 pm | Lunch |
| 12:45 – 1:45 pm | Topic 3: Treatments for Pancreatic Ductal Adenocarcinoma (PDAC) and its subtypes |
| 1:45 – 2:00 pm | Break |
| 2:00 – 3:00 pm | Topic 4: Molecularly Directed Therapies for Lung, Pancreas, or Bladder Cancer |
| 3:00 – 3:05 pm | Announcements/Final Thoughts |
| 3:05 pm | Adjourn |

# Meeting Objective and Procedures

- Procedures for Reviewing Topics
  - Goal:
    - Provide a brief summary on the previous, current and upcoming research related to specific topics under consideration for funding
  - Tasks:
    - Identify and summarize the existing information related to the topics proposed by PCORI
    - Engage local expert stakeholders to provide input on information that cannot easily be observed in the published literature
    - Identify potential research questions based on the literature and expert input
  - 4 CER topics:
    - 10 minute introduction of topic
    - Approximately 1 hour of discussion per topic
    - Discussion will be moderated by one Program Officer and one Advisory Panelist

# Conflict of Interest Disclosure Forms

***Jayne P. Jordan***

*Special Assistant to the General Counsel*

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# Background and Status of Previous Topics

***Stanley Ip, MD***
*Associate Director, PCORI, Clinical Effectiveness Research*

***David Hickam, MD, MPH***
*Program Director, PCORI, CER Methods*

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# Status of 2016 CER Topics

| Topics | Status |
|---|---|
| *Comparative effectiveness of different treatment sequences for castrate resistant prostate cancer* | Inactive |
| *Examining effectiveness of 17P versus other progestogens to reduce risk of subsequent preterm birth* | IPD – Meta-analysis is being planned |
| *Comparative effectiveness of lifestyle changes, diet modification, behavioral interventions and phytotherapy on the clinical symptoms of BPH* | Inactive |
| *Comparative effectiveness of non-statins for treatment of patients with high cholesterol* | Stakeholder Workshop: 6/22/16 |
| *Comparative effectiveness of dietary manipulation and medications for the prevention of kidney stones* | Inactive |

# BREAK

**9:20 am – 9:30 am**

# Topic 1:

## *Comparative Effectiveness of Treatments for Asymptomatic Bacteriuria including Watchful Waiting*

Expert:
Geetika Sood, MD
*John Hopkins University Evidence-based Practice Center*

PCORI Lead:
Stanley Ip, MD

Advisory Panel Lead:
Daniel Wall, BS

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# General Approach

- Goal: Provide a brief summary on the previous, current and upcoming research related to specific topics under consideration for funding
- Tasks
  - Identify and summarize the existing information related to Asymptomatic Bacteriuria
  - Engage local expert stakeholders to provide input on information that cannot easily be observed in the published literature
  - Identify potential research questions based on the literature and expert input

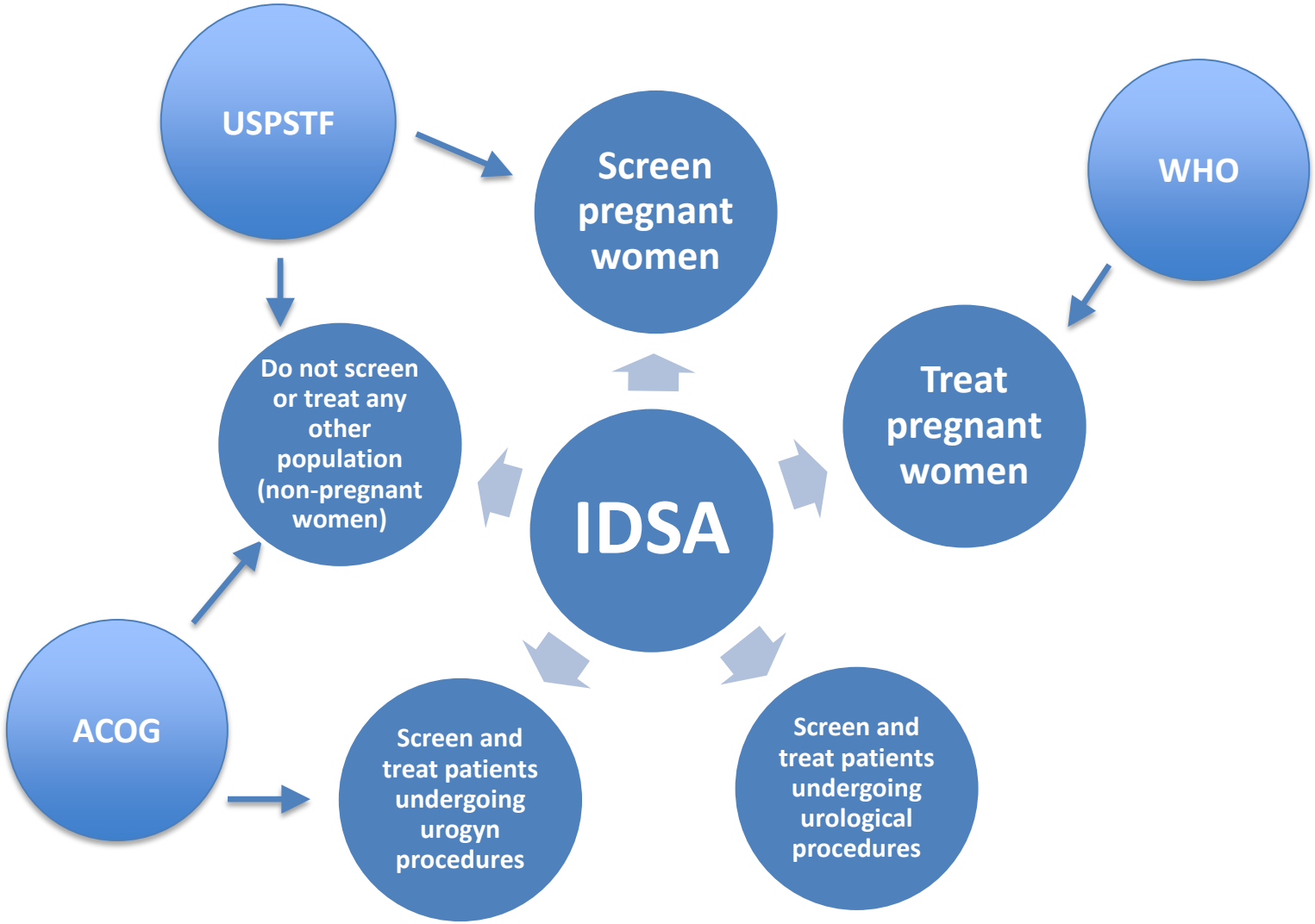
# Definition of Asymptomatic Bacteriuria

Asymptomatic bacteriuria occurs when specific bacteria are present in the urine without signs or symptoms of a urinary tract infection

# Guidelines for the Screening and Treatment of Asymptomatic Bacteriuria

- 2005 Infectious Diseases Society of America (IDSA)
- 2010 United States Preventive Services Task Force (USPSTF)
- 2016 World Health Organization (WHO)
- American College of Obstetricians and Gynecologists (ACOG)
  - Recommendations against screening non-pregnant women (Practice bulletin 2008)
  - Recommendations for screening and treatment during all urogynecologic procedures (Practice bulletin 2014)
- American Association of Family Physicians (AAFP) and American Urological Association (AUA) in line with IDSA

# Guidelines for the Screening and Treatment of Asymptomatic Bacteriuria



# Methodology

- **Literature Search**
  - Recent systematic reviews
    - Cochrane Database of Systematic Reviews,
    - Agency for Healthcare Research and Quality's website
    - PubMed
  - Practice guidelines, disease burden and impact of the condition on the population
    - Governmental entities (CDC, NIH, USPSTF, WHO, and NICE)
    - Professional associations and societies (IDSA, ACOG, and AAFP)

# Methodology

- Ongoing studies
  - ClinicalTrials.gov
  - NIH reporter
  - PCORI
- Input and guidance from Experts
  - Jenell Coleman, MD- Gynecology and Obstetrics
  - Geeta Sood, MD - Infectious Diseases
  - Eric Bass, MD, MPH - Internist and primary care physician

# Symptoms and Patient-Centered Outcomes

- By definition there are no symptoms of asymptomatic bacteriuria
- However, urinary tract infections (symptomatic bacteriuria) have non-specific symptoms
  - It can be difficult to distinguish between urinary tract infections and asymptomatic bacteriuria in some populations
    - Elderly
    - Impaired cognition
    - Comorbidity (masking symptoms)

# Patient-Centered Outcomes

- Patients who test positive for asymptomatic bacteriuria who are not offered treatment with antibiotics may worry about the lack of treatment. Most people in the U.S. are familiar with antibiotics and consider them to be safe.
- The social, economic and political implications of antibiotic treatment and microbial resistance are growing in importance at the national and international level
- Despite recommendations against antibiotic treatment for asymptomatic bacteriuria in non-pregnant women, clinicians are still prescribing antibiotics against the guidelines and the inappropriate prescribing has risks

- Diabetes mellitus
- Elderly patients
- Inpatients
- Long-term facilities

- Incorrect prescriptions
- Rising costs
- Infections with *Clostridium difficile*
- Multi-drug resistant organisms

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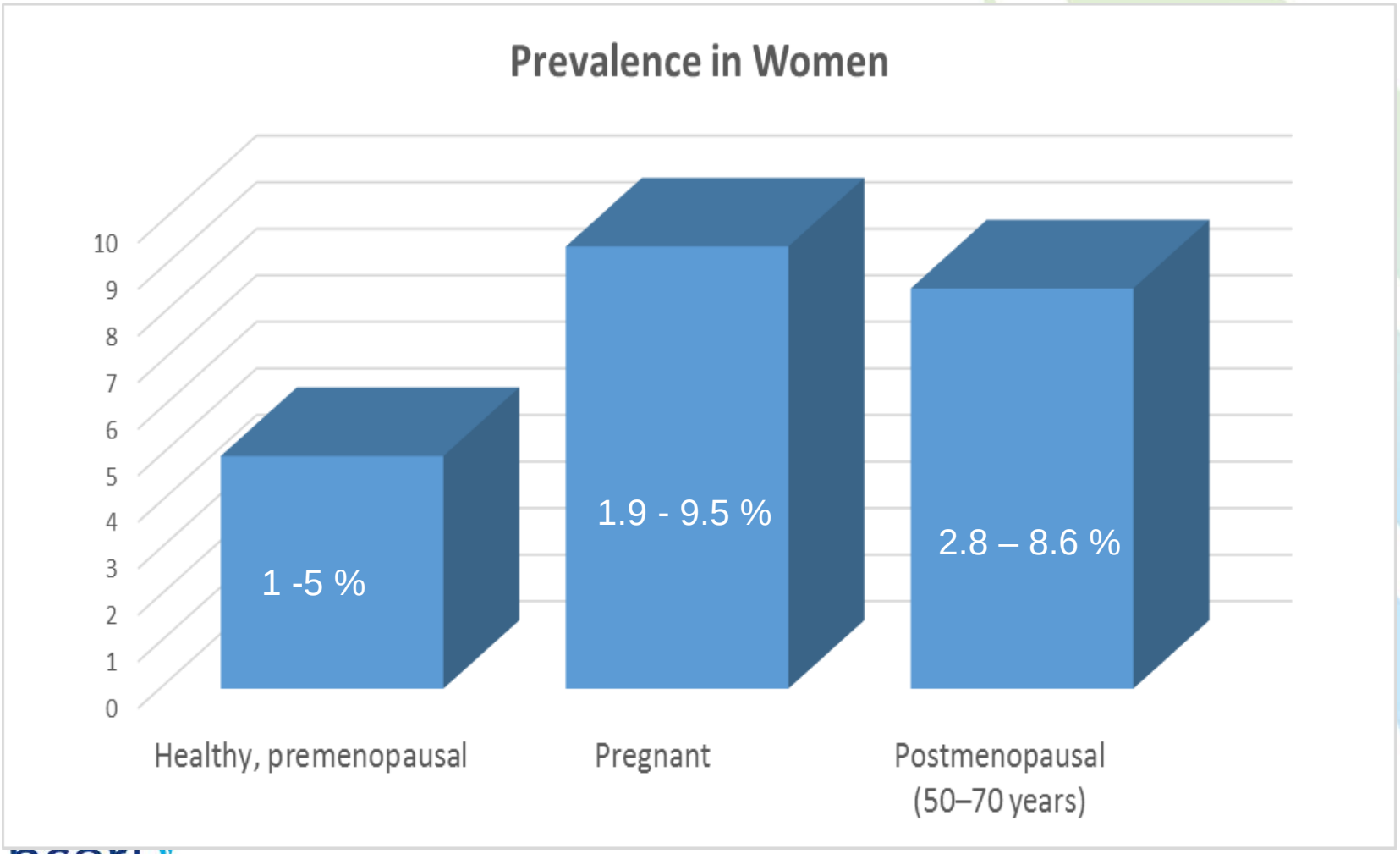
# Prevalence of Asymptomatic Bacteriuria in the US

**Nicolle, 2005**



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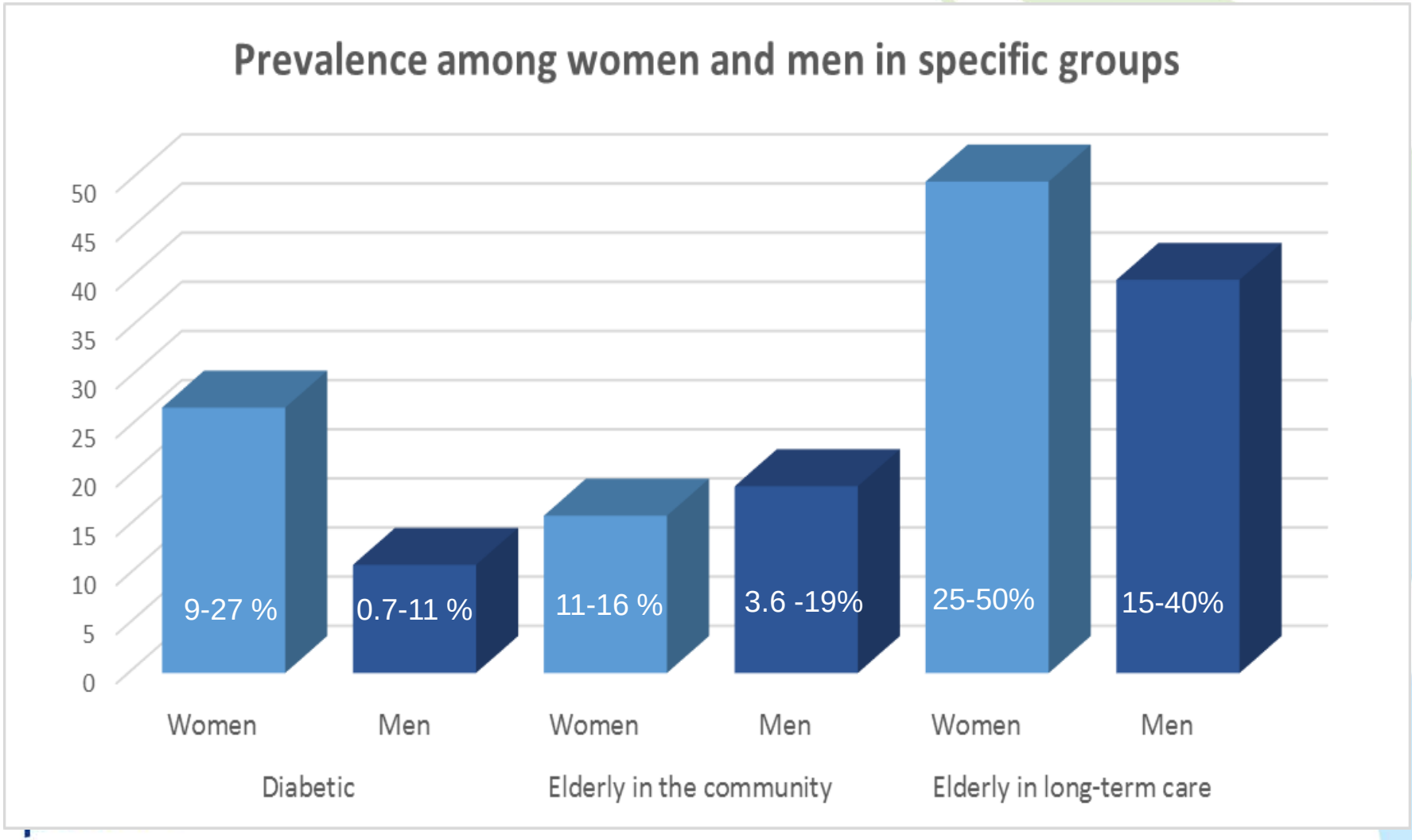

# Prevalence of Asymptomatic Bacteriuria in the US

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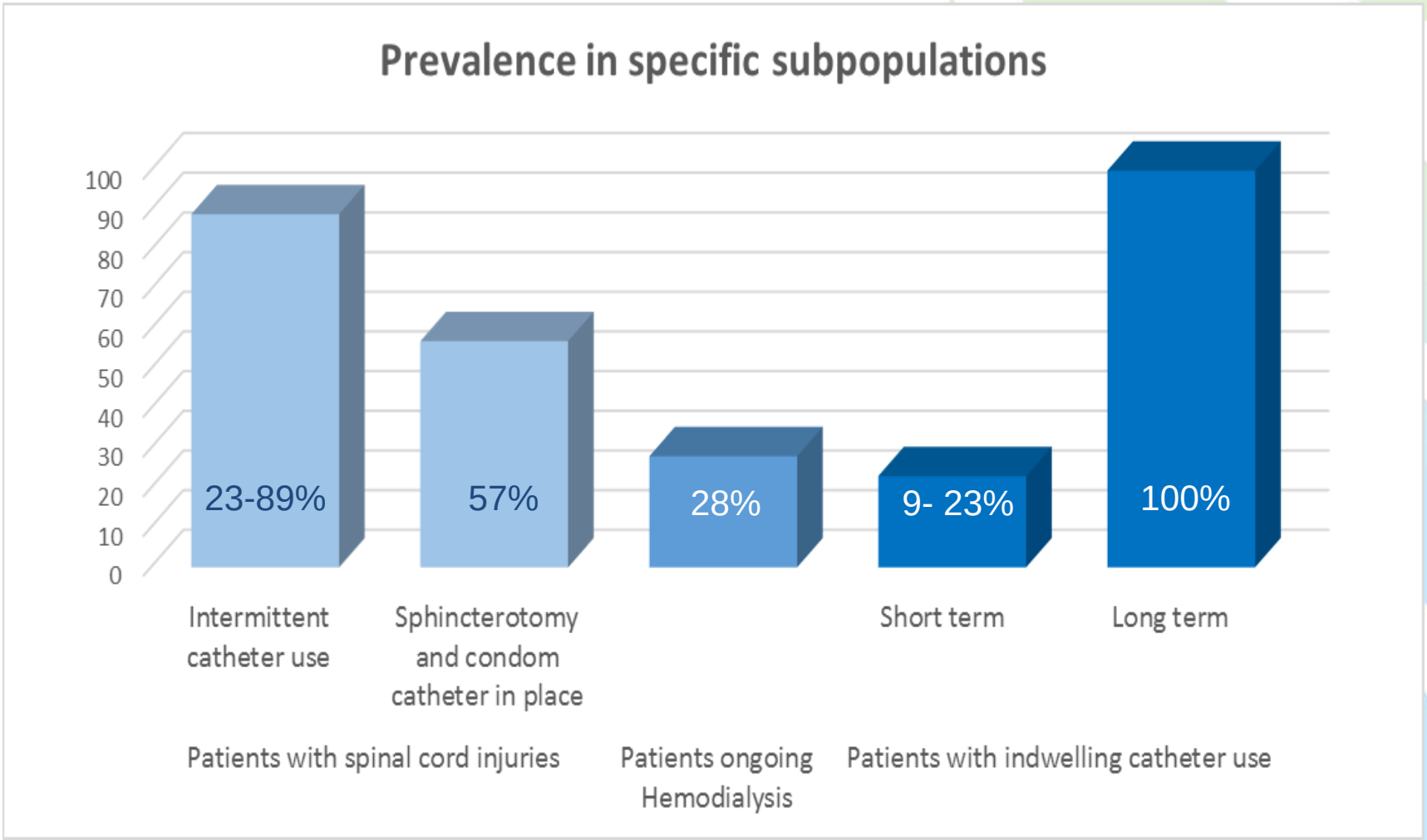
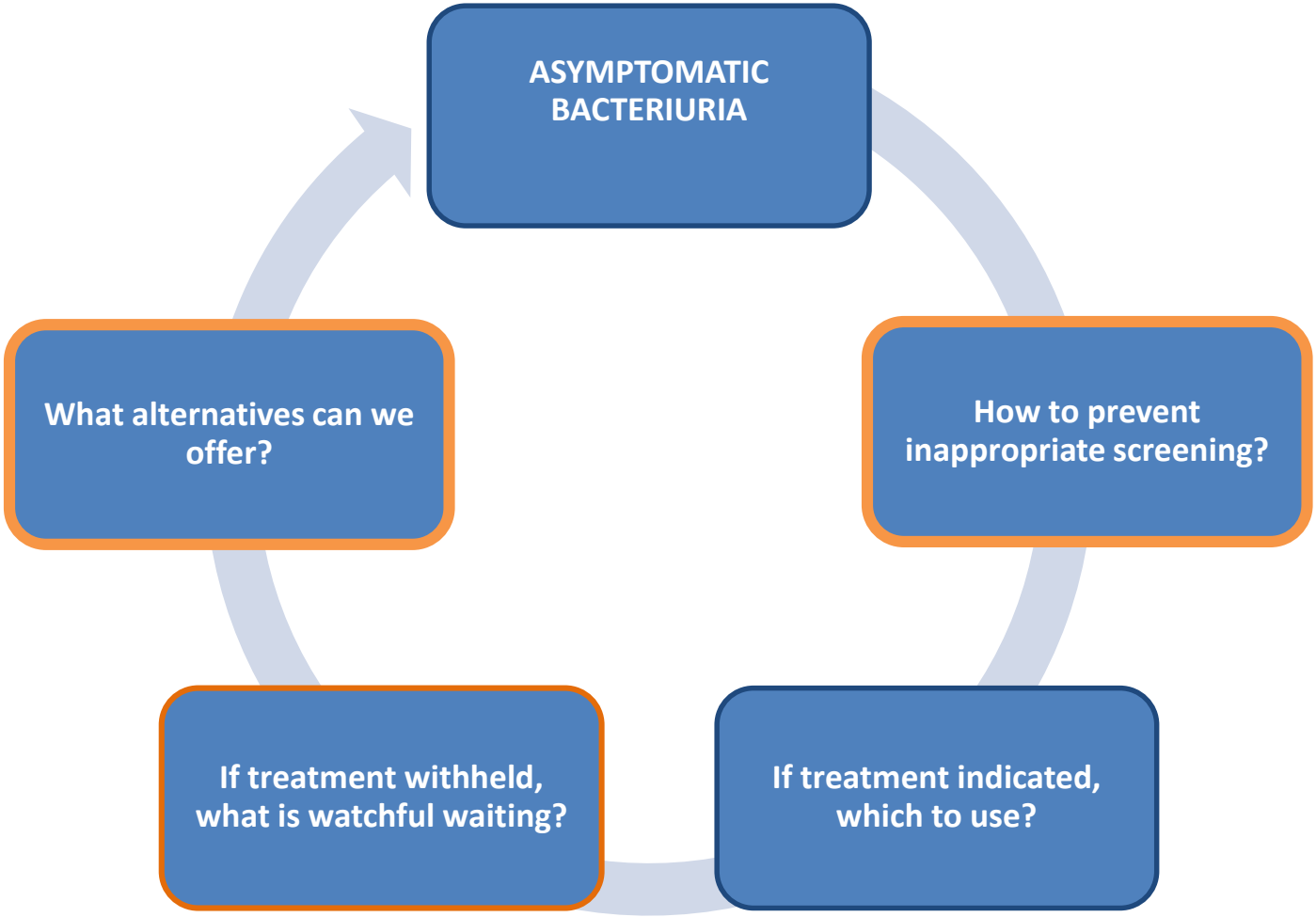


# Evidence Gaps



# Ongoing Research

## ClinicalTrials.gov

We identified 29 studies. 15 studies were relevant

- One study on guideline adherence: patients had less screening but rates of treatment did not change (NCT01052545)
- One study modified laboratory reports: scheduled for completion in December 2016
- Six studies in transplant recipients compare antibiotics versus no treatment
  - Only one has results: NCT02373085- no difference in any outcome
- Four studies on alternatives to antibiotics
  - Only one has results: NCT00506025 - no benefit seen with cranberry extract
- Three studies on rates of UTI and asymptomatic bacteriuria in specific populations (hemodialysis patients, patients undergoing cardiac surgery, and patients with intermittent catheterization): none with results

# NCT01052545: Asymptomatic Bacteriuria Guideline Implementation Study(VA Healthcare System)

## Purpose:

- To bring clinical practice in line with published guidelines.
- To reduce unnecessary antibiotic use for asymptomatic bacteriuria.
- To improve the quality and safety and provide insight on how to implement and sustain evidence-based clinical practice.

## Intervention:

- Personalized audit-feedback versus distributing copies of guidelines.

## Results (after 3 years):

- Successfully decreased inappropriate screening
- Decreased Asymptomatic Bacteriuria overtreatment (not statistically significant)
- No difference in under treatment

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# Ongoing Research

## NIH Reporter

- One trial to test dissemination of a toolkit to improve prescribing of antibiotics in the setting of suspected urinary tract infections
- Career development  to study the transition from asymptomatic bacteriuria to urinary tract infection
- Core grant to identify metabolomic biomarkers of high-risk bacteriuria in hospitalized patients
- Study to profile the metagenome, metaproteome and metabolome of catheter-associated biofilms and dispersed bacterial aggregates from clinical cases in a longitudinal study

## AHRQ

- Funding in place for antimicrobial stewardship programs related to the President's National Strategy for Combating Antibiotic Resistant Bacteria (CARB)

# Likelihood of Implementing Research Results in Practice & Durability of Funded Research

- Research results are likely to be incorporated into practice
  - Urgent need to decrease unnecessary antibiotic use
- Results are likely to remain relevant
  - Antimicrobial resistance is a recognized problem in healthcare facilities
  - Overtreatment has a recognized economic and ecologic toll

# Potential Research Questions

- What are the benefits and harms of using the Loeb criteria (or a similar algorithm) to create a treatment decision tool?
- What does watchful waiting entail?
  - What is the most effective approach to communicating with patients about how to watch for relevant symptoms?
- What are the outcomes of screening and treatment prior to urologic procedures versus no screening?
- Is there a need to rethink the use of broad spectrum versus targeted antibiotics or alternate treatments to treat asymptomatic bacteriuria?
  - What is the comparative effectiveness and safety of broad spectrum vs. targeted antibiotics for asymptomatic bacteriuria?
- What is the best way to communicate the decision to not treat asymptomatic bacteriuria to patients?

# Discussion Reminders

1. Consider the topic with respect to the following:
   a) Patient-centeredness
   b) Impact
   c) Important evidence gap
   d) Likelihood of implementation in clinical practice
   e) Durability of information
2. Are there contextual issues that would hinder or facilitate the research?
3. How important is this topic for PCORI to pursue to fund CER?

*source: http://www.pcori.org/research-results/how-we-select-research-topics/generation-and-prioritization-topics-funding-4*

# Topic 2:

## *Treatment of patients with non-muscle invasive bladder cancer*

Expert:
David I. Buckley MD, MPH
Roger Chou MD, FACP
*Pacific Northwest Evidence-based Practice Center*

PCORI Lead:
Stanley IP, MD

Advisory Panel Lead:
Angie Smith, MD, MS

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# Introduction

## Non-Muscle-Invasive Bladder Cancer (NMIBC)

- Bladder cancer: 4th most common cancer in men; 10th in women
- Approx. 75% of newly diagnosed are NMIBC
- NMIBC have not invaded smooth muscle layer (Tis; Ta; T1)
- Five-year survival > 88% (c/w muscle-invasive: 63% to 15%)
- Likelihood of recurrence or progression to MIBC depends on various factors, including: cancer stage, tumor grade, number, size, initial vs. recurrent; patient's age and general health

# Introduction

**Treatment:**

- Main treatment: transurethral resection of bladder tumor (TURBT)
- Adjuvant intravesical therapy: BCG; various chemotherapy agents; or interferon immunotherapy
- Radical cystectomy option when high risk of progression to MIBC

**Relevant patient-centered outcomes:**

- Mortality; need for cystectomy; progression to MIBC; recurrence; quality of life

# Burden on Society

- **Incidence and Prevalence**
  - ACS estimates 76,960 new cases of bladder cancer in US in 2016 (58,950 in men; 18,010 in women)
  - Bladder cancer represents ~ 5% of all incident cancers in US
  - Lifetime probability: 3.8% in men; 1.2% in women
  - Primarily in people age 55 and older; Approximately twice as common in whites compared with African Americans or Hispanic Americans
- **Economic:** costliest cancer to treat per capita, accounting for diagnostic testing, management, & long-term follow-up

# Burden on Society

## Effects on Patients

- TURBT: dysuria and/or hematuria for 1 to 2 weeks; repeat may cause scarring with urinary frequency or incontinence
- Intravesical treatment: cystitis, urinary frequency, dysuria (pain with urination), hematuria (blood in urine), bladder pain, or flu-like symptoms (e.g., fever, chills, and fatigue)
- Induction course: once/week for 6 weeks; hold solution in bladder for 1 to 2 hours
- Maintenance therapy: duration varies, commonly for 1 year or longer; frequency varies, commonly once/month (MMC) or every 3 to 6 months (BCG)

# Burden on Society

## Effects on Patients (con't)

- After initial treatment, surveillance cystoscopy typically done every 3 to 6 months for at least 2 years, often indefinitely
- Some high risk patients have surveillance cytology and upper tract imaging
- Radical cystectomy may have profound adverse effects on functional capacity and quality of life, some due to urinary diversion and urostomy
- Urinary diversion and urostomy may lead to infections, urine leaks, pouch stones, and/or blockage of urine flow
- Radical cystectomy and/or urostomy may have adverse sexual effects

# Risk Stratification

## Risk Stratification and Predicting Recurrence or Progression

- "EORTC" and "CUETO" risk assessment tools
- Discrimination (how well a risk assessment method separates persons with from those without an outcome)
  - Recurrence: poor to fair
  - Progression: fair to good
- No study evaluated clinical outcomes associated with use of a formal risk assessment tool in a risk-adapted approach to treatment of NMIBC versus other approaches

# Risk Stratification

## AUA/SUO Guideline Risk Stratification System

- Categorizes risk of recurrence and/or progression of NMIBC as ‘low’, ‘intermediate’, or ‘high’
- Meant for use in clinical practice for guiding patient counseling and treatment decisions
- Includes consideration of patient’s prior treatment with BCG
- Based on panel members’ consensus – not on meta-analyses or original data – and the panel recognized the need for validation of the model’s performance

# Risk Stratification

## AUA Risk Stratification for Non-Muscle Invasive Bladder Cancer

| Low Risk | Intermediate Risk | High Risk |
|---|---|---|
| LG[a] solitary Ta ≤ 3cm | Recurrence within 1 year, LG Ta | HG T1 |
| PUNLMP[b] | Solitary LG Ta > 3cm | Any recurrent, HG Ta |
| | LG Ta, multifocal | HG Ta, >3cm (or multifocal) |
| | HG[c] Ta, ≤ 3cm | Any CIS[d] |
| | LG T1 | Any BCG failure in HG patient |
| | | Any variant histology |
| | | Any LVI[e] |
| | | Any HG prostatic urethral involvement |

[a]LG = low grade; [b]PUNLMP = papillary urothelial neoplasm of low malignant potential; [c]HG = high grade; [d]CIS=carcinoma *in situ*; [e]LVI = lymphovascular invasion

Reprinted from: Chang SS, Boorjian SA, Chou R, et al. *Diagnosis and Treatment of Non-Muscle Invasive Bladder Cancer: AUA/SUO Guideline.* 2016.

# Options for Addressing the Issue

A recent systematic review commissioned by AHRQ and associated supplement commissioned by AUA addressed various active questions related to the comparative effectiveness of treatments for NMIBC:

- Intravesical immunotherapy or chemotherapy
  - Comparative effectiveness
  - Treatment frequency and duration
  - Patient and tumor characteristics
- Fluorescent cystoscopy
- Treatment for recurrence or persistence after intravesical therapy

# Options for Addressing the Issue

## Adjuvant Intravesical Therapy

| Relative risk of *recurrence* of NMIBC versus no intravesical therapy | | | |
|---|---|---|---|
| Intravesical Agent | Number of trials | RR (95% CI) | Strength of Evidence |
| BCG | 3 | 0.56 (0.43 to 0.71) | low |
| Mitomycin C | 8 | 0.71 (0.57 to 0.89) | moderate |
| Doxorubicin | 10 | 0.80 (0.72 to 0.88) | moderate |
| Epirubicin | 9 | 0.63 (0.53 to 0.75) | moderate |

# Options for Addressing the Issue

## Adjuvant Intravesical Therapy

- Only BCG was associated with reduced risk for ***progression*** (4 trials; RR 0.39; 95% CI, 0.24 to 0.64; SOE: low)
- No agent was associated with decreased risk of all-cause or bladder cancer specific ***mortality***
- Head-to-head trials of intravesical therapy using different drugs showed few clear differences

## Adverse Effects

- BCG: local and systemic effects relatively common (SOE: low)
- Few trials reported on other intravesical agents

# Options for Addressing the Issue

## Treatment Frequency and Duration (intravesical therapy)

- Single installation (with TURBT) vs. TURBT alone reduced risk of ***recurrence*** (15 trials; RR 0.74; 95% CI, 0.64 to 0.86; SOE: moderate); No clear effects on ***progression*** or ***mortality***
- Limited evidence that BCG maintenance (> 6 weeks) is more effective than induction (≤ 6 weeks) at reducing ***recurrence*** in patients with higher risk NMIBC
- Evidence limited and inconclusive on maintenance vs. induction with other agents

# Options for Addressing the Issue

## Patient and Tumor Characteristics (intravesical therapy)

- No trial evaluated how effectiveness may vary in subgroups defined by patient characteristics such as age, sex, race/ethnicity, performance status, and comorbidities

- No clear differences in effectiveness in subgroups defined by tumor stage, tumor grade, tumor size, number of tumors, recurrence status, or DNA characteristics (SOE: low)

# Options for Addressing the Issue

## Fluorescent Cystoscopy

- Enhances visualization of tumors and may improve resection
- Associated with decreased ***recurrence*** (SOE: moderate); non-statistically significant decreased ***progression*** (SOE: low); but no association with ***mortality***
- Findings inconsistent; Potential publication and methodological bias (surgeons not easily blinded to use of fluorescence)

## Recurrence or persistence after intravesical therapy

- Evidence on treatment for recurrence or progression after induction intravesical therapy is sparse (2 trials inconclusive)

# Potential Benefits of New Information

- New research that evaluates and validates the accuracy of risk-adapted approaches in predicting recurrence and progression of NMIBC could help to achieve better patient-centered outcomes
- Head-to-head trials of intravesical therapies that use more standardized instillation regimens and doses, report outcomes in subgroups by patient and tumor characteristics, and include more long-term outcomes related to progression and mortality would help clarify optimal treatment strategies, including optimal dosing and duration

# Potential Benefits of New Information

- New research into optimal treatment strategies after failure of first-line intravesical therapy with BCG or other agents could help to improve patient outcomes. This research should assess the comparative effectiveness of various intravesical agents, cystectomy or bladder-preserving alternatives to cystectomy, and/or novel agents

- Recent guidelines – based on limited evidence – recommend considering *initial* radical cystectomy for high-risk patients. New randomized trials that compare initial cystectomy with intravesical therapy or other bladder-preserving therapies for high risk NMIBC could provide needed information to inform treatment decisions

# Potential Benefits of New Information

- More research is needed to understand effects of fluorescent cystoscopy on risk of bladder cancer progression and mortality
- Cystoscopy, bladder tumor resection, intravesical therapy, and cystectomy are each associated with discomfort and possible adverse effects. New research into approaches that might reduce discomfort and/or adverse effects could improve patient-centered outcomes

# Conclusions

**New research could provide better evidence particularly for:**

- The accuracy and value of formal risk-adapted approaches to treatment decisions
- The comparative effectiveness of various treatments for persistent or recurrent disease after intravesical therapy with BCG or other agents
- The comparative effectiveness of initial cystectomy in patients with high-risk NMIBC
- The comparative effectiveness of enhanced cystoscopy techniques such as fluorescent cystoscopy
- Approaches for reducing discomfort and adverse effects associated with treatments for NMIBC

# Discussion Reminders

1. Consider the topic with respect to the following:
   a) Patient-centeredness
   b) Impact
   c) Important evidence gap
   d) Likelihood of implementation in clinical practice
   e) Durability of information
2. Are there contextual issues that would hinder or facilitate the research?
3. How important is this topic for PCORI to pursue to fund CER?

*source: http://www.pcori.org/research-results/how-we-select-research-topics/generation-and-prioritization-topics-funding-4*

# LUNCH

**12:00 pm – 12:45 pm**

# Topic 3:

## *Comparative effectiveness of treatments of patients with pancreatic ductal adenocarcinoma (PDAC) and its subtypes*

Expert:
Remy Coeytaux, MD, PhD
*Duke University*

PCORI Lead:
Sarah Daugherty, PhD, MPH

Advisory Panel Lead:
Felix Fernandez, MD, MSc

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# Overview

- How we developed this topic brief
- The pancreas and pancreatic cancer
- Key uncertainties in clinical decision making
- Results of our scan of the published literature
- Conclusions
- Discussion

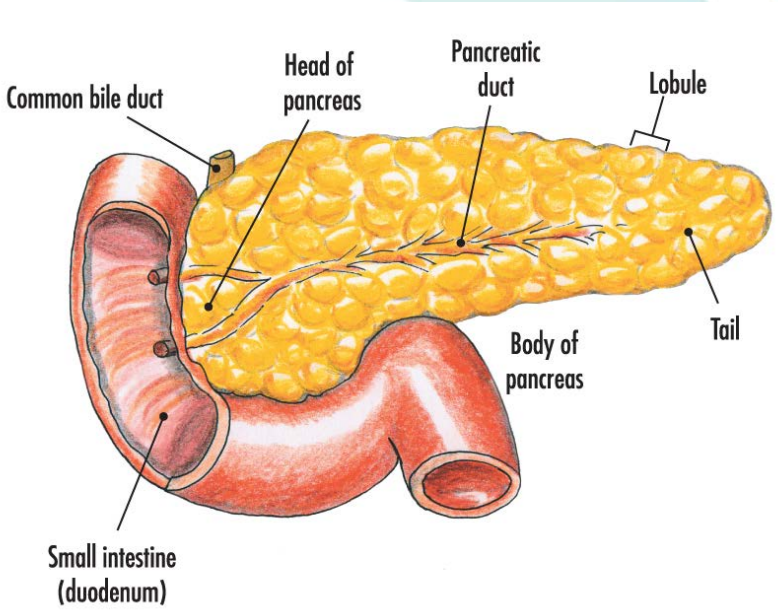
# Topic Brief: Methods

- The Duke Evidence-based Practice team searched PUBMED and ClinicalTrials.gov for published and ongoing RCTs and systematic reviews of treatments for PDAC
- Focus was on treatment and not screening or early detection strategies
- Our content expert is James Abbruzzese MD, Chief of the Duke Division of Medical Oncology. Dr. Abbruzzese serves as Chair of the NCI Pancreatic Ductal Adenocarcinoma Progress Working Group

# The Pancreas

- The pancreas is an organ located in the upper left upper quadrant of the abdomen.

- The pancreas has both exocrine and endocrine functions
  - Exocrine: Releases digestive enzymes into the small intestine
  - Endocrine: Produces/releases the bloodstream



# Pancreatic Cancer Types

- Most (>95%) neoplasms of the pancreas arise from exocrine tissues
- Pancreatic adenocarcinoma (PDAC) arise from ductal cells or from acinar cells that undergo acinar-to-ductal metaplasia
- PDAC represents ~85% of all pancreatic cancers
- For the purpose of this Topic Brief, we focus exclusively on exocrine cancers, with a primary focus on PDAC

# Epidemiology

- **Prevalence:** About 50,000 people in the U.S. with PDAC
- **Incidence**: Also 50,000 new cases per year in the U.S.
- **Trends:** Incidence increasing by 0.6% each year in the last 10 years
- **Risk factors:** Increasing age, family history, obesity, diabetes, presence of DNA repair defects (eg, PALB2, ATM, BRCA 1/2)

# Mortality

- The 5-year survival rate of PDAC (<8%) is among the lowest of all cancers
- PDAC is the third leading cause of cancer death in the U.S. (after lung and colon cancer)
- PDAC expected to become the second leading cause of cancer death by 2030, largely because of increasing incidence with no discernable improvement in prognosis over the past 10 years

# Symptoms

- The most common symptoms associated with PDAC are:
  - Abdominal or back pain
  - Weight loss
  - Anorexia (loss of appetite)
  - Nausea
  - Fatigue
- Patients who present with pain and weight loss typically have more advanced disease and demonstrate shorter survival
- The frequency of thromboembolic events in pancreatic cancer is very high

# Quality of Life and Costs of Treatment

- PDAC is typically associated with debilitating symptoms, followed by death within months or a few years after diagnosis
- All of the most common symptoms associated with PDAC (pain, weight loss, anorexia, nausea, etc.) have a profound impact on patient quality of life.
- Once patients are diagnosed with pancreatic cancer, they are generally no longer able to work
- Cost of treatment for pancreatic cancer among Medicare beneficiaries in 2012 estimated to be $65,000 per patient

# Diagnosis

- At the time of diagnosis with PDAC, about 30% of patients have locally advanced disease and over 50% have metastases at distant sites
- Diagnosis is usually by imaging studies (eg, ultrasound, MRI, or CT)

# Screening

- Genomic sequencing data from primary and metastatic PDACs indicate that it takes approximately 17 years for PDAC to progress from the tumor-initiating cell to the development of metastatic disease
- This suggests that there is ample time to diagnose and intervene, if diagnostic barriers to earlier detection could be overcome
- However, it is not yet known if early diagnosis would improve clinical outcomes, given current treatment options

# Screening and Early Diagnosis

- Screening tests include ultrasound, MRI, CT, biomarkers
- No current test is feasible and reliable for screening
- A 2004 US Preventative Services Task Force (USPSTF) report did not recommend screening for PDAC in the general population
- In 2012, the International Cancer of the Pancreas Screening (CAPS) Consortium recommended screening of patients with increased risk of familial pancreatic cancer
- A 2014 AHRQ systematic review did not find evidence to support the relative effectiveness of any given imaging test for screening of asymptomatic high-risk individuals

# Treatment Options

- Most treatment options fall into one of the following categories:
  - Surgery
  - Radiation therapy
  - Chemotherapy
  - Chemoradiation therapy
  - Targeted therapy (e.g., tyrosine kinase inhibitors such as erlotinib)
- There are also investigational approaches, including biologic therapy, stromal disruption, immunotherapy; and novel targeted therapies
- Treatment broadly varies by stage, and for earlier stage cancers combined modality treatment is generally used:
  - Potentially resectable cancers – surgery and chemotherapy/chemoradiation
  - Locally advanced cancers – chemotherapy and chemoradiation
  - Metastatic – chemotherapy

# Surgery

- Currently, surgery (pancreaticoduodenectomy) provides the only possible curative therapy for PDAC, but less than 20% of patients are suitable candidates for this difficult procedure because the disease has already spread
- Overall, surgery produces long-term, disease-free survival in only 3-4% of all individuals presenting with this disease—generally in patients with “early” PDAC (i.e., tumors $\leq$ 20 mm) and without tumor involvement in the surgical margins at resection

# Treatment with Drugs

- Drugs with FDA approval for the treatment of pancreatic cancer are:
  - erlotinib
  - fluorouracil
  - gemcitabine
  - irinotecan hydrochloride liposome
  - mitomycin C
  - Paclitaxel albumin-stabilized nanoparticle formulation
- Generally the single agents have only modest activity as judged by tumor regression; the best results are with combinations of 5FU/Irinotecan/Oxaliplatin or Gemcitabine/Nab-paclitaxel and with these agents the median improvement in overall survival is measured at 2-3 months

# Recent Innovations: PDAC Subtypes

- There have been recent innovations in the understanding of the biology of PDAC and its various subtypes
- Recently published expression analysis of 456 PDACs defined 4 subtypes: (1) squamous; (2) pancreatic progenitor; (3) immunogenic; and (4) aberrantly differentiated endocrine exocrine (ADEX)
- This recent understanding of the molecular evolution of pancreatic cancer subtypes provides potential new opportunities for therapeutic intervention

# Key Uncertainties in Clinical Decision Making

- Optimal front-line chemotherapy for patients with PDAC without co-morbidities
- Management of pain, anorexia, weight loss and other symptoms associated with PDAC
- Optimal nutrition for patients with PDAC
- Optimal management of patients with resectable or borderline resectable PDAC
- Optimal sequences of therapies, e.g., neo-adjuvant therapy vs. adjuvant therapy for patients with resectable cancer
- Role of screening in early detection, such as who and how to screen
- Role of prophylactic anti-thrombotic therapy

# Result: Randomized Controlled Trials

- Within PubMed (2011-present), we identified 12 relevant RCTs that evaluated treatment strategies for pancreatic cancer
- Study interventions included: gemcitabine; mycobacterium obuense, nanoliposomal irinotecan; fluorouracil and folinic acid; masitinib, adjuvant intra-arterial chemotherapy; surgery; ethanol celiac plexus neurolysis (ECPN); sunitinib; sequential GV1001 chemoimmunotherapy; CO-101 (a lipid-drug conjugate of gemcitabine); and induction chemoradiation vs. induction gemcitabine.

# Results: Randomized Controlled Trials

The available RCTs highlight both the lack of effectiveness of many studied treatments and for those treatments demonstrating benefit, the need for confirmatory studies of these findings through larger high-quality CERs which assess a broader area of important patient-centered outcomes

# Results: Systematic Reviews

- Within PubMed (2011-present), we identified 10 relevant Systematic Reviews that evaluated treatment strategies for pancreatic cancer (Table 2 in Topic Brief)
- The systematic reviews synthesized evidence about a variety of treatments in specific subgroups of interest but all emphasized the scarcity of data from large multi-center randomized clinical trials and the need for additional CER

# Results: Ongoing Trials

- A review of treatment-related trials registered in ClinicalTrials.gov during the period 2011 to the present identified 71 trials that evaluated 1 or more interventions for pancreatic cancer (primarily PDAC)
- Of the 71 treatment trials, 55 were identified by the study investigators as Phase 1 or 2 trials, and three were identified as Phase 3 RCTs
- The study drugs and target sample size of these 3 Phase 3 RCTs, all of which are ongoing, are:
  - mFolfirinox vs. adjuvant therapy (N=490)
  - PEGylated Recombinant Human Hyaluronidase vs. placebo (N=420)
  - Momelotinib vs. placebo (N=25)

# Study Outcomes

With one exception, none of the published or ongoing trials we identified appear to have symptom reduction or health-related quality of life as primary or secondary outcomes

# New, Large Trial in Preparation

- The Pancreatic Cancer Action Network (https://www.pancan.org/research/precision-promise/) is sponsoring Precision Promise, which is a large-scale precision medicine trial for patients with pancreatic cancer. The trial will start enrolling in Spring 2017 and 12 clinical trial consortium sites are involved. The goal of Precision Promise is to double pancreatic cancer survival by 2020. This initiative will investigate multiple treatment options under one clinical trial design. DNA damage repair defects, stromal disruption, and immunotherapy are the first treatment strategies to be evaluated. Future sub-studies may evaluate newly discovered biomarkers and treatment approaches.

# Conclusions

- Pancreatic cancer is a deadly disease for which treatment options are limited in their number and effectiveness in terms of patient survival and alleviation of symptoms
- Recent evidence suggests potential benefit from screening high-risk populations, but currently there is little evidence to support early detection strategies for the general population
- There is ongoing research that is contributing to the understanding of the biology and pathophysiology of various PDAC subtypes, but this new understanding has not yet translated to more effective treatment options

# Conclusions

- There are many uncertainties in clinical decision making, including:
  - role of screening in early detection
  - optimal front-line therapies for different PDAC subtypes or different clinical presentations
  - optimal sequences of therapies for patients with resectable cancer
  - effective symptomatic management
  - optimal nutrition
  - the role of prophylactic anti-thrombotic therapy

# Conclusions

- There is a paucity of good-quality RCTs that evaluate the effectiveness of emerging therapeutic strategies on survival, or that evaluate the effectiveness of therapeutic strategies for symptoms of pancreatic cancer and other patient-centered outcomes
- In the absence of high-quality RCTs evaluating emerging therapeutic strategies, opportunities for comparing known effective treatments may be limited
- However, given existing treatment options, CER could be helpful to sort out the optimal approach to patients with resectable pancreatic cancer and the optimal strategies for palliation of cancer-related symptoms such as pain, weight loss/cachexia, fatigue

# Conclusions

- Given the limited effectiveness of available treatments and screening strategies, there is a high likelihood that appropriately designed CER studies which targeted identified uncertainties and demonstrated safe and effective strategies would be well received and impact patient care and clinical practice
- Significant advancements in the treatment of PDAC may require a two-pronged approach that includes research on both early detection and treatment strategies
- Future research should be designed with the knowledge of the Precision Promise research initiative sponsored by the Pancreatic Cancer Action Network

# Questions for Consideration

1. What is the key evidence gap related to the treatment of PDAC that CER could address?
2. What patient centered outcomes are missing with respect to the treatment and/or palliation options for PDAC?
3. Given the limited efficacy demonstrated by new treatments for PDAC in early trials, is CER of treatment options for PDAC a point of emphasis? Are other domains related to PDAC more ready for CER?

# Discussion Reminders

1. Consider the topic with respect to the following:
   a) Patient-centeredness
   b) Impact
   c) Important evidence gap
   d) Likelihood of implementation in clinical practice
   e) Durability of information
2. Are there contextual issues that would hinder or facilitate the research?
3. How important is this topic for PCORI to pursue to fund CER?

*source: http://www.pcori.org/research-results/how-we-select-research-topics/generation-and-prioritization-topics-funding-4*

# BREAK

**1:45 pm – 2:00 pm**

# Topic 4:

## *Comparative Effectiveness of molecularly directed therapies in patients with lung, pancreas, or bladder cancer*

Expert:
Brian Wilkinson, MA
*ECRI Institute Evidence-based Practice Center*

PCORI Lead:
Danielle Whicher, PhD, MHS

Advisory Panel Lead:
Margaret Clayton, PhD, APRN

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# Overview

- Definition of Molecularly Directed Therapy
- Overview of Molecularly Directed Therapy in EGFR Mutation-Positive Non-Small Cell Lung Cancer
- State of Molecularly Directed Therapy in Bladder Cancer and Pancreatic Ductal Adenocarcinoma

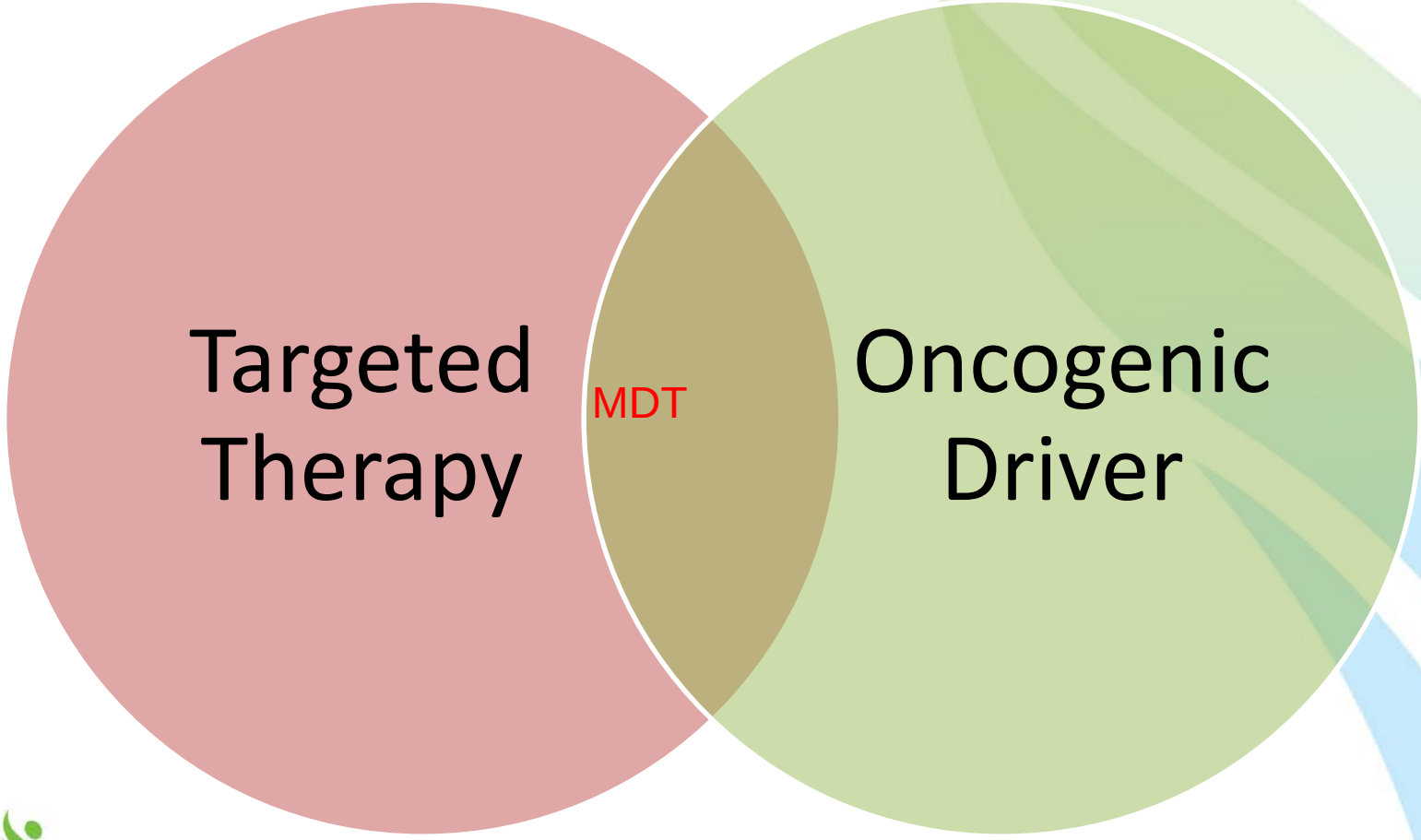
# Targeted Therapy

- Targets one or more molecules (typically proteins) involved in cancer progression and/or survival.
- Examples
  - Targeting of VEGF-A by bevacizumab (Avastin) to limit angiogenesis
  - Targeting of BCL-2 by venetoclax (Venclexta) to promote apoptosis
  - Targeting of BCR-ABL by imatinib (Gleevec) to limit inappropriate pro-growth signaling

# Oncogenic Driver Mutations

- Cancer can be considered a genetic disease in which inherited (germline) and acquired (somatic) genetic variants contribute to cancer pathogenesis.
- Genetic variants that contribute to the development, progression, or maintenance of cancer are oncogenic drivers.
- Examples
  - BCR-ABL gene fusions in Chronic Myeloid Leukemia
  - Activating B-RAF mutations in Melanoma
  - Loss of function mutations in BRCA1 or BRCA2 in numerous cancers

# Molecularly Directed Therapy

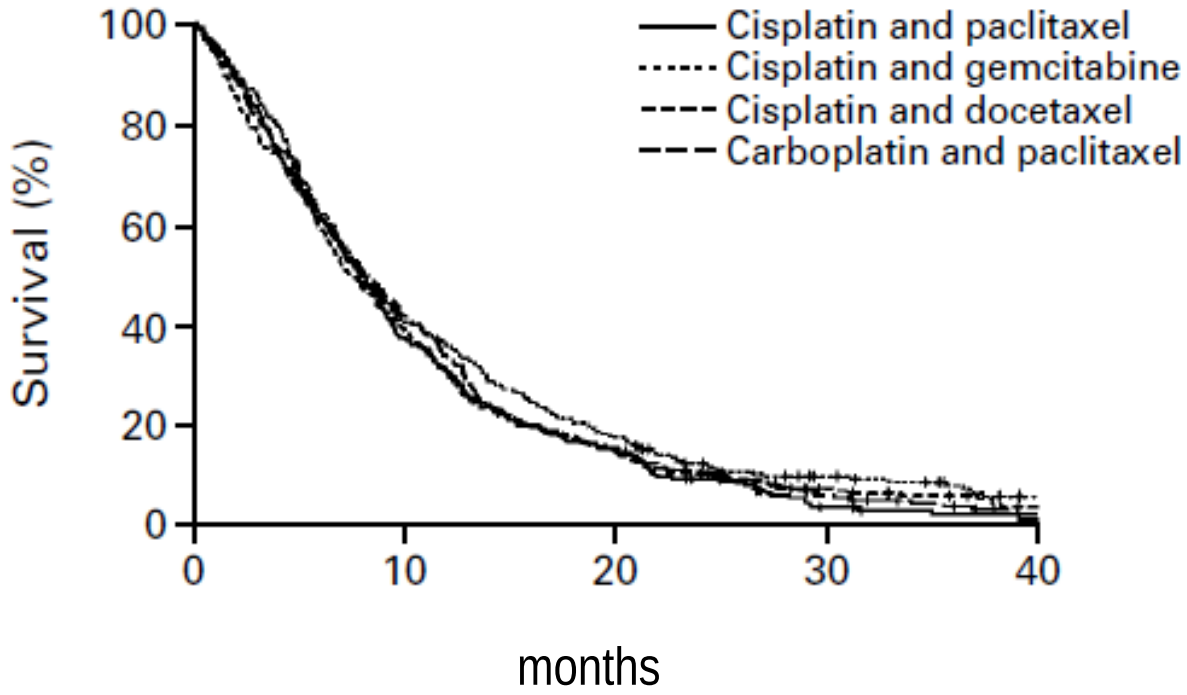


# Non-Small Cell Lung Cancer

- Lung cancer is the leading cause of cancer-related death in the United States; approximately 158,000 deaths per year.
- Approximately 85% of lung cancers are non-small cell lung cancers
- Molecularly directed therapies have begun to change the treatment landscape in NSCLC

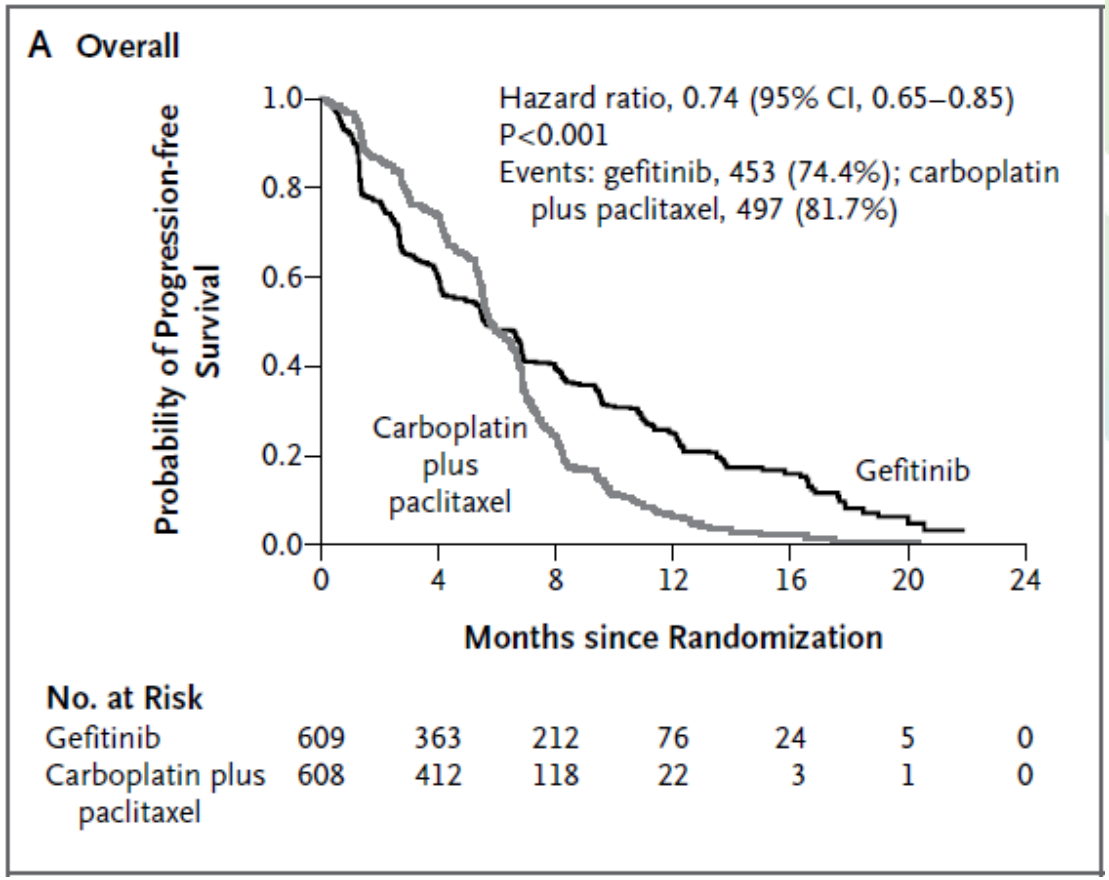
# Cytotoxic Therapy for Treatment of Metastatic NSCLC

- Platinum-based doublets




Schiller et al. 2004

# EGFR Inhibitor vs. Cytotoxic Chemotherapy in Non-Selected NSCLC




Mok et al. 2009
IPASS Study
East Asian, light/never smokers with lung adenocarcinoma

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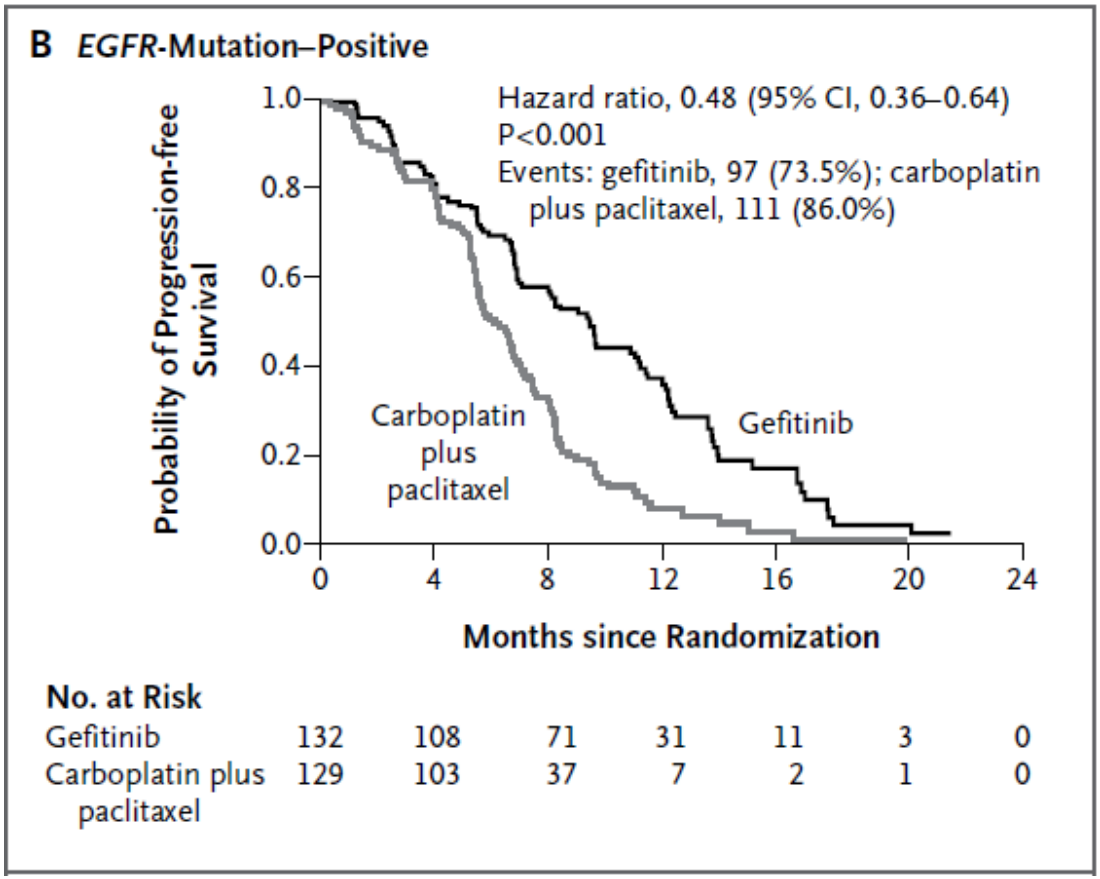
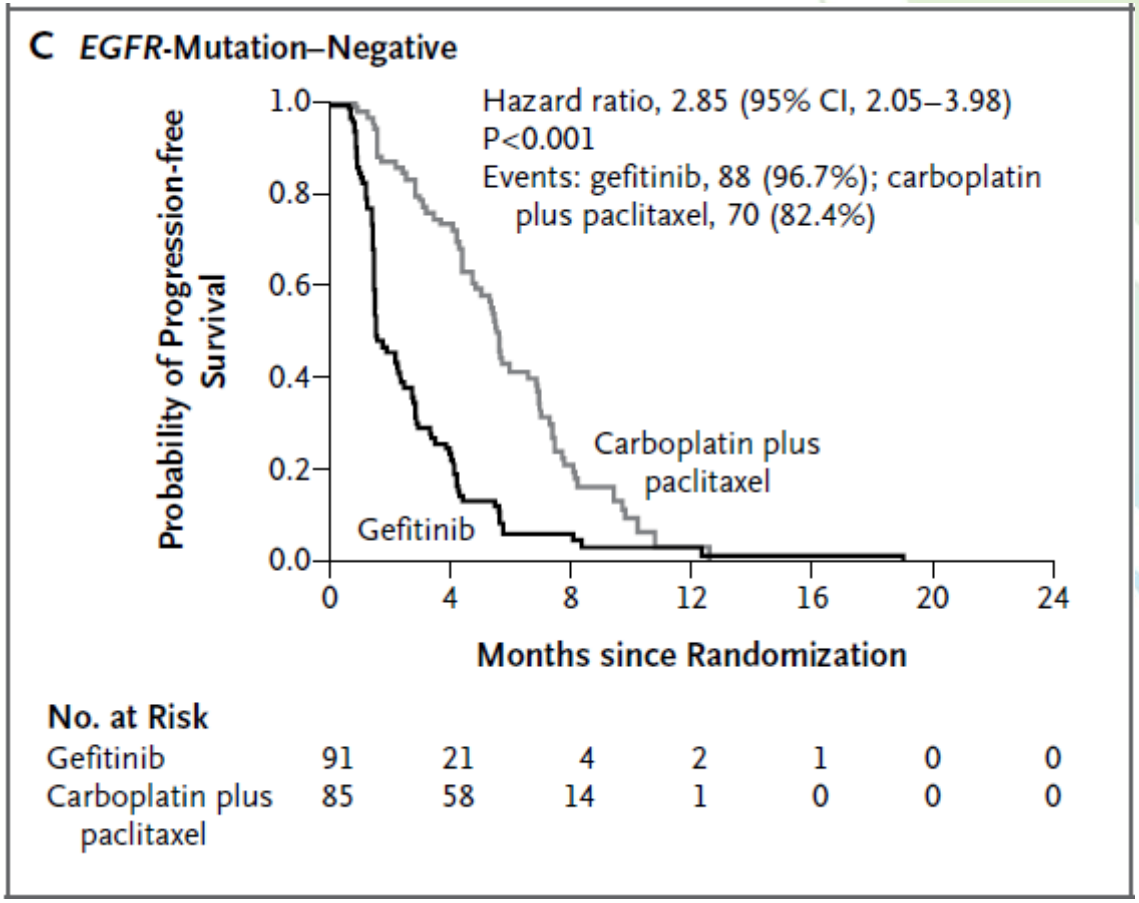
# EGFR Inhibitor vs. Cytotoxic Chemotherapy in EGFR Mutation-Positive NSCLC




Mok et al. 2009

# EGFR Inhibitor vs Cytotoxic Chemotherapy in EGFR Mutation-Negative NSCLC




Mok et al. 2009

# Trials Comparing EGFR Inhibitors to Cytotoxic Chemotherapy In mEGFR-Positive NSCLC

| EGFR Inhibitor | Number of Patients | Progression-Free Survival | Overall Survival |
|---|---|---|---|
| Afatinib (Gilotrif) | 709 | HR 0.42; 95% CI 0.34 to 0.53 | HR 0.93; 95% CI 0.74 to 1.17 |
| Erlotinib (Tarceva) | 378 | HR 0.30; 95% CI 0.24 to 0.38 | HR 0.95; 95% CI 0.75 to 1.22 |
| Gefitinib (Iressa) | 491 | HR 0.39; 95% CI 0.32 to 0.48 | HR 0.95; 95% CI 0.77 to 1.18 |

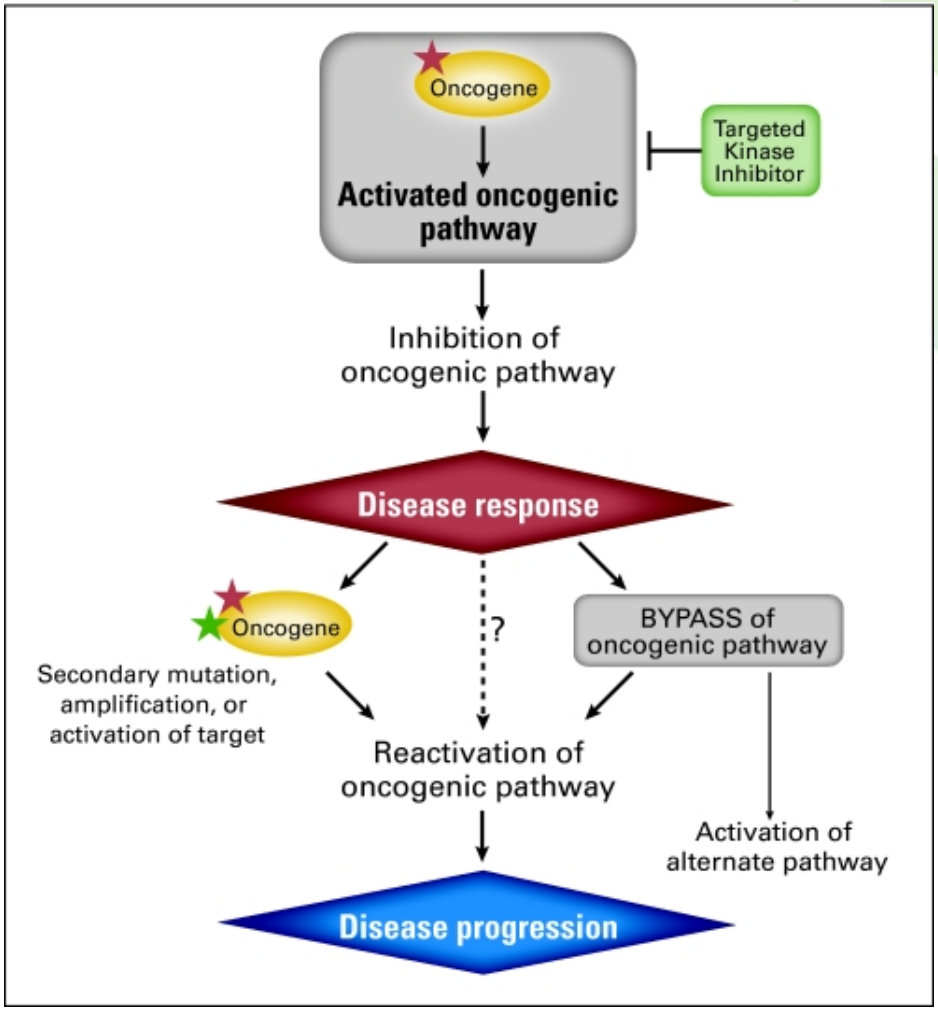
Greenhalgh et al. 2016

# Trials Comparing EGFR Inhibitors in mEGFR-Positive NSCLC

| EGFR Inhibitor | Number of Patients | Progression-Free Survival |
|---|---|---|
| Erlotinib (Tarceva) vs Gefitinib (Iressa) | 256 | HR 0.80; 95% CI 0.61 to 1.05 |
| Afatinib (Gilotrif) vs Gefitinib (Iressa) | 319 | HR 0.73; 95% CI 0.57 to 0.95 |

Wang et al. 2015; Park et al. 2016

# Resistance to Molecularly Directed Therapy




Wagle et al. 2011

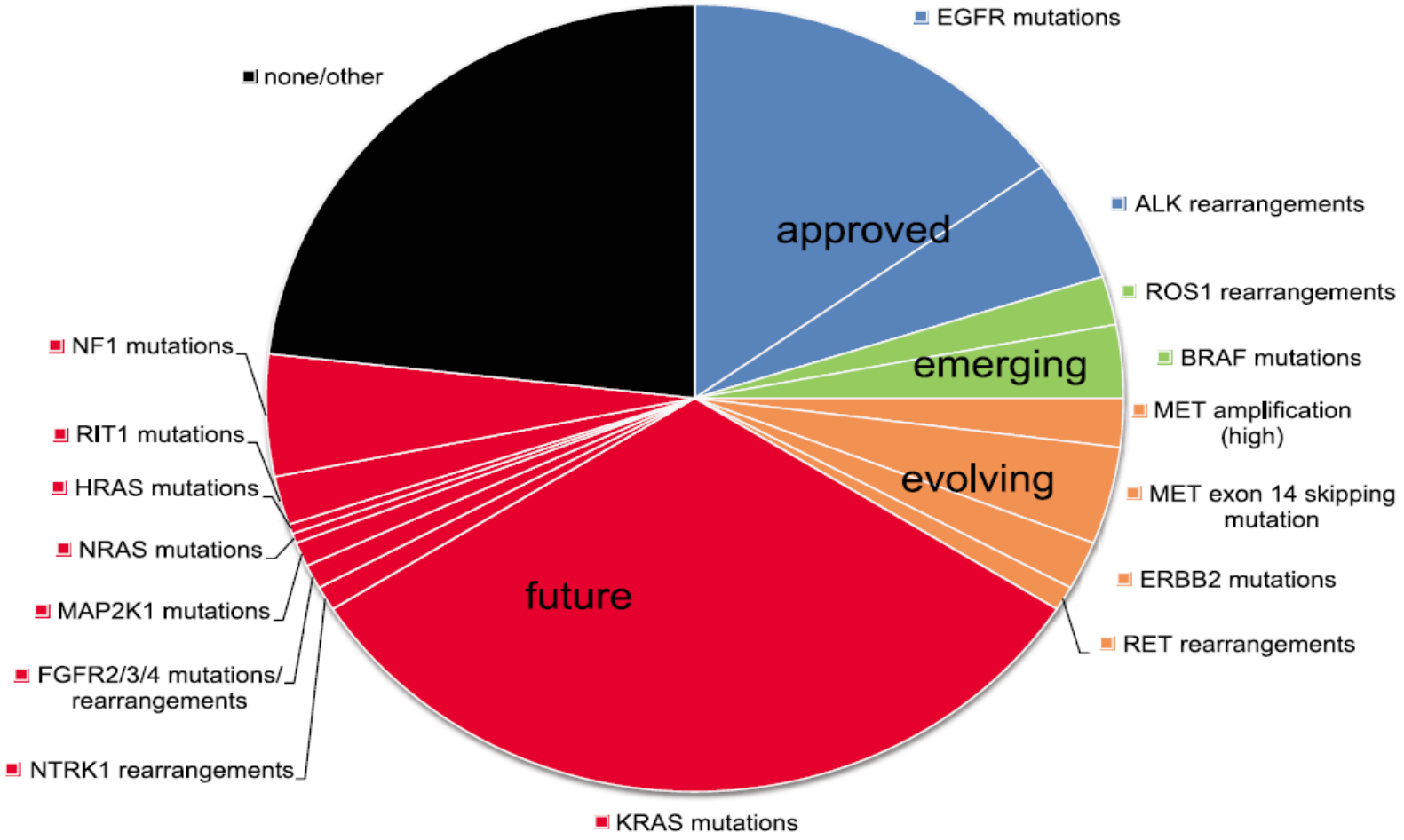
# Addressing Resistance to EGFR Inhibitors

- The most common cause of resistance to EGFR inhibitors is a secondary mutation in *EGFR.*
- Osimertinib (Tagrisso) is an EGFR inhibitor designed to have activity against the most common form of inhibitor-resistant EGFR (T790M).
- In a single-arm trial of patients with EGFR-T790M positive NSCLC previously treated with an EGFR inhibitor, osimertinib generated an overall response rate of 66% and progression-free survival of 9.6 months

# Randomized Trials of Osimertinib

| Patient Population | Comparators | Primary Endpoint | Completion Date |
|---|---|---|---|
| Patients with EGFR-T790M-Positive NSCLC Previously Treated with an EGFR Inhibitor | Osimertinib (Tagrisso) vs. Cytotoxic Chemotherapy | Progression-Free Survival | January 2018 |
| Patients with EGFR Mutation-Positive NSCLC who are Treatment-Naive | Osimertinib (Tagrisso) vs. EGFR Inhibitor (Erlotinib or Gefitinib) | Progression-Free Survival | October 2018 |

# Additional Driver Mutations in NSCLC

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Shea et al. 2016

# Additional EGFR Inhibitor-Containing Regimens Under Study

- Trials of the combination of EGFR inhibitors with chemotherapy
- Trials of the combination of EGFR inhibitors with other targeted therapies (e.g., anti-angiogenic drugs bevacizumab [Avastin] and ramucirumab [Cyramza])
- Trials of the combination of EGFR inhibitors with immunotherapies (e.g., checkpoint inhibitors)

# Non-Conventional Clinical Trial Designs

- Basket Trials – Enroll patients with cancers of different tissues of origin (i.e., lung, pancreas) that share a common oncologic driver into a common treatment arm
  - BRAF Basket Trial (Vemurafenib)
  - NCI Match Trial (Multiple Treatment Arms)
- Umbrella Trials – Enroll patients with cancers of a single tissue of origin into multiple treatment arms depending on the oncologic driver mutation identified
  - National Lung Matrix (Squamous NSCLC)
  - Precision Promise (Pancreatic Cancer)

# Molecularly Directed Therapy in Bladder Cancer

- No molecularly directed therapies currently recommended in treatment guidelines (NCCN, ESMO, EAU)
- The evidence base regarding the use of molecularly directed therapies in bladder cancer is very small; with two small trials demonstrating signs of anti-cancer activity in a handful of patients.
- 17 ongoing trials of 11 drug classes targeting 13 unique oncogenic drivers

# Molecularly Directed Therapy in Pancreatic Ductal Adenocarcinoma

- No molecularly directed therapies currently recommended in treatment guidelines (NCCN, ESMO, ASCO)
- The evidence base regarding the use of molecularly directed therapies in pancreatic cancer is very small; with two small trials demonstrating signs of anti-cancer activity in a handful of patients.
- 15 ongoing trials involving 8 drug classes targeting 16 unique oncogenic drivers
- One ongoing randomized control trial for PARP inhibitors in cancers with impaired DNA damage repair.

# Conclusions

- Certain molecularly directed approaches in NSCLC have accumulated sufficient data to warrant consideration of comparative effectiveness studies. However, a large number of trials in these established targets are ongoing.
- Feasibility of comparative effectiveness studies of emerging approaches in NSCLC (e.g., targeting BRAF or ROS1) could be limited by issues regarding feasibility.
- Given the paucity of data regarding the use of molecularly directed therapies in bladder cancer and pancreatic cancer, it appears premature to consider comparative effectiveness studies of molecularly directed therapies for these cancers at this time.

# Contributors

- Brian Wilkinson, M.A., ECRI Institute
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# Discussion Reminders

1. Consider the topic with respect to the following:
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   b) Impact
   c) Important evidence gap
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   e) Durability of information
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*source: http://www.pcori.org/research-results/how-we-select-research-topics/generation-and-prioritization-topics-funding-4*

# Announcements and Next Steps

- Next in-person meeting will occur in Spring 2017

# Thank you for your participation

## Advisory Panel on Assessment of Prevention, Diagnosis, and Treatment Options

November 16, 2016

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