Turning a clinical question into a testable hypothesis

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Clinical questions

- Controversies in patient care
- Knowledge gaps
- New diagnostic tests
- Better treatment options
- Characterization of outcomes
- Prognostic indicators
- Underlying etiology
I need a research direction!!!

- Journal club papers
  - Logical follow-up
- High caseload diseases
  - What is not known?
- Mentor discussions
Define the knowledge gap

- Literature search
  - PubMed
  - Multiple search terms
  - Reference lists from papers
- Scientific meetings
- Read full papers!!
- Annotate each paper
Outline your background

- Major conclusions from each paper
- Organize as a logical story
  - Why it is important
  - What is known in patients
  - What is known in animal models

- What remains to be answered?
- Does your question need revising?
Posing your question(s)

- *This is the most important step*
- Research questions or aims:
  - To characterize
  - To determine
  - To evaluate
  - To describe
**PICOT approach**

- Population
- Intervention
- Comparators
- Outcomes
- Time frame
Population

- Population source
- Inclusion criteria
- Gold standard for diagnosis
- Validated biomarker
Population

- Inclusion criteria
  - Age range
  - Gender, race
  - Stage of illness
  - Severity of presentation
Population

- Exclusion criteria
  - Only newly diagnosed?
  - Only expected to survive?
  - Prior treatments
  - Washout
  - Peds excluded?
Intervention

- Drug treatment
- Surgical procedure
- Diagnostic assay

- What other care is allowed?
- Avoid “clinician discretion” without guidelines
Intervention

- Blinded
- Double blinded
- Applies to *all* evaluators
- Placebo effect
Comparators

- Clinically relevant
- Concurrent
  - Avoid historical controls
- Placebo, or standard of care?
- Avoid bias in randomization
Outcomes

• Define a primary outcome
  • Ideally objective
  • Easily measured
  • Clinically available
  • Validated for patients
  • Relevant to clinical response
Outcomes

- Subjective primary outcomes
  - Validated scoring system
  - Complement with objective outcomes whenever possible
- Blinded evaluators!!
Outcomes

• Secondary outcomes
  • Of lesser importance, or harder to prove
  • Can generate further hypotheses
  • Add depth
Time frame

- Recruitment period
- Timing of intervention
- Duration of intervention
- Time points for evaluation
- Long term follow-up
Time frame

- Avoid complicated follow-up
- Consider drop-out rate
- For time frames < one year, consider seasonal variables
Your research question...

- Clinically interesting
- Addresses a knowledge gap
- Feasible!
  - Clinical expertise
  - Caseload
  - Support staff
  - Funds
  - Career time frame
Your research question...

- For prospective studies:
  - Question is of interest to patients (and nurses)
  - Intervention is low risk
  - Follow-up is convenient
  - Consider incentives
Common roadblocks

- Question is unfocused
- Question is boring
- Disease is uncommon
- Outcome being studied is rare
Common roadblocks

- Data collection is labor intensive
- Intervention is invasive
- Validated assays not available
Common roadblocks

- New equipment needed
- Project outside of clinical expertise
- Case identification out of your control
- Large grant needed
- Prolonged follow-up
Questions, aims, and hypotheses

• Are antibiotics indicated in acute exacerbation of COPD?
Questions, aims, and hypotheses

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- P:
- I:
- C:
- O:
- T:

Daniela et al. *Am J Respir Crit Care Med* 2009
Questions, aims, and hypotheses

- Are antibiotics indicated in acute exacerbation of COPD?
- P: Patients > 45 yo, with COPD stages I-IV, with acute dyspnea / increased sputum/ purulence
- I:
- C:
- O:
- T:

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- P: Patients > 45 yo, with COPD stages I-IV, with acute dyspnea / increased sputum/ purulence
- I: Doxycycline for 7 d, plus pred IV/inhaled BD
- C:
- O:
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• C: Placebo instead of doxy, plus SOC
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- **I:** Doxycycline for 7 d, plus pred IV/inhaled BD
- **C:** Placebo instead of doxy
- **O:** Scored clinical response; CRP, spirometry, antibiotic rescue
- **T:**

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- C: Placebo instead of doxy
- O: Scored clinical response; CRP, spirometry, antibiotic rescue
- T: Evaluation at days 0, 10, and 30

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Questions, aims, and hypotheses

- Are antibiotics indicated in acute exacerbation of COPD?
- Hypothesis: Doxycycline for 7 days, as an adjunct to SOC, will be superior to placebo in reaching clinical remission 30 days after acute exacerbation of COPD
Questions, aims, and hypotheses

- Is a commercially available urine assay accurate in the diagnosis of tuberculosis?
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Reither BMC Infect Dis, 2009
Questions, aims, and hypotheses

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- P: Patients with suspected pulmonary TB
- I:
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- O:
- T:
Questions, aims, and hypotheses

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- P: Patients with suspected pulmonary TB
- I: Lipoarabinomannan ELISA on urine
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• C: Patients ultimately negative for TB
• O: Cytologic or culture diagnosis of TB
• T: Consecutive enrollment over 3 months

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Questions, aims, and hypotheses

- Is a commercially available urine assay accurate in the diagnosis of tuberculosis?
- Hypothesis: Urinary LAM-ELISA will have high sensitivity and specificity (> 85%) in the diagnosis of pulmonary TB in patients suspected of TB
Questions, aims, and hypotheses

- Does microRNA expression have prognostic significance in melanoma?
Questions, aims, and hypotheses

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- P:
- I:
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- O:
- T:
Questions, aims, and hypotheses

• Does microRNA expression have prognostic significance in melanoma?
• P: Archived primary melanoma samples with detailed clinical data
  • I:
  • C:
  • O:
  • T:
Questions, aims, and hypotheses

- Does microRNA expression have prognostic significance in melanoma?
- P: Archived primary melanoma samples with detailed clinical data
- I: qPCR for several microRNAs (from in vitro)
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- O:
- T:
Questions, aims, and hypotheses

- Does microRNA expression have prognostic significance in melanoma?
- P: Archived primary melanoma samples with detailed clinical data
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- C: Melanocytic nevi, and tumors with range of outcomes
- O:
- T:

Satzger Int J Cancer 2009
Questions, aims, and hypotheses

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- O: Recurrence free survival, overall survival
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- I: qPCR for several microRNAs (from in vitro)
- C: Melanocytic nevi, and tumors with range of outcomes
- O: Recurrence free survival, overall survival
- T: Follow-up for minimum of 6 months

Satzger *Int J Cancer* 2009
Questions, aims, and hypotheses

- Does microRNA expression have prognostic significance in melanoma?
- High expression of miRNA-15b in primary melanomas will be associated with poor recurrence-free and overall survival
Summary

- Study what you know
- Use your caseload
- Use your staff expertise
- Frame your questions with PICOT
- Choose reasonable outcomes and follow-up
And don’t give up!